

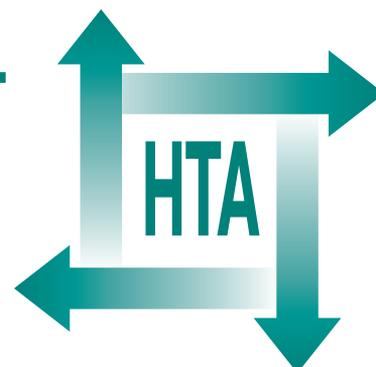
Issues in data monitoring and interim analysis of trials

AM Grant, DG Altman, AB Babiker,
MK Campbell, FJ Clemens, JH Darbyshire,
DR Elbourne, SK McLeer, MKB Parmar,
SJ Pocock, DJ Spiegelhalter, MR Sydes,
AE Walker, SA Wallace
and the DAMOCLES study group



March 2005

**Health Technology Assessment
NHS R&D HTA Programme**





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Abstract

Issues in data monitoring and interim analysis of trials

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Objectives: To address issues about data monitoring committees (DMCs) for randomised controlled trials (RCTs).

Data sources: Electronic databases. Handsearching of selected books. Personal contacts with experts in the field.

Review methods: Systematic literature reviews of DMCs and small group processes in decision-making; sample surveys of: reports of RCTs, recently completed and ongoing RCTs and policies of major organisations involved in RCTs; case studies of four DMCs; and interviews with experienced DMC members. All focused on 23 prestated questions.

Results: Although still a minority, RCTs increasingly have DMCs. There is wide agreement that nearly all trials need some form of data monitoring. Central to the role of the DMC is monitoring accumulating evidence related to benefit and toxicity; variation in emphasis has been reflected in the plethora of names. DMCs for trials performed for regulatory purposes should be aware of any special requirements and regulatory consequences. Advantages were identified for both larger and smaller DMCs. There is general agreement that a DMC should be independent and multidisciplinary. Consumer and ethicist membership is controversial. The chair is recognised as being particularly influential, and likely to be most effective if he or she is experienced, understands both statistical and clinical issues, and is facilitating in style and impartial. There is no evidence available to judge suggested approaches to training. The review suggested that costs should be covered, but other

rewards must be so minimal as to not affect decision-making. It is usual to have a minimum frequency of DMC meetings, with evidence that face-to-face meetings are preferable. It is common to have open sessions and a closed session. A report to a DMC should cover benefits and risks in a balanced way, summarised in an accessible style, avoiding excessive detail, and be as current as possible. Disadvantages of blinded analyses seem to outweigh advantages. Information about comparable studies should be included, although interaction with the DMCs of similar ongoing trials is controversial. A range of formal statistical approaches can be used, although this is only one of a number of considerations. DMCs usually reach decisions by consensus, but other approaches are sometimes used. The general, but not unanimous, view is that DMCs should be advisory rather than executive on the basis that it is the trial organisers who are ultimately responsible for the conduct of the trial.

Conclusions: Some form of data monitoring should be considered for all RCTs, with reasons given where there is no DMC or when any member is not independent. An early DMC meeting is helpful, determining roles and responsibilities; planned operations can be agreed with investigators and sponsors/funders. A template for a DMC charter is suggested. Competing interests should be declared. DMC size (commonly three to eight people) is chosen to optimise performance. Members are usually independent and drawn from appropriate backgrounds, and some, particularly the chair, are experienced. A

minimum frequency of meetings is usually agreed, with flexibility for more if needed. The DMC should understand and agree the statistical approach (and guidelines) chosen, with both the DMC statistician and analysis statistician competent to apply the method. A DMC's primary purpose is to ensure that continuing a trial according to its protocol is ethical, taking account of both individual and collective ethics. A broader remit in respect of wider ethical issues is controversial; arguably, these are primarily the responsibility of research ethics committees, trial steering committees and investigators. The DMC should know the range of recommendations or decisions open to it, in advance. A record should be kept describing the key issues discussed and the rationale for decisions taken. Errors are likely to be reduced if a DMC makes a thorough review of the evidence and has a clear understanding of how it should function, there is active participation by

all members, differences are resolved through discussion and there is systematic consideration of the various decision options. DMCs should be encouraged to comment on draft final trial reports. These should include information about the data monitoring process and detail the DMC membership. It is recommended that groups responsible for data monitoring be given the standard name 'Data Monitoring Committee' (DMC). Areas for further research include: widening DMC membership beyond clinicians, trialists and statisticians; initiatives to train DMC members; methods of DMC decision-making; 'open' data monitoring; DMCs covering a portfolio of trials rather than single trials; DMC size and membership, incorporating issues of group dynamics; empirical study of the workings of DMCs and their decision-making, and which trials should or should not have a DMC.



Contents

Glossary and list of abbreviations	ix	Question 17: What should be the role of formal statistical methods in DMCs?	38
Executive summary	xiii	Question 18: Should specific trial designs influence the proceedings?	39
I Introduction and background	1	Question 19: How should ethical issues be handled in DMCs?	41
Introduction	1	Question 20: What should DMCs do with their decisions or recommendations?	42
Background	1	Question 21: What should be done in 'difficult' situations?	44
2 Systematic review of published literature on data monitoring committees	7	Question 22: Should some DMC decisions be considered to be 'errors'?	45
Background	7	Question 23: What should the DMC's role be concerning publications?	47
Question 1: Which trials need an independent DMC?	10	Subsequent literature	47
Question 2: Who should decide the details of how a DMC operates?	13	Conclusions	48
Question 3: What should the DMC's terms of reference cover?	13	3 Review of small group processes relevant to data monitoring committees	49
Question 4: Does the DMC have a role before the trial recruitment phase?	16	Introduction	49
Question 5: How should regulatory issues impact on the DMC?	17	Methods	49
Question 6: What should the membership of a DMC be?	18	Results: error and bias in decision-making	51
Question 7: How is independence to be maintained?	20	Results: factors associated with error or bias in decision-making on judgemental tasks	53
Question 8: Should the DMC deliberations be open or closed (confidential or secret as opposed to publicly available)?	23	Results: effects of formal and informal decision-making procedures on decision process and quality	66
Question 9: What are the optimal practical arrangements for interim analysis and data monitoring?	26	Implications and recommendations for DMCs	67
Question 10: What sort of training or preparation should DMC members have? ..	27	4 Cross-sectional review of the reported use of data monitoring committees in the main published reports of randomised controlled trials	71
Question 11: What material should be available to a DMC?	27	Introduction	71
Question 12: Who should own the interim data and analyses?	31	Methods	71
Question 13: Should non-comparative analyses (which are 'administrative' and not separated by treatment arm) be carried out?	32	Results	73
Question 14: Is the DMC advisory (to make recommendations) or executive (to make decisions)?	33	Discussion	79
Question 15: What decisions and recommendations should be open to the DMC?	33	5 Surveys of policies and practice	83
Question 16: How should the decisions or recommendations be reached within the DMC?	37	Introduction	83
		Survey of DMC practices in recent trials	83
		Survey of current data monitoring practices	87
		Survey of DMC policies of key organisations involved with RCTs	94

6 General interviews with experienced data monitoring committee members and case studies of trials with difficult data monitoring decisions	101	What should be done in 'difficult' situations? (Question 21)	128
Introduction	101	Should some DMC decisions be considered to be 'errors'? (Question 22)	128
Part I: General interviews with experienced DMC members	101	What should the DMC's role be concerning publications? (Question 23)	129
Part II: Case studies of trials with difficult data monitoring decisions	108	8 Conclusions and recommendations	139
7 Discussion	119	For the conduct of data monitoring in RCTs	139
Introduction	119	For further research on behavioural and organisational aspects of data monitoring in RCTs	143
Which trials need an independent DMC? (Question 1)	119	Acknowledgements	145
Who should decide the details of how a DMC operates? (Question 2)	120	References	147
What should the DMC's terms of reference cover? (Question 3)	120	Appendix 1 Summary of statistical approaches to data monitoring	157
Does the DMC have a role before the trial recruitment phase? (Question 4)	120	Appendix 2 Search terms used for the systematic review of published literature on data monitoring committees	163
How should regulatory issues impact on the DMC? (Question 5)	121	Appendix 3 Number of quotes found per question in <i>Box 1</i> in the systematic review of the published literature on data monitoring committees	165
What should the membership of a DMC be? (Question 6)	121	Appendix 4 List of included references in the systematic review of published literature on data monitoring committees	167
How is independence to be maintained? (Question 7)	123	Appendix 5 Summary of databases searched for the review of small group processes	171
Should the DMC deliberations be open or closed? (Question 8)	123	Appendix 6 Electronic databases with search terms used for the review of small group processes	173
What are the optimal practical arrangements for interim analysis and data monitoring? (Question 9)	123	Appendix 7 Number of review papers identified at each stage of the review of small group processes	177
What sort of training or preparation should DMC members have? (Question 10)	124	Appendix 8 Summary of review articles included in the review of small group processes	179
What material should be available to a DMC? (Question 11)	124	Appendix 9 Data extraction form (review of small group processes)	183
Who should own the interim data and analyses? (Question 12)	125	Appendix 10 Data extraction form (cross-sectional review of reported use of data monitoring committees in main published reports of randomised controlled trials)	185
Should non-comparative analyses (which are administrative and not separated by treatment arm) be carried out? (Question 13)	125		
Is the DMC advisory (to make recommendations) or executive (to make decisions)? (Question 14)	126		
What decisions and recommendations should be open to the DMC? (Question 15)	126		
How should the decisions or recommendations be reached within the DMC? (Question 16)	126		
What should be the role of formal statistical methods in DMCs? (Question 17)	126		
Should specific trial designs influence the proceedings? (Question 18)	127		
How should ethical issues be handled in DMCs? (Question 19)	127		
What should DMCs do with their decisions or recommendations? (Question 20)	127		

<p>Appendix 11 Sampling strategy for completed trials in surveys of policies and practice 187</p> <p>Appendix 12 Letter to principal investigator(s) for the survey of data monitoring in recently completed trials 189</p> <p>Appendix 13 Proforma for recent trials identified (part III) in surveys of policies and practice 191</p> <p>Appendix 14 Sampling strategy for survey of ongoing trials in surveys of policies and practice 195</p> <p>Appendix 15 Letter to principal investigator(s) for the survey of current data monitoring practices 197</p> <p>Appendix 16 Proforma for data extraction from the studies sampled (part II) in surveys of policies and practice 199</p> <p>Appendix 17 Proforma used to gather policy information from funding organisations in surveys of policies and practice 203</p> <p>Appendix 18 Classification of organisations included in the survey of data monitoring</p>	<p>policies and summary of response in surveys of policies and practice 207</p> <p>Appendix 19 Letter to key organisations involved with randomised controlled trials 213</p> <p>Appendix 20 Summary of the DAMOCLES study in surveys of policies and practice 215</p> <p>Appendix 21 Letter to experienced data monitoring committee members requesting a general interview 217</p> <p>Appendix 22 Semistructured interview schedule used for general interviews and case studies 219</p> <p>Appendix 23 Letter to principal investigator(s) requesting permission to include a trial in case-study interviews 221</p> <p>Appendix 24 Letter to data monitoring committee members requesting an interview for case studies 223</p> <p>Health Technology Assessment reports published to date 225</p> <p>Health Technology Assessment Programme 235</p>
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Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Administrative analysis The evaluation of factors that could affect the integrity of the trial but that can be assessed without returning relative efficacy results.

Bayesian approach An approach to the design, monitoring, analysis and interpretation of studies that explicitly uses external evidence.

Blinded analysis The presentation of data summarised by treatment arm, in which the treatment arms are not identified.

Choice-dilemma task A decision-making task with no right answer (see also Judgement task).

Choice shift Psychological phenomenon describing the shift in people's decision preferences after taking part in a group discussion.

Clinical trial An investigation in human participants to discover the clinical effects of a medicinal product or non-medicinal technology (e.g. surgical procedure).

Closed session (of DMC meeting) The session of the DMC meeting that is restricted to the independent members of the DMC – those who may see unblinded data. The trial statistician is often invited to attend this session of the meeting.

Collective ethics The ethical approach of putting the interests of future patients who may benefit from the results of a trial before those of the individual participants within the trial.

Conditional power analysis A statistical calculation made on the basis of the interim data available to assess the likelihood, given the interim data, that a beneficial effect of the treatment under consideration will be detected if the trial were to continue as planned.

CONSORT statement An international statement to help authors to improve the reporting of randomised controlled trials through the use of a structured checklist and flow diagram. (www.consort-statement.org)

Data monitoring committee (DMC) Any committee set up to assess, at intervals during the course of a trial, the progress of the trial, the trial safety data and the trial outcome data with a view to recommending whether the trial should continue, be modified or be terminated.

Decision bias Decision-making behaviour that deviates from what normative decision-making models would suggest, i.e. when the decision reached differs from that which should be reached according to the theory.

Decision errors Decision-making activities that fail to achieve their intended outcome.

Decision fiasco Known situations where decision errors occurred.

Defining issues test Psychometric test to assess the level of reasoning used by an individual to solve a particular dilemma.

Effectiveness A measure of the benefit resulting from an intervention for a given health problem under normal conditions of clinical care.

Efficacy A measure of the benefit resulting from an intervention for a given health problem under ideal conditions.

Equipoise The belief that alternative treatments being compared within a trial have the same expected utilities.

continued

Glossary continued

Equivalence trial A trial whose primary aim is to establish equivalence rather than a difference (see Superiority trial) between interventions.

External evidence Results from trials (or other studies) of similar interventions, external to the current trial.

Framing The way in which a problem is presented. This can be either positive (e.g. the success rate of an intervention) or negative (e.g. the failure rate of an intervention).

Frequentist approach An approach to the design, monitoring, analysis and interpretation of studies that is based on the long-run frequency properties of statistical procedures (often known as the 'classical' approach to statistical inference).

Futility The result in a superiority trial (see definition below) when there is no longer a reasonable chance that the null hypothesis can be disproved.

Group cohesion The strength of group members' positive feelings towards one another and/or the strength of their shared commitment to group tasks or goals.

Group polarisation The tendency for the initial position of a group to be exaggerated as a result of group discussion, e.g. if group members are initially cautious about a dilemma, the outcome of the group discussion will be more cautious than the aggregated individual opinions.

Groupthink A psychological model of small group processes describing the decision-making phenomenon where the people engaged in the decision-making are so deeply involved in a cohesive 'in-group' that the members override their motivation realistically to appraise alternative courses of action to achieve unanimity.

Heuristics General rules that guide decision-making.

Independent (committees or committee members) Committees or committee members completely uninvolved in the running of the trial and who cannot be unfairly influenced (either directly or indirectly) by people, or institutions, involved in the trial.

Individual ethics The ethical approach of putting the interests of individual participants

within a trial before those of future patients who may benefit from the results of the trial.

Institutional review board See entry for Research ethics committee.

Interim analysis Analysis of the trial data, summarised by treatment arm, undertaken before the planned formal analysis at the end of the trial.

Judgement task A decision-making task with no right answer (see also Choice-dilemma task).

Majority influence Influence on decision-making process of those who hold the majority decision preference.

Members (of DMCs) Individuals serving on the DMC who have full voting rights.

Minority influence Influence on the decision-making process of those who hold the minority decision preference.

Moral reasoning The processes of reasoning that individuals employ about moral dilemmas.

Non-inferiority trial A trial whose primary aim is to establish that an intervention being investigated is not clinically inferior to its comparator.

Observers (of DMCs) Individuals who may be invited to attend all (or part) of the DMC meetings but who do not have decision-making rights.

Open session (of DMC meeting) The session of the DMC meeting that is attended by the independent members of the DMC, trial investigators, the trial statistician and, on some occasions, representatives of the sponsor.

Placebo An inert substance designed to look (and taste, if appropriate) the same as the active intervention.

Principal investigator(s) The person(s) who is (are) responsible for the conduct of the trial.

Prospect theory The dependence of risk-taking behaviour on whether the decision is positively or negatively framed.

Protocol A document that describes the objectives, design, methodology, statistical considerations and organisation of a trial. The protocol is a complete specification for the research plan and the treatment of individual participants.

continued

Glossary continued

Randomised controlled trial A clinical trial where interventions are assigned by random allocation rather than by conscious decisions of clinicians or participants. This study design avoids problems of bias and confounding variables by assuring that both known and unknown determinants of outcome are evenly distributed between treatment and control groups.

Research ethics committee An independent committee whose purpose is to review proposed studies with regard to protecting the dignity, rights, safety and well-being of all actual or potential research participants. All trials must receive research ethics committee approval before they can commence. In the UK there are both multicentre and local research ethics committees. These committees are known as institutional review boards in the USA.

Responsibilities (of DMCs) The relations with those groups to which the DMC has some responsibility, whether explicit or implied.

Risky-shift Psychological phenomenon where people are more likely to advocate risky courses of action after taking part in a group discussion.

Roles (of DMCs) The tasks and activities that DMCs undertake.

Sequential analysis The routine analysis of trial data as they accumulate.

Serious adverse event Any untoward medical occurrence that results in either: a hospital admission; a life-threatening event, persistent or significant disability or incapacity; or death. This includes congenital abnormalities or birth defects.

Small group processes The processes by which small groups (typically <20 members) interact and make decisions.

Social loafing The tendency of individuals to expend less effort when working in a group compared with working alone.

Sponsor An organisation, institution or individual that takes overall responsibility for the initiation, management and/or financing of a trial.

Standard operating procedures Detailed written instructions designed to ensure uniformity in the performance of a specific trial function.

Statistician, analysis The statistician responsible for the analysis of the data presented to the DMC.

Statistician, DMC The (independent) statistically experienced member(s) of the DMC who consider and comment on the accumulated data presented to the DMC.

Statistician, trial A member of the trial organising body, responsible for overseeing the statistical issues of the trial, who is often responsible for the production of the report to the DMC.

Stopping rule Formal definition of the circumstances under which a trial would be stopped depending on the results obtained.

Superiority trial A trial whose primary aim is to establish a difference in outcome between the interventions being compared.

Trial investigators The clinicians who are supporting the trial by entering patients under their care.

Trial management group Group set up to provide day-to-day input into the running of a trial. Usually comprises the principal investigator(s), other relevant clinicians and data coordinating centre staff.

Trial steering committee Committee set up to provide overall supervision of a trial and to ensure that the trial is conducted to rigorous standards for good clinical practice.

Type I error The probability of concluding that one treatment is better than another when, in truth, no difference exists, i.e. the chance of a false-positive result.

Type II error The probability of concluding that there is no difference between treatments when, in truth, one treatment was better than the other, i.e. the chance of a false-negative result.

Unblinded analysis The presentation of trial data summarised by treatment arm, in which the treatment arms are identified.

List of abbreviations

ASSIA PLUS	Applied Social Sciences Index and Abstracts Plus	ICH	International Conference on Harmonisation (of technical requirements for registration of pharmaceuticals for human use) guidelines: <ul style="list-style-type: none"> • ICH E6 – Good Clinical Practice • ICH E9 – Statistical Principles for Clinical Trials
CI	confidence interval	IDMC	independent data monitoring committee
CONSORT	Consolidated Standards of Reporting Trials	IRB	institutional review board
CRD	Centre for Reviews and Dissemination	ISIS	International Study of Infarct Survival
CRO	contract research organisation	LREC	local research ethics committee
DAMOCLES	Data Monitoring Committees: Lessons, Ethics and Statistics	MCA	Medicines Control Agency
DCC	data coordinating centre	MRC	Medical Research Council
DIT	Defining Issues Test	MREC	multicentre research ethics committee
DMB	data monitoring board	NA	not applicable
DMC	data monitoring committee	NCI	National Cancer Institute
DSMB	Data and Safety Monitoring Board	NIH	National Institutes of Health
DSMC	Data and Safety Monitoring Committee	ns	not significant
EMA	European Agency for the Evaluation of Medicinal Products	OR	odds ratio
EORTC	European Organisation for Research and Treatment of Cancer	PI	principal investigator
EU	European Union	REC	research ethics committee
FDA	Food and Drug Administration	RCT	randomised controlled trial
GCP	good clinical practice	RR	relative risk
GDSS	group decision support system	SAE	serious adverse event
HMIC	Health Management Information Consortium	SEC	Securities and Exchange Commission
HR	hazard ratio	SSCI	Social Sciences Citation Index
		TEMC	treatment effects monitoring committee
		TSC	trial steering committee
		UCL	University College London

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.



Executive summary

Objectives

To address issues about data monitoring committees (DMCs) for randomised controlled trials (RCTs): why and when they are needed, their roles and responsibilities, their structure and organisation, what information is required and who owns it, and decision-making and reporting arrangements.

Methods

The study included systematic literature reviews of DMCs and small group processes in decision-making; sample surveys of: reports of RCTs, recently completed and ongoing RCTs and policies of major organisations involved in RCTs; case studies of four DMCs; and interviews with experienced DMC members. All focused on 23 pre-stated questions.

Results

Although still a minority, RCTs increasingly have DMCs. There is wide agreement that nearly all trials need some form of data monitoring. Criteria suggested for RCTs not needing an independent DMC are: where it is not possible for a DMC to make a contribution, where any observed differences would not prompt any protocol change (such as early stopping), and where there is no reason why a DMC's decisions would differ from those after internal monitoring.

A range of roles has been suggested for DMCs. Central is monitoring accumulating evidence related to benefit and toxicity; variation in emphasis has been reflected in the plethora of names. DMCs for trials performed for regulatory purposes should be aware of any special requirements and regulatory consequences.

Advantages were identified for both larger and smaller DMCs. There is general agreement that a DMC should be independent (no commercial, clinical or intellectual competing interests) and multidisciplinary (at least one statistician and one clinician). Consumer and ethicist membership is controversial. The chair is recognised as being particularly influential, and likely to be most effective if he or she is experienced, understands

both statistical and clinical issues, and is facilitating in style and impartial. There is no evidence available to judge suggested approaches to training.

The review suggested that costs should be covered, but other rewards must be so minimal as to not affect decision-making.

It is usual to have a minimum frequency of DMC meetings, with the committee able to meet at shorter notice. There is evidence that face-to-face meetings are preferable, especially for the first meeting or when difficult decisions are predicted; teleconferencing can be used when the discussion is expected to be straightforward or when there are practical difficulties convening the committee. It is common to have open sessions (where general issues, such as recruitment, are discussed with investigators) and a closed session (where confidential information, such as interim analyses, is discussed by the DMC supported by the analysis statistician).

The general view is that a report to a DMC should cover benefits and risks in a balanced way, summarised in an accessible style, avoiding excessive detail, and as current as possible. Disadvantages of blinded analyses seem to outweigh advantages. Information about comparable studies should be included, although interaction with the DMCs of similar ongoing trials is controversial.

A range of formal statistical approaches can be used. However, this is only one of a number of considerations that a DMC should take into account. DMCs usually reach decisions by consensus, but other approaches are sometimes used. The general, but not unanimous, view is that DMCs should be advisory rather than executive on the basis that it is the trial organisers who are ultimately responsible for the conduct of the trial.

Conclusions

The conclusions of the study are summarised below.

Some form of data monitoring should be considered for all RCTs, with reasons given where there is no DMC or when any member is not independent.

An early DMC meeting is helpful. Roles, responsibilities and planned operations can be agreed with investigators and sponsors/funders. A template for a DMC charter is suggested. Competing interests should be declared.

DMC size (commonly three to eight people) is chosen to optimise performance. Members are usually independent and drawn from appropriate backgrounds, and some, particularly the chair, are experienced. Hitherto, members have received little training.

A minimum frequency of meetings is usually agreed, with flexibility for more if needed. Meetings are best held face-to-face, if practicable. There are advantages of having both open and closed sessions. Often, the trial's statistician conducts the confidential analyses and attends the closed sessions (but not as a member).

The DMC should understand and agree the statistical approach (and guidelines) chosen, with both the DMC statistician and analysis statistician competent to apply the method.

A DMC's primary purpose is to ensure that continuing a trial according to its protocol is ethical, taking account of both individual and collective ethics. A broader remit in respect of wider ethical issues is controversial; arguably, these are primarily the responsibility of research ethics committees, trial steering committees and investigators.

The DMC should know the range of recommendations or decisions open to it in advance. A record should be kept describing the key issues discussed and the rationale for decisions taken.

Errors are likely to be reduced if a DMC makes a thorough review of the evidence and has a clear understanding of how it should function, there is active participation by all members, differences are resolved through discussion and there is systematic consideration of the various decision options.

DMCs should be encouraged to comment on draft final trial reports. These should include information about the data monitoring process and detail the DMC membership.

It is recommended that groups responsible for data monitoring be given the standard name 'Data Monitoring Committee' (DMC).

Recommendations for research

Areas that warrant further research include:

- widening DMC membership beyond clinicians, trialists and statisticians (e.g. to include consumer representatives or ethicists)
- initiatives to train DMC members
- methods of DMC decision-making, such as voting and formal decision-making tools
- 'open' data monitoring
- DMCs covering a portfolio of trials rather than single trials
- DMC size and membership, incorporating issues of group dynamics
- empirical study of the workings of DMCs and their decision-making
- which trials should or should not have a DMC.

Chapter I

Introduction and background

Introduction

In July 2002, a large, multicentre randomised controlled trial (RCT) in the USA was terminated on the recommendation of its data monitoring committee (DMC). The trial was testing hormone-replacement therapy in healthy, postmenopausal women. The DMC had judged that the evidence available to it was sufficiently convincing to be made available to current and future trial participants to help them to make decisions about their future use of hormone-replacement therapy. This decision by a small group of people was arguably the most important made in the context of research on this therapy. It would not only potentially have a dramatic impact on the future use of hormone-replacement therapy, but also define the evidence base on which future decisions would be made. The viability of a parallel UK Medical Research Council (MRC)-funded trial was immediately reviewed in the light of the findings in the US trial. While the MRC trial's DMC and steering committee both recommended that the UK trial should continue as planned – their view was that there was still significant uncertainty about many potential risks and benefits of this therapy and neither committee was convinced that the results of the the US trial were sufficient to guide its future use – the MRC eventually decided that its trial should stop too. By that stage millions of pounds had been invested in establishing the UK trial. Closure at this stage, prompted by a decision taken by a DMC of another trial in another country, would mean little scientific payback from this investment.

This example illustrates the heavy responsibility carried by a trial's DMC, the difficulty of the decisions that it sometimes has to make, and the profound and wide-ranging effects such decisions may have. The Data Monitoring Committees: Lessons, Ethics and Statistics (DAMOCLES) project described in this monograph aimed to examine the processes of monitoring accumulating trial data, and to identify ways to maximise the likelihood that DMCs make the 'right' decisions. The project took a broad perspective concentrating on behavioural and organisational aspects of DMCs and procedural issues of interim analyses. The work was commissioned by the NHS

Health Technology Assessment (HTA) programme and was performed by a collaborative group, the majority of whose members had significant experience of DMCs. The project focused on RCTs and did not cover Phase I and Phase II trials, or non-randomised trials or epidemiological studies.

Background

The RCT is now widely accepted as the principal research methodology for healthcare evaluation because it minimises the chances of obtaining a wrong answer due to bias. Random allocation of participants to one of the forms of care being compared avoids selection bias and attention can be given to other sources of potential bias because all data collection is prospective.

As a general rule, a trial's sample size is prespecified before recruitment starts. This is largely dictated by clinical and statistical considerations. While the calculation is based on a 'primary' measure of outcome, the sizes of effect that can be identified in relation to other measures such as possible hazards of the treatments are also often considered in relation to the sample size selected.

The sample size chosen can be viewed as a balance between two considerations. The first is the interests of trial participants and potential future participants, and the second the interests of society, particularly in respect of people who may benefit from (or be harmed by) the treatment in the future. The interests of participants should be best served if recruitment is closed as soon as a clear answer is available (so that they and/or future patients then get the best treatment). The interests of society should be best met if recruitment continues until there is a clear answer (such that the results are sufficiently conclusive to lead to changes in the clinical management of future patients). Often these coincide, but sometimes there may be a tension between the two. Although early stopping may be seen to confer benefits for those allocated the apparently poorer treatment, the results may be incorrect owing to random highs and lows with small sample sizes and be less persuasive than they would be after continuing the trial. They then may

not be sufficiently convincing to change standard practice (or if the intervention is unlicensed, to justify a licence) and hence the wider benefit to society is reduced. The deliberations of DMCs thus have a fundamental ethical dimension, which has been discussed in detail elsewhere.¹

These considerations have led to widespread acceptance of the need to monitor trial data as they accumulate to check that there is no clear reason to change a trial's protocol. Changes in a protocol could include terminating recruitment early for some (e.g. a subgroup most likely to benefit) or all patients, or extending recruitment to secure a larger sample size. During long-term follow-up after recruitment has been completed, a decision may be taken based on monitoring accumulating data to report results earlier than planned in the protocol.

The ways in which accumulating data are monitored vary, however, and have changed over time. Doll² described how arrangements for monitoring interim data developed in the UK as the methodology of RCTs evolved. Early RCTs were small and led by single investigators. Because of their small sizes, they rarely showed differences at completion and so early stopping was not seen as an issue. As collaborative groups emerged, more formal organisational structures developed. The trials were run by committees, which included a chairperson, secretary and statistician. Although there was no formal DMC, the statistician and secretary "kept an eye on the results and told the chairman if they thought that there was any reason for stopping the trial". Doll² dates the formal independent DMC from the late 1970s and early 1980s, coinciding with the start of the era of large trials. These were exemplified by the series of ISIS (International Study of Infarct Survival) trials of interventions^{3,4} to reduce the risk of death following myocardial infarction, which were coordinated from Oxford and for which Doll was the chairman of the DMC. Because of their larger sizes, the possibility of interim data analysis providing the basis for early stopping was greatly increased. The choice of independent members of the DMC reflected concern about investigators being responsible for such decisions, particularly if made on their own, because of the potential for conflicts of interest. Investigators may, for example, be particularly keen to see a very clear result, which may delay a decision to stop early. Alternatively, knowledge of trends in accumulating data may undermine their relationship with other participating clinicians or jeopardise their ability to recruit patients under their own care.

Following the example of the ISIS trials,^{3,4} independent DMCs became increasingly common in the UK, although the rate of adoption varied between specialities. Reflecting the change in attitude to data monitoring that occurred in the 1980s, the UK MRC, in 1998, made the establishment of an independent DMC mandatory for all its trials. This was in parallel with the adoption of the International Conference on Harmonisation (ICH) Good Clinical Practice guidelines of 1996, which recommended the establishment of DMCs in randomised trials.

In the USA, the development of current policies and practices for DMCs has been linked to a 1967 task force report for the National Heart Institute. This is commonly called the Greenberg report⁵ after the chairman of the task force. This recommended an external and independent 'Policy Advisory Board', whose role was to provide guidance to the Institute on the conduct and progress of a trial. The report outlined a mechanism for interim analysis and data monitoring of accumulating data. Over time, these specific functions were taken on by DMCs, and these are now standard National Institutes of Health (NIH) policy. As in the UK, the rate of adoption of data monitoring varied between speciality types. DMCs were also a relatively late development in pharmaceutical industry trials.

Interim trial data have only rarely been made accessible to current or potential trial participants, on the basis that trends in accumulating data may lead current participants to withdraw from a trial and dissuade others from joining. The standard policy used in the large majority of trials is to keep accumulating data confidential to the DMC and the trial statistician who prepares reports, although this practice has been questioned.¹ This is discussed in more detail in Chapter 2 (Question 8).

The principal role of DMCs, as their name implies, is to monitor data and alert the organisers of the trial if they think the pattern of data – on benefits or hazards, or both – is sufficiently persuasive to warrant either closing recruitment to a trial or changing the protocol, such as terminating recruitment in one or more subgroups of trial participants. This is the aspect of data monitoring that has received most attention and there is a considerable literature on statistical 'stopping rules'. Rather than review this, as others have already done, the present study group has chosen to summarise the broad statistical principles and this overview is presented in Appendix 1 of this report.

Although statistical issues are central to the functions of DMCs, statistical criteria for stopping are now accepted as providing guidelines rather than rules that should be considered alongside other information, which demand an element of judgement from a DMC. These include external evidence from other trials and an assessment of the likelihood that the interim results would persuade clinicians to change practice. In addition, some DMCs are taking on a wider range of roles and responsibilities, such as those related to ensuring ethical standards and quality assurance in the conduct of a trial. Practices in these and other respects vary widely, and there is no standard approach. Such broader issues in DMC decision-making and the factors that may influence the way a DMC performs its functions are the focus of this report.

The ways in which the range of issues was addressed were organised around 23 questions, and these are listed in *Box 1*. These were developed by the DAMOCLES group at the start of the project building on the original proposal to the HTA programme. The questions were in four sections related to: (1) the roles of DMCs; (2) their structure

and organisation; (3) what information should be available to DMCs; and (4) decision-making and reporting in DMCs. The project consisted of discrete components, each performed by a subgroup from within the collaboration. Chapter 2 describes a systematic review of published literature on DMCs. Chapter 3 is a systematic analysis of reviews of small group processes relevant to DMCs. Chapter 4 describes a cross-sectional survey of the use of DMCs and of interim analyses based on a sample of recent reports of trials. Chapter 5 presents the results of surveys of current DMC policies of key organisations involved in trials, and of DMC practices in ongoing and completed trials. Chapter 6 describes general interviews with experienced DMC members, and case studies of trials selected because DMC decision-making was not straightforward. In Chapter 7 the project is discussed as a whole. Chapter 8 draws together conclusions, finishing with recommendations for future DMCs and related research. The report also includes a template for a DMC 'charter', the purpose of which is to provide a structure for detailing in advance the operation and procedures of a newly established DMC.

BOX 1 Questions addressed in this report

Role of a DMC

1. Which trials need an independent DMC? (And when should there *not* be a DMC?)
2. Who should decide the details of how a DMC operates?
3. What should the DMC's terms of reference cover?
4. Does the DMC have a role before the trial recruitment phase?
 - Should the DMC have input into the protocol?
 - Should the DMC meet before the start of the trial?
5. How should regulatory issues impact on the DMC?

Structure and organisation

6. What should the membership of a DMC be?
 - What size should a DMC be?
 - How should the members be chosen?
 - What range of expertise is needed?
 - Should there be a chair? And a vice-chair? If so, how should they be chosen?
 - What should the responsibilities of the chair and DMC statistician be?
 - What should the responsibilities of the trial statistician be?
 - Should DMCs include consumer/user representatives?
7. How is independence to be maintained?
 - What position should the DMC have with respect to sponsor, trialist and participant?
 - Should payment go to members as individuals or to their employers?
 - Should conflict of interest be explicitly addressed?
 - Should DMC members be paid, and by whom?
8. Should the DMC deliberations be open or closed (confidential or secret as opposed to publicly available)?
 - Who outside the committee should see the interim analysis and how is this changed by whether the analyses were blinded or unblinded?
 - Who should be present during discussions?
 - Who outside the DMC should see, or be informed about, the decisions that are reached?
 - Should the committee destroy their papers after the meeting?

continued

BOX I Questions addressed in this report (cont'd)

9. What are the optimal practical arrangements for interim analysis and data monitoring?

- Frequency of meetings
- Timing of meetings relative to the trial
- Who chooses the dates of the meetings?
- Means of communication (e.g. face-to-face, teleconference)
- Who can suggest unplanned analyses?

10. What sort of training or preparation should DMC members have?

- Who should provide it?
- How much experience should they have?

Information available to the DMC

11. What material should be available to a DMC?

- Who produces it: trial statistician/DMC statistician/principal investigator/other?
- What should be produced (e.g. primary and secondary outcomes, by centre, blinded, safety, efficacy, completeness, compliance)?
- Who sees the interim results?
- Should information be available before the meeting or only during the meeting?
- Should external evidence be included and how (e.g. from other trials/systematic reviews)? Who should be responsible for identifying and circulating this?
- Are there specific issues related to type of intervention (e.g. surgery)?
- Are there specific issues related to type of outcome (e.g. survival data, surrogate outcomes)?
- Should there be interaction with other DMCs?
- Should trial investigators be available to the DMC?

12. Who should own the interim data and analyses?

- Who has the right to share them with people outside the DMC?
- Should interim data be released externally (e.g. for use in a systematic review)?

13. Should non-comparative analyses (which are administrative and not separated by treatment arm) be carried out?

Decision-making and reporting in the DMC

14. Is the function of the DMC advisory (to make recommendations) or executive (to make decisions)?

15. What decisions and recommendations should be open to the DMC?

- Early stopping due, for example, to positive active finding, positive control finding, safety on secondary outcome, futility, slow recruitment, external evidence?
- Stopping in subgroups?
- Extending recruitment?
- Stopping single arm?
- Sanctioning and/or proposing protocol changes?

16. How should the decisions or recommendations be reached within the DMC?

- What methods and criteria should be adopted for guiding deliberations?
- What is the process of decision-making?
- What factors may impact on that process?
- Is there a role for formal methods of achieving consensus?
- What is the role of consumer members?
- What should be the role of the chair?

17. What should be the role of formal statistical methods in DMCs?

- Stopping rule versus guidelines?

18. Should specific trial designs influence the proceedings?

- e.g. cluster trials, equivalence trials, multi-arm trials?

19. How should ethical issues be handled in DMCs?

- Should ethical issues be made explicit?
- Who should raise ethical issues?
- How should these issues be handled?
- Should different weights be given to different end-points (e.g. safety, efficacy)?

20. What should DMCs do with their decisions or recommendations?

- Who should the DMC report to?
- Should the DMC be advisory or executive?
- What form should the report take?
- Are minutes of the meetings or notes of decisions made? If so, by whom and how detailed?

21. What should be done in 'difficult' situations?

- e.g. unforeseen circumstances?
- Under external pressure?

continued

BOX 1 Questions addressed in this report (cont'd)

22. Should some DMC decisions be considered to be 'errors'?
 - On what grounds?
 - If errors can exist, how can they be identified?
 - Can they be predicted or prevented?
 - Were decisions overruled?
 - Liability?

23. What should the DMC's role be concerning publications?
 - What information about the DMC should be included in published trial reports?
 - Should the DMC approve publications, especially with respect to reporting of any DMC recommendation regarding termination of a trial?

Chapter 2

Systematic review of published literature on data monitoring committees

Background

Although DMCs are becoming increasingly used within RCTs, it is clear that their composition, practice and remit vary between countries, disease areas and work environments. The purpose of this part of the project was to summarise the information relating to DMCs on practices and beliefs. The aim was to be systematic but not comprehensive or exhaustive: relatively few people had written on this topic and many of them had presented their ideas in more than one paper. The review was structured to address the series of guiding questions (*Box 1*) and this literature review was structured to identify published material relating to each of these questions.

Identification: methods

Information was sought from several sources: electronic bibliographic databases, reference lists of relevant articles, handsearching of selected books, personal contacts with experts in the field, Internet searching and library catalogues.

Electronic bibliographic databases

The primary method for the identification of papers was searching bibliographic databases. In the first instance, a subgroup responsible for this part of the project agreed a number of potential search terms (e.g. that may be appropriate MEDLINE keywords). Each of these terms was then iteratively tested in electronic databases using the first 20–50 abstracts that were identified to evaluate their potential relevance. Terms that generated potentially relevant articles at a rate of at least three per 20 articles from each test set were retained. The search strategies that evolved from these are shown in Appendices 2 and 3. No language or other restrictions were applied.

Titles, abstracts and keywords were searched in the following databases:

- MEDLINE
- EMBASE
- CINAHL
- HealthSTAR
- Cochrane Library.

The resulting references, including the abstract where possible, were stored in a Reference Manager database, Reference Manager 9.5N (ISI ResearchSoft, Carlsbad, CA, USA). Automated searching for duplicates was performed and any duplicate articles were removed. After the removal of further duplicates by handsearching, the remaining abstracts were then assessed. All the available details of each identified article were read separately by pairs of researchers from the group of five, including one researcher who reviewed all of them. Each article was scored by consensus into one of the following groups:

- 0: not relevant to the project
- 1: paper discussing DMCs
- 2: case study with a DMC mentioned in the abstract
- 3: case study with no DMC mentioned in the abstract
- 4: statistical or technical paper.

The resulting data were stored in an MS Access 2000 (version 9.0) database. Primarily, the researchers were interested in group 1 articles as these were to be considered for the systematic review that is described in this chapter. However, it was anticipated that the search strategy used would also identify articles that would describe examples of DMCs in practice, or situations where decisions were made on interim analyses. Therefore, articles were assigned to groups 2 and 3 if they could be considered for inclusion as short illustrative case studies (ten of which appear as boxed case studies throughout this chapter); and articles assigned to group 4 were to be considered for inclusion in the non-systematic review of statistical methods applicable to DMCs (see Appendix 1).

Articles that were assigned to group 2, 3 or 4 were also given subjective interest ratings ranging from 1 (not interesting) to 5 (very interesting). In the case of uncertainty during the assessment phase, classification into the five groups and the allocation of interest, ratings erred on the side of inclusion.

All articles classed as group 1 plus those in groups 2, 3 and 4 with high interest ratings (4 or 5)

passed to a second stage of review. (Each of these papers is referenced in the reference section of this report.)

- Group 1: at the second review stage, the subgroup responsible for this review reached a consensus about which of the articles in group 1 would be most useful. These were ranked into 'To acquire', 'To consider if time permits' and 'Not to acquire'. There was a necessary element of subjectivity in the selection process.
- Groups 2 and 3: the potential case studies in groups 2 and 3 that were regarded as 'interesting' were also ranked into 'To acquire', 'Consider if needs be or time permits', 'Unlikely to consider' and 'Discard' by consensus. The 'To acquire' articles were collected, and those considered as interesting and highlighting a pertinent issue are presented throughout this chapter in boxes.
- Group 4: those articles classed into group 4 and rated 'interesting' were later considered in the context of the summary of statistical methods associated with DMCs and interim analyses (Appendix 1).

Reference lists of relevant articles

Lists of references from included articles were searched and those that appeared relevant from the text of the included article and had not already been assessed were examined.

Handsearching

The *Encyclopedia of Biostatistics* was handsearched.^{6,7} Additional handsearches were performed in books pertaining to RCTs in the personal possession of members of the DAMOCLES team or in the MRC Clinical Trials Unit. Only books or book chapters that were authored by people whose views had not already been included through other means were included. Although this method was not exhaustive, it was presumed that the majority of the major books covering data monitoring in trials were handsearched.

Library catalogues

Owing to time and resource constraints only the University College London (UCL) Cruciform library was searched for relevant books and book chapters.

Personal contacts and other experts in the field

The majority of the relevant literature was expected to be written in the English language. However, through personal contacts of the group, the possibility of appropriate additional major

foreign language articles on this topic was explored, but not in a systematic fashion.

Internet searching

General Internet searching was considered but not performed because of time and resource constraints. Only articles, books and book chapters that would be classed as containing group 1 material were sought using the five methods described in the above subsections.

Identification: results

The searching of electronic databases was undertaken in June 2001. It identified 4007 articles after the automated removal of duplicates. A total of 483 further duplicates were removed by hand. The remaining 3524 articles were classified and rated in the first review stage. *Table 1* shows the groups and interest ratings of these articles. With regard to group 1 articles, the group reached a consensus to include 11 articles that had initially been categorised as a grade 1 by one in the pair of reviewers and not relevant by the other member of the pair. A total of 301 articles passed to the next stage of review (those shaded in *Table 1*).

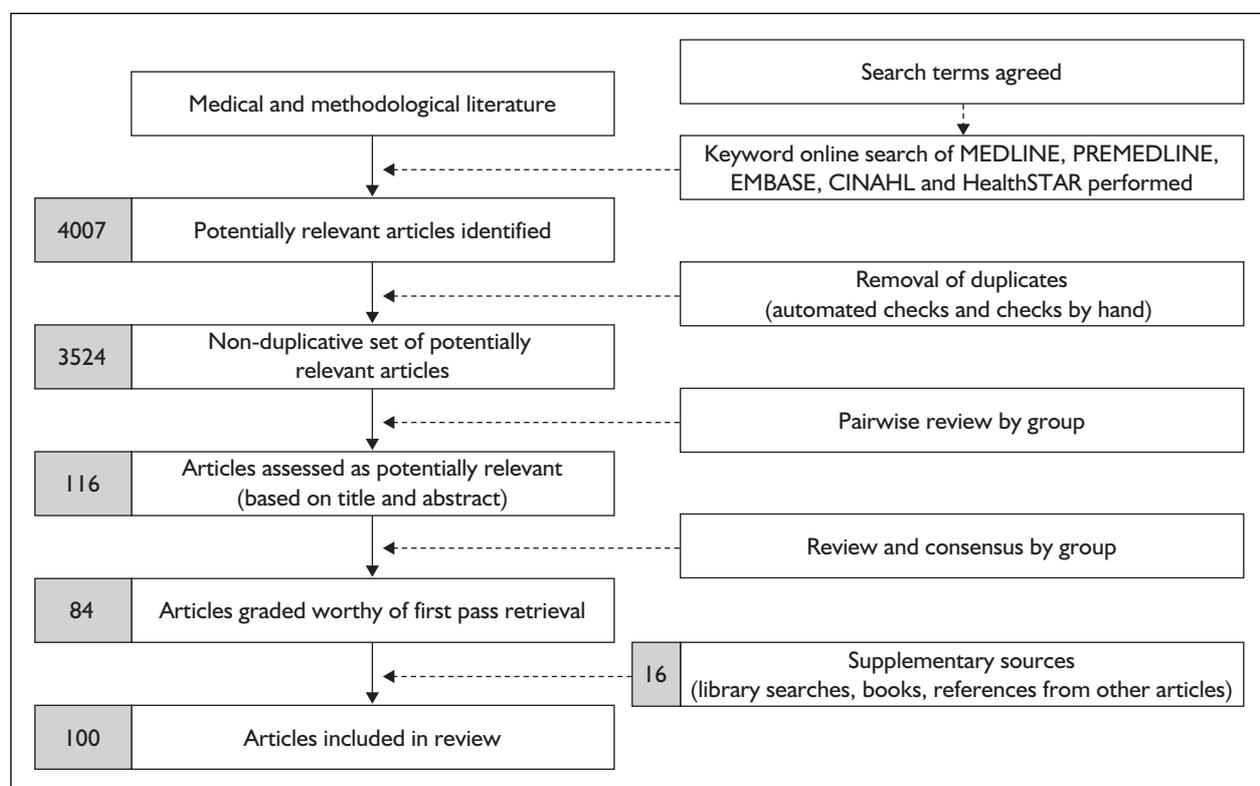
- Group 1: of the 116 group 1 articles, the researchers reached a consensus on 84 articles that were allocated to the 'To acquire' category. Such was the amount of data generated from these articles that the 'To consider if time permits' articles were not revisited.
- Groups 2 and 3: judgement was exercised by two subgroup members. Articles from groups 2 and 3 were chosen for further consideration depending on the publication journal, the consensus on interest level by the group and whether other, more informative articles illustrating the same issues had already been chosen. Ultimately, ten short summaries from these published case studies are presented in boxes throughout this chapter.
- Group 4: articles classed as group 4 were considered when writing the review of statistical aspects pertaining to data monitoring in trials (Appendix 1).

The other methods of searching (described above) yielded few extra data. The reference lists from other abstracts provided some extra book chapters; two sections were used from the *Encyclopedia of Biostatistics*,^{6,7} no additional major foreign language papers were identified, and handsearching for book chapters led to the inclusion of sections of 16 chapters classified as group 1.

TABLE 1 Grading and interest scores of articles identified by electronic database searching

Grade	Interest level							Total
	NA	1	2	3	4	5	Uncertain	
0: Irrelevant	2684	0	0	0	0	0	0	2684
1: Relevant to DMCs	116	0	0	0	0	0	0	116
2: Case study (+ DMC in abstract)	0	15	28	29	51	7	0	130
3: Case study (- DMC in abstract)	0	59	80	101	59	3	0	302
4: Technical	0	53	94	69	62	3	3	284
99: Uncertain	8	0	0	0	0	0	0	8
Total	2808	127	202	199	172	13	3	3524

Shaded cells indicate those articles that passed to the next round ($n = 301$).
NA, not applicable.

**FIGURE 1** Flowchart of the identification procedure

Thus, a total of 100 publications was finally accepted for inclusion in the systematic review of published literature pertaining to DMCs, and these are considered in the following section.

Figure 1 summarises the identification procedure, and Appendix 4 is a list of the 100 references.

It should be noted that the majority of literature is North American and pertains primarily to RCTs of drug treatments. This is counterbalanced, somewhat, in the surveys of current practice (see Chapter 5).

Extraction: methods

Full text copies of all the eligible articles (taking articles, now, to include book chapters) were obtained. In each case, electronic versions were obtained (1) by downloading online text from appropriate websites, (2) by photocopying and scanning paper copies and then producing electronic versions using optical character recognition software (ABBYY FineReader 5.0 Pro), (3) from typed electronic versions obtained from translators of foreign papers, or (4) by requesting the journal's current editor to e-mail an electronic copy directly.

Each article was saved as a plain text file, with any picture files saved separately, and uploaded into a qualitative analysis software package (ATLAS.ti 4.2). Within this software, a series of codes was defined, each reflecting one of the questions or subquestions listed in *Box 1*. Each article was read by a single researcher, and each section of relevant text had the appropriate code(s) applied to it.

Subsequently, files were produced from ATLAS.ti that contained the relevant quotes that had been linked to each code. Each member of the subgroup used the data from files allotted to them to draft a summary of the published data relating to each of the questions and subquestions listed in *Box 1*. These summaries were considered by the group and the consensus versions follow.

Drawing conclusions

This review describes the published literature on DMCs and as a result may be biased towards what may be considered ‘traditional opinion’. Systematic reviews of opinions are difficult to summarise. Simple vote counting is inappropriate, and there is inevitable authorial subjectivity in identifying consensus opinion and important dissenters. (An attempt was made to identify minority points by presenting them in italics.) Cited references are generally indicative; not every source is cited for every summary of the literature.

Question 1: Which trials need an independent DMC?

It is broadly agreed by most commentators that the majority of trials should be monitored to some degree.^{8,9} DMCs are becoming increasingly common for RCTs. For example, Morse and colleagues⁸ noted that DMCs “have emerged as a means of assessing appropriateness of continuing clinical trials based on evolving trial data”. But do all trials need a DMC? *Box 2* summarises the suggestions presented in the published literature of which trials need a DMC, and *Box 3* summarises the suggestions for those that may not need a DMC.

The widely held opinions are well summarised by O’Neill:²³

“... any clinical trial evaluating a therapy with a mortality or irreversible morbidity endpoint should probably use externally independent [DMCs]. This would include mega-trials, trials with mortality endpoints, and trials of treatments for life-threatening diseases with no alternative therapies. Trials which are exploratory, early phase trials or [trials] which deal with chronic disease, palliative therapy, or non life-threatening diseases probably can be monitored by designated internal bodies who, although not independent from the sponsor, are insulated from management in decision making and follow guidelines as to who has access to their unblinded data.”

BOX 2 Suggestions from the literature for trials that may need a DMC

- Trials likely to have a profound effect on clinical practice; pivotal trials^{10–12}
- “... Trials designed to enable definitive assessments of therapeutic interventions”⁸
- High-profile trials⁸
- Trials with vital status as an outcome measure, e.g. “Life-threatening diseases or cause serious morbidity”^{8,13}
- When a clinical trial is large enough to detect important effects on mortality and irreversible morbidity rates¹³
- Trials where “Serious safety concerns exist”^{8,14}
- When the risk of a treatment (whether experimental or control) is unknown^{13,15}
- When a therapy has a known risk of severe side-effects, special and targeted oversight is needed¹³
- All studies where outcome is not predictable or where outcome can imply a hazard to the patients should have safety committees¹⁶
- “When independent evaluation is necessary”¹¹
- Trials which have been contracted out¹⁴
- Long trial duration¹¹, e.g. longer than 1 year
- Trials in which therapy is masked¹⁷
- Trials in which the end-point is masked¹⁷
- “When the [DMC] meets other general analysis needs of the study (e.g. is responsible for developing analytic approaches for dealing with special analytic problems)”¹⁸
- “When treatment monitoring activities require frequent meetings and where each meeting requires a half day or more to carry out the necessary data reviews”¹⁸
- “When the trial is investigator-initiated and grant-supported”¹⁸
- Trials in vulnerable populations, e.g. where the patient cannot provide consent themselves or where the patient would not be able to refuse further treatment¹⁹

BOX 3 Suggestions from the literature for trials that may not need a DMC

- Short trial duration,¹¹ i.e. “When the time required for treatment monitoring is small relative to the time required to perform more general advisory and review functions”¹⁸
- Where events or patients would be accrued before the DMC could provide input, and especially “studies of short duration involving well-known interventions in non-life-threatening situations”²⁰
- “Small trial with minor hazards”: the trial investigators can be charged with the monitoring role²¹
- “Trials where the outcomes and side effects are trivial do not need to have a safety committee ...”¹⁶
- “... studies where the effects (negative or positive) occur some time in the future when the recruitment and follow-up of patients has been completed”¹⁶
- “Behavioral and administrative studies (although some oversight is required)”¹³
- “Trials aimed at demonstrating a biologic principle might be monitored in a less formal manner”¹³
- *Unblinded trials, e.g. “Some trials, such as those comparing surgery with best supportive care, cannot be blinded. The need for a [DMC] in such cases is less pronounced, as their function could be subsumed by the Steering Committee”²²*
- *Trials without vital status endpoints: “... trials not directed at survival or irreversible morbidity”¹¹*
- *When there is little or no need for advice or guidance concerning the analysis procedures used for assessing treatment effects*¹⁸
- *“When the trial is sponsor-initiated”¹⁸*
- *“When the sponsor and/or investigator desire a single combined committee”¹⁸*

Points in italics are minority opinions.

Therefore, there are a number of issues to consider regarding whether or not a clinical trial may require an independent DMC. The following points are proposed by Morse and colleagues.⁸

- How serious are the consequences of the disease under study?
- What are the potential risks associated with the treatment being evaluated?
- What is the total length of time planned for the trial?
- How high a profile does the trial have? (Will there be pressure for information to be released?)
- Is the trial intended to provide a definitive answer to the question regarding which treatment is superior?
- Do the study investigators or sponsors have potential conflicts of interest?
- Are the study investigators experienced in the conduct and monitoring of clinical trials?
- Will an independent [DMC] enhance the integrity or credibility of the trial?

One may argue like Meier in Yusuf¹¹ that *Boxes 2* and *3* describe characteristics of trials that need some form of monitoring, not trials that need a DMC per se: “What’s essential is that a trial be monitored, not necessarily that there be a special body called the data monitoring committee But all trials should have monitoring and it should be made explicit who is doing the monitoring It wouldn’t always necessarily be an independent free-standing data monitoring committee.” Indeed, Meinert¹¹ agrees, stating “I would not necessarily be arguing for a formal data

monitoring board for every trial but for a lot more data monitoring boards than we have ...”.

Indeed, it is impossible to tease apart the need for a DMC from the role that the DMC would be expected to play in the trial. The possible functions that a DMC may assume are addressed in question 3. Two of the main reasons for the presence of a DMC are to stop the trial early if needs be^{15,24} and to enhance the credibility of the trial.^{25,26} The possible recommendations available to DMCs are considered under question 15.

The support is there for monitoring to be undertaken and the use of a DMC to be considered for each trial. A previous HTA report²⁷ noted that “... It has been argued that it is not feasible for all trials to have a DMC ...”. The response to this is typified by Friedewalde, in O’Neill:²⁸ “It may not be necessary [to have a DMC] in each case, but the burden should be on the trial sponsor to say we don’t need a board for the following reasons. I personally wouldn’t accept reasons such as, ‘it was too expensive’, or ‘there aren’t enough people to serve on the committees’.”

Ellenberg and colleagues¹⁹ describe the potential use of “internal DMCs” that could “perform many of the functions” of an independent DMC. In settings where independent DMCs are not essential but where some form of structured monitoring would be desirable it is suggested that such a committee could “review (blinded) interim data and formulate recommendations to trial leadership to help ensure optimal decision-

TABLE 2 General models proposed in the literature for the independence of a DMC and the role of analysis statistician

Model	DMC members	Analysis statistician	Example
1 ^a	Independent	Independent	All DMC members and the analysis statistician are independent of the trial, i.e. the analysis statistician is neither the main trial statistician nor the DMC statistician, and attends any part of the meeting the DMC wishes
2 ^a	Independent	Trial statistician	The DMC members are independent of the trial. The trial statistician is responsible for producing the interim analyses and attends any part of the meeting the DMC wishes
3	Not all independent	Trial statistician	At least one of the DMC members is not independent including, e.g. the PI, but there may be some independent members. The trial statistician is responsible for producing the interim analyses and attends any part of the meeting the DMC wishes

Models 1 and 2 present an independent data monitoring committee (IDMC) whereas model 3 presents a non-IDMC which may be internal or open.

^a The DMC members attend all parts of the meeting. However, there may be other non-decision-making (and non-independent) attendees for open sessions of the meeting. These would include at least the analysis statistician, but also could include the sponsor and representatives of the investigators who do not attend closed sessions. The trial statistician is responsible for producing the interim analyses in model 2, but not in model 1.

making during the course of the trial”.¹⁹ The internal DMC should have similar multidisciplinary representation to independent DMCs.

Three main models of DMCs from the literature are summarised in *Table 2*. Model 1 is that favoured by the Food and Drug Administration (FDA). Model 2, in which all DMC members are independent and the analyses are performed by the trial statistician, is the most commonly cited as appropriate. It allows all parties to express their feelings about the trial and to bring relevant information, but retains independence from the sponsor while allowing the trial statistician to be involved. A vocal minority supports the third model on the grounds that “... objectivity should not be at the expense of competency”.²⁹

Can the DMC role be performed by an ethics committee?

Pickworth³⁰ noted that “Local research ethics committees have access to the original research protocol and are arguably in an ideal position to increase their monitoring function”, at least in single-centre trials. In the USA, institutional review boards (IRBs) often presume the right to review (at least some of) the interim data presented to DMCs (see question 19). Cairns and colleagues¹³ also considered this issue: “Each individual IRB monitors the conduct of its own institution in multi-centre trials.” No data are given on how this monitoring is performed. They continue: “The involvement of an IRB alone,

without a [DMC], may be sufficient in a trial that involves a single institution, especially when a mechanism is established for the significant involvement of a subcommittee or a particular individual. Most local IRBs, however, lack the expertise to monitor multicentre trials or lack sufficient time for the intensive work required in such cases.”

This is further confounded by practicalities in multicentre trials, as noted in the UK example: “... Though progress reports, changes to protocol and adverse events should be reported to both the MREC and LREC [multicentre and local research ethics committees], proactive monitoring could be an extremely costly and impractical process if performed by the MREC. For this reason it is expected that any proactive REC [research ethics committee] monitoring will be a local rather than a multicentre activity.”³⁰

Morse and colleagues⁸ differentiate more clearly between DMCs and local ethical committees: “Institutional review boards should not be forced to function as DMCs, and there should be no overlap of their functions.” While there seems to be some potential overlap in function regarding monitoring, each trial would be best served if the DMC alone (if one exists) were allowed to be the sole monitor of trial data.

In summary, the general consensus is that some trials definitely need monitoring and that a DMC

is the most appropriate committee to undertake this role. Such trials include large, pivotal trials, trials with vital status end-points, trials with long-term follow-up, trials where credibility can be enhanced by having independent review of accumulating data and trials where early stopping of the trial owing to benefit or harm is likely.

Question 2: Who should decide the details of how a DMC operates?

Several authors have suggested that it is valuable for the DMC to have a written document (standard operating procedures or a charter) outlining its mode of operation and perhaps also the responsibilities of different parties.³¹ Detailed suggestions have been made on the content of such a charter.^{31,32} Any variation in understanding of what the DMC will do can thus be identified and resolved at an early stage. (See also comments under questions 3 and 4 regarding a charter.) Although its initial drafting may be made by any of the parties, the document should be agreed by all parties before the trial starts or at least before the first interim analysis.³³ The content of such a charter could be incorporated in the protocol,¹⁶ but in general would be a separate document. Nonetheless, the wording of a charter is likely to leave unspecified certain aspects of the DMC actions, especially with respect to unforeseen circumstances.¹⁷ In addition, it is widely recognised that much judgement is needed in the DMC's deliberations, especially in more complex trials in which there are both intended and unintended effects, and there may be other considerations too (such as accumulating external data).

Despite the consensus about the desirability of a charter for the DMC, only a few authors have detailed what should go in such a charter.^{19,31,32,34} Further, the extent to which the DMC is constrained by such a charter was unclear. Thus, while it is widely noted that the plans for interim analysis and stopping guidelines would generally be incorporated in the trial protocol, there is no comment on the extent to which the DMC is bound by these. In addition, hardly any discussion was found in the literature on questions such as the following: can the DMC request interim analyses at additional or different times; can it request additional or alternative analyses; and can it choose to use different criteria as a basis for recommendations about stopping or continuing

recruitment? It is, however, implicit in the designation 'independent' that the DMC has some degree of self-determination.

In summary, the general view is that many of the details of how a DMC operates can beneficially be laid down in a document that is agreed by all parties: DMC, investigators and sponsors or funders. Nevertheless, it seems implicit that the DMC has some flexibility in how it actually carries out its roles. A suggested charter is presented in Chapter 7.

Question 3: What should the DMC's terms of reference cover?

Many commentators have addressed what DMCs do and/or should do. As the duties of a DMC "are not necessarily obvious",³⁵ it is surprising that until recently there have been very few comprehensive sources of guidance.^{19,36} There is no clear agreement on what the roles or responsibilities of DMCs are, although most authors state their views with little recognition of the lack of consensus.

Variation in the suggested functions of DMCs may partly stem from authors trying to give a brief summary of a rather complex situation. Thus, despite the variation between publications there is little direct disagreement. Rather, different commentators vary in the roles that they mention. Some heterogeneity of views may also reflect context-specific variation in how committees do and should operate, in relation to the nature of the funding, the size and duration of trial, type of outcome, disease, and so on. For example, the balance of concern for current and future patients is likely to depend on whether the disease being studied is rare or very common, whether the disease or condition is life-threatening or minor, whether the treatment may have serious adverse effects, and whether or not the treatment is already in common use.

The terms 'roles' and 'responsibilities' are widely used, but loosely and somewhat interchangeably. Here, 'roles' is used to indicate what DMCs do, and 'responsibilities' to describe the relations with those groups to which the DMC has some responsibility, either explicit or implied.

As a general rule, commentators agree that a DMC has a duty to keep confidential all information received about the trial (see question 8).

Roles

Many roles have been suggested for DMCs. It is generally agreed that the DMC's role is not limited to statistical monitoring of the accumulating data, although that is clearly the key activity.³⁷ A good brief summary is that the DMC is "... responsible for reviewing accruing data, monitoring performance of the trial, assuring safety of the participants in the trial, and assessing the efficacy of treatment".¹⁷

Table 3 lists the possible roles of a DMC, separated rather loosely into major and ancillary activities. Those labelled major could apply to almost all DMCs, while the ancillary roles may be relevant in

only a minority of cases. It is desirable that the DMC has an explicit set of operating procedures. These can be documented in the form of a charter (see question 2).

Major roles of the DMC

Before the start of the trial the DMC may review the protocol. This potentially important activity is discussed in the following section (see question 4).

Most of the main tasks of the DMC take place while the trial is running and stem from the interim analysis. This activity encompasses a large number of different aspects (Table 3a). Non-data-related issues include assessments of patient

TABLE 3 Roles suggested in the literature for DMCs

Timing in relation to recruitment	Role
<i>(a) Major roles</i>	
Before	Review and approval of trial protocol, including logistics (see question 4)
During	Interim review of trial progress including updated figures on recruitment, data quality, loss to follow-up, and primary, secondary and safety outcome data, so as to: <ul style="list-style-type: none"> • assess data quality, including completeness (and by so doing encourage collection of high-quality data) • monitor recruitment • monitor sample size assumptions • monitor trial conduct: organisation and implementation of trial protocol • monitor compliance with the protocol by participants and investigators • monitor evidence for treatment benefit, and thus decide when/whether the main trial question has been answered • monitor evidence for treatment harm (e.g. toxicity data) • ensure ethical conduct of the trial • decide whether to recommend changes to the protocol, recruitment procedures, planned sample size, data collection, etc. • decide whether to recommend that the trial continues to recruit participants or whether recruitment should be terminated either for everyone or for some treatment groups and/or some participant subgroups (see question 15) • advise PIs about ethical issues • suggest data analyses • advise on protocol modifications suggested by investigators or sponsors (e.g. to inclusion criteria, trial end-points or sample size) • monitor continuing appropriateness of patient information • assess the impact and relevance of external evidence
After	<ul style="list-style-type: none"> • Discuss final data with PIs/sponsors • Advise PIs and/or writing team about data interpretation • Ensure that trial results are published in an unbiased, correct and timely manner (see question 23)
<i>(b) Ancillary roles</i>	
During	<ul style="list-style-type: none"> • Consider suggested dropping of some centres from a multicentre trial³⁸ • Adjudicate on controversies, e.g. disagreements between/within PIs and steering committee⁹ • Evaluate and act on special requests from trial investigators or sponsors to provide limited access to some evolving trial information³⁹ • Determine whether or to whom interim results should be released^{40,41} • Make recommendations for dissemination of primary results⁴² • Review/approve auxiliary studies^{37,43}
PI, principal investigator.	

accrual and data quality (including completeness). Data-related issues will focus on the assessment of the accumulating information on the intended and unintended effects of the treatments. The possible recommendations (actions) available to DMCs are considered under question 15.

In addition, the DMC will need to consider whether any changes to the protocol may be indicated. They should also consider any external evidence that has become available (see question 11), including whether patient information sheets may need to be modified.

All these roles are important and it may not be sensible to try to identify a single specific main role. However, several authors have attempted to suggest what the primary role of a DMC is. These views vary considerably:

- to review interim analyses of outcome data^{9,27,40}
- to monitor the ongoing trial for safety and for early convincing evidence of a treatment benefit from the therapy under investigation⁴⁴
- to protect the trial subjects from exposure to an inadequate or a harmful investigational therapy¹²
- to ensure that risks to patients in the trial are reasonable in relation to anticipated benefit^{31,45,46}
- participant safety and trial integrity³⁵
- to protect patients ... included in the trial but also other patients with the disease in question.⁴⁷

This variability is reflected in the wide variety of names for DMCs, in which different aspects are stressed (see Chapter 4, *Table 16*). The common use of the term 'data' in the names for DMCs disguises the wide-ranging nature of their roles.

The role of the DMC at the end of the trial needs to be considered.⁴⁸ Whether or not a trial stops early, the DMC could usefully meet with the PIs (and sponsors) after the trial has stopped.³¹ Even though they will probably not have seen the final results the DMC may well be much more familiar with the nature of the data than the PIs (especially if the trial has stopped after an interim analysis). They can thus help with the interpretation of the results, especially in the case where rapid dissemination is planned. The specific question of DMC involvement in publication is discussed under question 23.

Ancillary roles of the DMC

In addition to the primary activities, some other activities of a DMC are relevant only in a minority

of instances (*Table 3b*). Several of these possibilities relate to resolving difficult situations that can arise.

What the DMC should not do

Activities generally considered to be outside the remit of the DMC include the specification of the statistical approach to data analysis, although they may advise on the analysis plan (see Chapter 5). The DMC does not have responsibility for assessing the effects of trial treatments on individual patients as it cannot ensure that it will identify adverse effects quickly.³²

Integrity of the trial

Amongst the specific roles, it has been noted that the existence of a DMC implicitly lends additional integrity and credibility to a clinical trial.⁴⁹ The DMC enables the PIs to remain free from knowledge of the interim data on the effects of treatment, thus allowing them to deal honestly with other investigators and trial participants, and to make judgements on revisions to the trial protocol or procedures that are not data driven.

Surveys of what DMCs do

The published surveys of what DMCs do are few, restricted to major grant funders, of small size (ten to 20), and not recent.^{37,43,50} (See Chapter 5 for surveys on DMC function undertaken as part of this project.)

Responsibilities

The groups to whom the DMC has responsibilities are listed in *Box 4*. While it is often pointed out that there is a need to balance the interests of trial participants and future patients when monitoring a trial, it is useful to distinguish further between patients already enrolled in the trial and those who would enter the trial if it continues to recruit. The responsibility to the sponsor is through helping to ensure that the trial is carried out to a high standard.

BOX 4 Groups to whom DMCs have responsibilities

- Patients in the trial
- Future patients to be enrolled in the trial
- Future patients in target population treated after the trial
- Society in general
- Principal investigators
- Steering committee
- Sponsor

Question 4: Does the DMC have a role before the trial recruitment phase?

Although much has been written about the roles and responsibilities of DMCs (see question 3), few authors have considered the specific question of whether the DMC has a role before the trial starts (22 of 100 publications). Specific questions to consider are:

- Should the DMC have input into the protocol?
- Should the DMC meet before the start of the trial?

The main reasons for the DMC to meet either before the trial starts or very early after recruitment (and before many data are available) are to review the trial protocol and procedures including stopping rules and analysis plan, to develop terms of reference and operating procedures, and to get to know each other.^{45,51} While most of these activities can be undertaken early after the start of the trial, there are strong grounds for suggesting that the first meeting should take place before the trial starts. Not appointing the DMC until after the start has been described as “poor policy”.¹³

Protocol review

A meeting before the start of the trial gives the DMC the opportunity to suggest amendments to the protocol. Presumably most people would not accept an invitation to join a DMC without seeing and broadly accepting the protocol (although this aspect was not mentioned by anyone), but a detailed discussion can be valuable. As Whitehead²² explained: “A [DMC] should be appointed before the trial begins. This allows them to meet, in person, with representatives of the Steering Committee and the sponsor to learn about the trial and to review the protocol while there remains a chance to make changes. In reviewing the protocol, the [DMC] needs to be comfortable about the purpose, methodology and ethical aspects of the trial, but should accept that responsibility for detail rests with the Steering Committee.” Such a meeting gives the DMC “greater insight into the difficult design issues [the] investigators [are] confronting”.⁴⁹ This meeting could be difficult other than face to face (see question 9 on practical arrangements).

Review of the protocol can include a variety of aspects: the objectives, all aspects of the trial design, including the inclusion criteria and outcome measures; philosophy and mechanisms

for monitoring the accruing data, including decision-making criteria and safety monitoring procedures; whether the anticipated rate of recruitment to the trial is adequate;⁴⁵ patient consent procedures; and quality assurance issues. Although it is “not unusual for the data monitoring committee to review and approve the protocol”¹¹ there is the real possibility of some protocol modifications as a result of the meeting. Such changes would rarely be major. For example, the DMC may discuss with the investigators the appropriate choice of outcome measure, say, between clinical end-points and surrogate markers.⁴⁹ For an equivalence trial the DMC would wish to be satisfied that the “standard treatment was performed as expected from previous experience”.⁵²

Several authors suggested that DMC input into the protocol was a good thing, but two publications^{35,53} suggested that there was a lack of consensus on this issue; for example, George reported that in the USA most cancer cooperative groups agree that DMCs do not review or approve the trial design.⁴³

Charter and standard operating procedures

It is desirable that the DMC has terms of reference and an explicit set of operating procedures, perhaps in the form of a charter⁵⁴ (see also questions 2 and 3). Although a standard format may not suit all trials⁵⁵ there is a large degree of common ground across all trials. Unless these issues have already been addressed, the first meeting of the DMC (ideally, before the trial starts) is the time to agree terms of reference and to discuss whether there is to be a charter and if so what it should say. “Topics to be addressed would normally include a schedule and format for meetings, format for presentation of data, specification of who will have access to interim data and who may attend all or part of DMC meetings, procedures for assessing conflict of interest of potential DMC members, and the method and timing of providing interim reports to the DMC.”³⁶

None of the articles mentioned the issue of specification of the format of data at subsequent meetings (see question 11). Other issues addressed later in this chapter could well be included in a charter, such as voting procedure (see question 16). Such a charter should be agreed by the DMC and PIs/steering group. (A charter developed on the basis of this project is provided in Chapter 7.)

Other issues

One paper reported the discussion of possible scenarios prior to any data being available. "A variety of hypothetical scenarios depicting data sets which lead to continuation or stopping were presented to the [DMC] prior to the first safety inspection of this trial. These illustrated in less mathematical terms under what conditions the trial would recommend termination."⁵⁶ Such dress rehearsals "increase the likelihood of success",⁴⁹ that is, satisfactory decision-making.

Another issue that can be addressed at this time is what specific information will be provided to the DMC at its subsequent meetings (see question 11 for data to be presented to the DMC).

Question 5: How should regulatory issues impact on the DMC?

Trials of interventions that may provide the basis for submissions to regulatory bodies are subject to additional constraints: general guidance applicable to all regulatory bodies has been issued by the ICH,^{57,58} although much of it has also been adopted by public sponsors such as the MRC⁵⁹ (see Chapter 5). Additional draft guidance has been issued by the FDA³⁶ and is discussed below.

Such trials may be sponsored directly by industry or by public bodies with additional industry funding, but in both circumstances the FDA considers it essential that "clinical trials of new drugs are designed and carried out in a manner that will insure the integrity and validity of the study inferences".³⁸ O'Neill²³ and others have argued that "it is important for those responsible for trial monitoring and termination to be aware of the regulatory consequences of their decisions because of FDA's view of data monitoring".

There are no current special requirements of DMCs in the context of a regulatory trial (except in situations where informed consent is impossible³⁶). The primary differences between regulatory and non-regulatory trial monitoring concern justification for a DMC, reporting the DMC's deliberations, the risk of releasing interim data to external bodies, and taking into account the regulatory consequences of early termination for a positive result. When it comes to making a decision whether or not to stop a trial, the draft guidelines state that the "FDA will rarely, if ever, tell a sponsor which decision to make. In certain settings, however, consultation with the FDA

before making a decision may provide the sponsor with important information regarding the regulatory and scientific implications of decisions and may lead to better decisions".³⁶

Justification for DMCs

Herson⁶⁰ predicted in 1993 that DMCs "will be employed even more frequently by pharmaceutical firms as a source of independent review to increase the credibility of clinical trials that must be eventually presented to the FDA". ICH Efficacy topic 9 (ICH E9: statistical principles for clinical trials)⁵⁷ recommends a DMC "for many clinical trials of investigational products, especially those that have major public health significance", and states that there should be written operating procedures and records of meetings (see question 20), and the DMC should be independent of the sponsor (see question 7). The FDA draft guidance points out that an independent DMC "promotes objectivity that benefits not only the participants and the trial but the sponsor as well, in that the credibility of the trial's conclusions is enhanced".³⁶ In particular, remaining blinded to interim results "protects the sponsor (and thus the trial) from pressure towards premature disclosure of results due to SEC [the Securities and Exchange Commission] requirements, fiduciary responsibility, or other business considerations"³⁶ ('SEC' refers to obligation to release information to investment agencies).

Reporting to a regulatory body

For trials of new drugs in the USA, it is standard that the FDA will have prior review of protocols with details of proposed data monitoring procedures.³⁶ Similarly, in Europe, the Medicines Control Agency (MCA) and the European Agency for the Evaluation of Medicinal Products (EMA) expect to see, in advance, the protocols of any trials that include unlicensed drugs. A forthcoming European Union (EU) Directive⁶¹ plans to widen this to all trials involving any drug.

Both ICH E9⁵⁷ and the draft FDA guidance document³⁶ state that all DMC meeting records, including confidential reports to the DMC, should be submitted to the regulatory body. This will include any recommendations based on safety considerations.

Serious adverse events or reactions (SAEs) must be reported to the relevant regulatory body. This could be via the DMC, but is said to be "an onerous burden".³² Data presented to the regulatory body will generally be blinded; therefore, it is not able to attribute this to

treatment and the DMC must make the comparison anyway.¹⁹ Packer and colleagues³² report a compromise whereby the sponsor supplies blinded reports to the FDA, which can then contact the DMC directly if concern arises.

Regulatory bodies do not usually want access to interim data unless the data are known by the sponsor at time of the interim report.¹⁹ “The FDA should not and does not want to be a routine observer nor a voting member in a [DMC].”³⁸ However, AIDS trials in the 1990s brought about the concept of “expedited development” of therapies for life-threatening diseases, and in this situation the draft guidance states that the FDA “may need on occasion to interact with a DMC of an ongoing trial”,³⁶ with the possibility of sharing interim data. Ellenberg and colleagues¹⁹ point out that this may suggest a potential conflict with common DMC policies, and Walters⁶² argues strongly against any FDA access to interim data except in a “bona fide national health emergency”. Important protocol changes recommended by the DMC need to be notified to the FDA.³⁶

Risks of exposure of interim data

Trials with potential regulatory impact provoke particular attention to keeping the sponsor from knowledge of the interim results. The following issues arise.

- Unblinding to the sponsor could provoke further unblinding, which can influence decisions and can introduce biases.³⁶ ICH E9⁵⁷ says the role of any sponsor representation on the DMC should be clearly defined and control of information addressed.
- Sponsor access to interim data for planning purposes has been explicitly considered and strongly discouraged, but if necessary could be carried out under tightly controlled circumstances³⁶, for example, if production would need to be scaled up to make a drug available if a trials stops early (see question 13).
- The FDA should be notified if the sponsor is going to have access to interim data.³⁸
- An independent statistician is recommended to act as the analysis statistician and prepare reports to the DMC.³⁶

Special issues that may arise for a DMC when stopping early for benefit

The DMC should be aware of regulatory implications when stopping early for benefit.⁴¹ If regulatory requirements are not met (e.g. there are insufficient cases to assess safety or the final analysis does not fully confirm the interim

findings), an application for regulatory approval could fail. This could make any subsequent trial difficult, jeopardise treatment development and penalise the sponsor.

Question 6: What should the membership of a DMC be?

What size should a DMC be?

There is little agreement on the size of a DMC. Suggestions range from three⁵¹ to more than 20,¹⁸ although the former just focuses on decision-making members, while the latter presumably includes both decision-making and non-decision-making attendees. However, it is continually emphasised in the published literature that a large DMC can be difficult from a number of perspectives. It may be difficult to find sufficient individuals suitable and willing to serve (as those best suited are likely to be in demand); it can be difficult to arrange dates for meetings; it can be difficult to arrange meetings at short notice, which may be needed from time to time, which are suitable to all members; and it is more difficult to ensure that leaks are prevented.

One helpful practical suggestion is that, in anticipating the possible need to resolve difficult issues by voting, it may be prudent to have an odd number of members.⁴⁵

What model is best for a DMC? How should the members be chosen and what range of expertise is needed?

There are numerous models for the membership of the DMC. However, most DMCs fit into three models that may be considered representative. These were presented in *Table 2*.

- The extreme model is that all members of the DMC should be completely independent of the trial being monitored; this includes the analysis statistician.³⁶ This model is rarely used in the public sector.
- An alternative, more widely used model is that the DMC meeting should include both decision-making and non-decision-making attendees. The decision-making members should be independent in that they do not have any actual or potential conflict of interest (see question 7). The decision-making members attend all parts of the meeting. Other attendees, who would not be involved in decision-making, could include the sponsor, representatives of the investigators and the trial statistician. They do not attend all parts of the meeting. They should not be

considered DMC members at all according to the definitions used in this report. The sponsor and investigators should attend only any open parts of each meeting, if at all⁵⁴ (see question 8). The analysis statistician, in contrast, may remain throughout parts of the closed session at the discretion of the DMC so as to present and give advice on the interim results. Many feel that this structure is the most appropriate, allowing all parties to express their feelings about the trial and to bring relevant information to the DMC, but retaining the independence of the DMC in making recommendations.^{17,20,63}

- However, a substantial minority of individuals disagree with the need for independence in decision-making. This view is best expressed by Meinert,²⁹ who says: "If the involvement of study investigators increases collective competency, then their exclusion [from the discussion on outcomes] has the potential of reducing competency and is open to challenge on that ground. Objectivity should not be at the expense of competency." In this model, the DMC is largely populated with relevant individuals from the trial who see all the data from the trial, but this group is often supplemented by one or two individuals who are independent of the trial (see question 7).

There is little guidance on how to choose members for a DMC. When considering individuals the suggested attributes to be desired include:

- broad knowledge (often of the area being studied)
- good judgement
- experience
- a reputation for objectivity
- being well respected
- impartiality (in particular, no conflict of interest, professional or financial)
- knowledge of the generally accepted principles of clinical trials methodology and practical issues in trial conduct
- knowledge of the statistical issues, in particular the ability to appraise the play of chance on trial results
- being supportive of the objectives of the trial and the design, including any early stopping guidelines
- the ability to work in a committee format
- the ability to deal with possible pressures, for example from sponsors or the media.

There is general agreement that DMCs should have multidisciplinary representation because the decision to stop a trial involves many non-

statistical considerations and is, in part, subjective.²⁴ Typically, this will involve at least one clinician and at least one statistician. There are different views on whether other specialities, such as laboratory scientists or, in particular, lay representation such as consumer representatives, ethicists or lawyers need to be included. Such individuals may need more training, as they are unlikely to have had wide exposure to DMCs (see question 10, which further considers training.) Their inclusion may depend on the disease under consideration. It is generally agreed that members of regulatory authorities should not be included on DMCs.¹³

Who should choose the DMC members?

This varies from proposals that it should be the sponsor (acting on suggestions from the trials investigators)^{13,15} to the investigators,¹¹ and maybe even the DMC chair being appointed and then choosing the other members.⁴⁵ The former approach is probably most appropriate, as the sponsor is ultimately responsible for funding and organising the trial. Whoever formally appoints the committee, all those with a major involvement in the trial should have a chance to review and comment on the membership.^{18,64}

Should there be a chair? And a vice-chair? If so, how should they be chosen?

It is generally accepted that a chair should be appointed.^{43,45} However, there is very little written about the basis on which the chair should be chosen. The opinions expressed range from the committee itself electing the chair,¹⁶ to the organising group¹⁸ or sponsor appointing the chair.⁴⁵ It is probably unrealistic to expect the former, and therefore the latter is often used. Other than a survey reporting the use of vice-chairs on DMC,¹⁸ there was no mention in the reviewed literature of DMC vice-chairs.

What should the responsibilities of the chair and DMC statistician be?

The chair of the DMC is seen as responsible for facilitating and coordinating the DMC. The chair usually serves as a liaison between the DMC and trial investigators and sponsors for the trial.⁵² The chair is responsible for drafting and agreeing the agenda for the meeting, and is also responsible for signing off the minutes of each DMC meeting.¹⁶ The chair is usually either a clinician or a statistician.

The DMC statistician is responsible for guiding the committee if statistical issues are raised during the discussions of the accumulating data; this is

particularly with regard to advising against overinterpretation (the most common problem).⁵¹ Sometimes it is the DMC statistician who has performed the analysis of the data (although, as outlined in question 11, this is rare). The DMC statistician sometimes takes on the role of secretary to the DMC if this is not done by a professional secretary or another DMC member, because issues and discussions of a technical nature often have to be documented.²²

What should the responsibilities of the trial statistician be?

The trial statistician will usually be responsible for drafting and agreeing an analysis plan with the various groups involved towards the start of the trial.³¹ As indicated above, the analysis statistician (who may be the trial statistician in many cases, as in model 2 of *Table 2*) will usually prepare a written report for the DMC in a digestible and standard format^{26,31,45} (which may be sent some weeks before the DMC meeting; see question 9). The analysis statistician will also typically present this report orally at the meeting,⁵⁵ and answer any questions that the DMC may have. Some authors suggest that the analysis statistician should present recommendations, alongside the analyses, although this is not universally agreed.⁴⁰ The analysis statistician is also usually responsible for performing any extra analyses agreed and requested by the DMC. In some models, the DMC statistician is responsible for ensuring that the interim analyses are performed, but does not perform the analyses.³³

Should DMCs include consumer/user representatives?

It is argued that consumer/user representatives help to ensure that ‘common sense’ prevails and that consumer issues are always raised.²² There are

mixed views on whether consumer/user representatives should be included on a DMC,^{8,40} with an overall tendency to favour their inclusion among those who have chosen to publish on this issue.^{35,46,65}

Question 7: How is independence to be maintained?

Much literature has been published on the maintenance of a DMC’s independence, and the arguments have been well rehearsed elsewhere.^{13,32,62} This section summarises the main points.

What is independence?

Independence for DMC members has been characterised in the many ways. These are shown in *Box 5* and are also summarised by Cairns and colleagues:¹³

“An independent [DMC] is free from financial conflicts, hands-on participation in a study, involvement with the DCC [data coordinating centre], and financial involvement with the sponsor. Financial conflicts may appear in many forms but, at a minimum, [DMC] members should not have stock holdings with any entity involved in the study they oversee, nor should they have ongoing consultancies or advisory positions with such entities. Because a [DMC] reviews data as needed during a trial, the objectivity of a member who knows the trends in the data could easily be compromised if he or she were to advise an individual study patient; thus [DMC] members should be independent of clinical sites. Just as with financial conflict, direct involvement with the affairs of a trial sponsor or its coordinating center could place a [DMC] member in a position in which his or her recommendations could jeopardise future relationships.”

BOX 5 Characteristics for defining independence of DMC members

- No stock ownership in drug company
- No stock transaction in the company (if previously holding stock)
- No large consulting arrangements with the sponsor
- No frequent speaking engagements on behalf of the intervention⁶⁴
- Career is not tied up in a product or technique
- No hands-on participation in the trial
- No involvement in the running of the trial
- No emotional involvement in the trial
- No intellectual conflict, e.g. prior belief in the trial’s experimental arm³²
- No involvement in regulatory issues relevant to the trial procedures
- No investment (financial or intellectual) in competing products
- *No involvement in the publication⁶⁶ (see question 23)*

Italics refer to minority opinion.

Some argue that these same criteria should be equally applied to the families of DMC members.⁴² “[As far] as possible, [DMC] members should refrain from involvement in these types of situations and avoid financial dealing with companies involved with products being evaluated or with competing companies.”³² The avoidance of such conflicts is not written in law (at least in the USA), but is ethical in nature.³²

Although the majority of published literature pertains to drug trials, in general terms, the issues are the same for other types of intervention and medical devices.^{11,41}

Is independence necessary?

The avoidance of any perception that members of a committee may be biased is important for the credibility of the decisions made by the committee and for the integrity of the trial.^{25,39} Maintaining credibility requires that the “voting members should be without actual or potential conflict of interest”.⁶³

However, Green and Crowley⁶⁷ noted, “I wouldn’t want the message to be conveyed that all trials need an independent committee. I don’t think that’s always necessary”.¹¹ Each medical speciality is a relatively small field with a limited number of experts. So, not infrequently, only individuals with direct involvement in the field of study have the expertise required to evaluate the complex data that a clinical trial will yield. Expertise in medical statistics is similarly hard to come by. Armitage noted that “In the few instances I have known where a small number of investigators were privy to the full results during the data monitoring procedure, I did not detect any lack of objectivity or undue distress on their part. I suggest that a flexible attitude should be adopted on this issue”.⁵⁵

Indeed, many pharmaceutical companies have formed internal DMCs³² primarily because the trials were not sufficiently high profile and if an external DMC were appointed for every trial there is a belief that there would not be enough qualified individuals to serve.

The issue of independence may be related to whether any statistical stopping rules exist for the trial and whether they are interpreted as rules or as guidelines (see question 17). Crucially, if the DMC has some leeway, as is the case with guidelines, it is necessary that the DMC is objective: and independence increases objectivity. Bias caused by subjectivity, both conscious and

unconscious, can affect the rationality of decision-making (see Chapter 3).^{11,68,69}

Previously, question 6 discussed membership for DMCs. *Table 4* summarises the arguments for and against many potential people being appointed as DMC members with regard to independence. Meinert¹¹ stated that he would argue for including anyone with knowledge of the trial in the decision-making process. “I would rather have a slightly biased committee which is informed, than a clean committee that does not have all the information it needs to evaluate the results.”¹¹

However, even if an individual is not a member of the DMC per se their knowledge should not be discarded. As stated by Fleming, “A key point is that if these individuals are not members of the committee, it does not mean they should not be involved in the process”¹¹ (see question 8 for the practicalities of DMC sessions).

Addressing conflict of interest

A 1993 survey of US cooperative trial groups showed that seven of 11 groups had formal rules or criteria that defined potential conflict of interest.⁵⁰ Meier has argued that conflict of interest is an inappropriate term and should be replaced with related interest, since “not every related interest should be seen as a conflict”,¹¹ but his terminology has not been widely accepted.

The generally accepted principle for dealing with potential conflicts of interest is one of voluntary disclosure, as adopted by the FDA, so that others can “make independent assessment about whether these could have significant impact”.¹¹ The involvement of people with such conflicts may still be justified if others with the same knowledge but without the conflict are not available. “Often, simple disclosure is sufficient to resolve these ... conflicts.”³²

Possible conflicts of interest should be disclosed to the appointing authority,¹⁸ the group chair⁴⁶ or whoever appoints the DMC (see question 6 on who decides membership). There is little discussion in the literature considered in this review of what should be done if a member of an ongoing DMC has conflicts of interest. Where the DMC is planned to be independent the decision may be more straightforward: remove the conflict or stop participating in the DMC.⁶⁴

Payment to DMC members

It is generally accepted that members of DMCs should be reimbursed for their travel and

TABLE 4 Arguments for and against inclusion of potential members with regard to independence

Position	Inclusion	Exclusion	Majority opinion with regard to participation
Sponsor representative: drug company	May have knowledge of drug not available elsewhere Reassures sponsor that the trial is being undertaken well and monitored adequately	Primary aim is profit, therefore clear pro-treatment bias expected. May wish to stop trial for financial reasons. In addition, the DMC members may have funding from the sponsor and believe that criticising this trial may prejudice their own funding	Do not allow drug company employees as DMC member, but perhaps invite to present information or answer DMC's questions
Sponsor representative: other funding (e.g. public, charity)	Reassures sponsor that the trial is being undertaken well and monitored adequately	May wish to stop trial for financial reasons. The DMC members may have funding from the sponsor and believe that criticising this trial may prejudice their own funding	Do not allow publicly funded sponsors as DMC member, but perhaps invite to present information or answer DMC's questions
Principal investigator or study chair	May have specific trial knowledge not available elsewhere	May later reveal confidential accruing data or be taken out of equipoise, thereby compromising ability to promote trial Career may be tied up with drug, product or technique	Do not allow as DMC member, but invite to present information or answer DMC's questions
Other trial investigators	May have some specific trial knowledge not available elsewhere	May be taken out of individual equipoise, compromising ability to recruit	Do not allow on as DMC member. Invite as appropriate (e.g. if PI unavailable)
Coordinating centre	Knowledge of day-to-day running of trial not available elsewhere; understanding of data	Invested much time and effort getting trial to this stage; intimately involved with data and with promoting trial	Exclude as members but report to DMC routinely
Trial statistician	Intimately involved with trial	Intimately involved with trial. May be under pressure from sponsor	FDA would prefer analysis to be performed by independent statistician in many cases, ³⁶ but this is not widely accepted as necessary or appropriate. Sessions attended by the trial statistician will be at the DMC chair's discretion
Regulatory authorities	"Would help regulatory reviewers make better informed decisions in a more timely way" ⁶²	The DMC reviews data from one trial, while regulators have to consider all available data. In a position to have greater knowledge of any drug information from outside the trial. Also have different type of relationship with drug companies than the general DMC members	Exclude from DMC unless completely necessary
Members of DMCs of similar trials	Perhaps able to provide a bigger picture and may help to protect against overreacting to random data trends	If on DMC for a similar trial, because may have pre-existing biases from viewing confidential data from other trials	(None)

communications expenses.³¹ It is also generally accepted that private companies should compensate for time expended at the 'usual' rates.^{34,45} While private company rates tend to be higher than those paid by public sector employers, they are usually "modest enough that there would

be little chance that the payment could influence the objectivity of the DMC members".⁶⁰ To put this another way, there is a broad consensus that compensation paid at a reasonable rate should not compromise the independence of the DMC,⁵² and should be small enough that members should "not

derive any financial support from the trial”⁷⁰, that is, service on DMCs should not be their primary source of income. Bergqvist and colleagues argue that the compensation should reflect the amount of time and the amount of expertise made available by the DMC members.¹⁶ They additionally argue that payment should be made to the employer (e.g. “research foundation, the university or health service employer”) rather than to the individual directly. No mention is explicitly made of payment to any non-members who report to the DMC or attend their meeting, but by extension it would be expected that travel expenses should be reimbursed, at a minimum.

Question 8: Should the DMC deliberations be open or closed (confidential or secret as opposed to publicly available)?

Many authors have considered the questions of whether DMC meetings should be open or closed, and whether anyone other than the DMC members be allowed to participate, and if so who? The difficulty to be surmounted is that the independent members of the DMC may not know very much about the details of the trial or other relevant external events, whereas the aim is to keep those who do know – the trial investigators – blind to the emerging results.⁵³ There is considerable agreement that the solution is for DMC meetings to comprise both open and closed sessions. The objective can be summarised as “to preserve confidentiality while maximising the opportunities for interaction with all individuals who would have valuable input for the committee”.²⁶

The open session is attended by DMC members, trial investigators, the trial/analysis statistician and possibly also the head of the statistical centre, members of the trial oversight committee and perhaps also representatives of the sponsor, funder or regulator (e.g. the FDA). It should not, however, be open to the public.⁷¹ At this session the progress of the trial is reviewed, including participant accrual rates, loss to follow-up, the timeliness and quality of the data, the performance of centres in a multicentre trial, possible modifications to the protocol, and so on. Toxicity of trial treatments might be discussed in general terms, but without reference to actual data. Trial efficacy should not be discussed in the open session, perhaps not even for the treatment groups combined as any deviation from the expected values may be assumed to be the result

of differences between the treatments. For example, in survival, if the expected 2-year survival rate is 20% on the control arm and the combined rate presented is 30% this may be due to improved survival in the research arm, but it may also be due to the control arm performing better than expected (regardless of any differences in treatment efficacy). There is no consensus as to whether toxicity data should be presented at the open session.^{40,46} Also, at this meeting any recently available external evidence can be presented and discussed (see questions 11 and 15). Some individuals, such as representatives of the sponsor, may not attend the meeting in person, but be available to answer questions by telephone.²² A minority view is that open sessions are not advisable and that, in particular, there should be no contact between the sponsor and the independent DMC (Gent, in Yusuf¹¹). In summary, it is generally agreed that open sessions in which any aspects of the trial that do not relate to the interim findings are discussed are desirable.

Participation in the closed session is restricted to those who may see the unblinded data from the trial: almost always this meeting is restricted to the DMC and trial/analysis statistician. In the closed session the DMC will see and discuss efficacy and safety data by treatment group. Care should be taken that “sloppy management of paper documents” does not lead to leaks to those attending only the open meeting.⁵⁴ Indeed, a more extreme view, given by Packer,³² is that “Any breach of confidence may ruin a trial ...”.

Most writers explicitly or implicitly assume that the interim results will be shown to the DMC unblinded, that is, with the treatment groups identified. It has occasionally been suggested⁸ that the DMC should be blinded to treatment (and perhaps able to ask to be unblinded at any time). Ellenberg and colleagues observe that “it is scientifically and ethically problematic to withhold from the DMC access to the efficacy and safety data that are fully unblinded by intervention group”.¹⁹ In practice blinding is often unsuccessful because of a clear difference in the frequency and nature of adverse effects. Although this problem can be surmounted by randomly changing the labelling for different parts of the trial results, it is then not possible to consider the linkage between different outcomes.¹⁹ Meinert has written scathingly about blinding of the DMC as “blind stupidity”.⁷²

Some commentators have suggested that after the closed session there should be an executive session

for which the analysis statistician leaves,⁴⁶ although the attendance of anyone additional to the DMC members at the closed session is at the discretion of the DMC. At this session the DMC can discuss any aspect of the trial conduct as well as the data, and make decisions about what to recommend (see question 15). Indeed, the analysis statistician may be present throughout the discussions and deliberations of the DMC. In the latter situation, the analysis statistician “has no vote in the decision making”.¹⁵ An additional open session is possible between the closed session and the executive session, at which the DMC can enquire about issues that have arisen during the closed session discussion.²⁶ Finally, it is possible to have a final open session at which the DMC can summarise its response.

The preceding comments apply to the present time. As recently as 10 years ago it was not uncommon for the trial investigators routinely to see the unblinded outcome data during the trial⁷³ (see question 7 for a discussion on independence; see question 11 for details of the information available to DMCs).

There is near unanimity that the interim data and the deliberations of the DMC should be absolutely confidential.^{15,31,40,46,64} At the end of the meeting the DMC will make a recommendation to the steering committee, but the DMC will not discuss the actual data with the steering committee or anyone else. Breaches of confidence are to be treated extremely seriously.^{32,43,45} one group suggested that “even the smallest breach of confidentiality by a [DMC] member should prevent that person from participating as a member of any future [DMC]”.³²

A contrary minority view is that interim data should be made publicly available⁷⁴ and that by keeping data confidential DMCs are acting unethically.⁷⁵ Lilford and colleagues⁷⁴ point out that a DMC, faced with fairly convincing data, may be implicitly making a trade-off between the general patient population that will benefit from a precise answer, and the patients in the trial, half of whom are currently receiving an apparently suboptimal treatment. They claim that DMCs “make big decisions using opaque (and doubtless variable) heuristics, while ignorance is perpetuated to stop potential participants voting with their feet”. This is an ethical issue, in that data arising from the trial are kept secret from both clinical and patient participants, whereas there is an imperative actively to disseminate similar data from another published trial. “Withholding,

without debate and endorsement of the policy, information that patients might find useful, is at best paternalistic, at worst authoritarian and arguably unnecessary.”⁷⁴

From a practical perspective, it may be feared that making interim data public would undermine recruitment and promote premature adoption of the apparently favourable treatment. However, Lilford and colleagues claim, if there exists a range of prior opinions then data in favour of one treatment will serve to bring additional clinicians into “equipoise” and hence they will be willing to recommend randomisation.⁷⁴ The Growth Restriction Intervention Trial (GRIT)^{76,77} has released its interim data to recruiting clinicians with no reduction in recruitment. It can also be argued that the media may overinterpret interim results that would not sway a DMC, but Lilford and colleagues feel that this “derives from a culture of scientific materialism and is self-fulfilling”,⁷⁴ in that secrecy allows uniformed views to flourish. Bayesian presentation may also prevent overinterpretation, as used in GRIT.⁷⁷

Who outside the committee should see the interim analysis and how is this changed by whether the analyses were blinded or unblinded?

Some have suggested that the trial statistician should remain blinded and that an independent unblinded statistician should be employed as the analysis statistician to carry out interim analysis and to work with the DMC.^{31,32} There is concern that the trial statistician cannot participate neutrally in steering committee discussions, for example, relating to changing the primary outcomes, if seeing the accumulating data.¹⁹ A suggestion in the recent draft FDA guidelines³⁶ to have an independent statistician has caused considerable consternation. For example, in a session of the Society for Clinical Trials annual meeting in 2002, concern was expressed that while the trial statistician knows the data set thoroughly, someone brought in from outside would find it difficult to produce the necessary analyses and may miss important information.

The DMC may allow “selected individuals (e.g. the chair of the executive steering committee) to become unblinded with respect to certain specific results if, in the view of the [DMC], the trial – and particularly, patient safety – would be better served by such action”.⁵⁴ It has been suggested that attendance of the trial sponsor at the closed session may be appropriate (as an observer) for a non-commercial sponsor.⁵⁵ For example, for many

trials sponsored by NIH, an NIH representative is present during the closed session.⁶⁴ Not all agree that this should happen.¹¹

The current prevailing view is that the trial investigators should not see the unblinded interim results, and that the argument that releasing interim results would aid enthusiasm and accrual is false.⁷⁸ However, for NIH trials the PI may attend the closed meetings.⁵⁴ (See *Case Study 1* for an example of the possible impact of this policy.)

Pocock⁴⁸ discussed the question of whether the pooled outcome data from the two arms of a trial might be released to the trial investigators. "Such knowledge satisfies curiosity and instills confidence that the trial is functioning well, but could it adversely affect continuation? Knowledge that the total of primary events was well below twice that expected in the control group might lead to (possibly false) speculation that the treatment was effective, in which case such data should not be released." He notes, however, that a referee of his

CASE STUDY 1 *Impact on accrual of having no independent DMC and showing interim results to participating clinicians, and impact of early stopping of a trial for efficacy where the late results were markedly different*

Trial

This was a European Organisation for Research and Treatment of Cancer (EORTC) trial⁷⁹ in locally advanced breast cancer conducted in centres across western Europe between December 1979 and November 1985. The trial was a 2 × 2 factorial RCT: all patients were to receive radiotherapy and were randomised between chemotherapy and no chemotherapy and between hormone therapy and no hormone therapy. The primary outcome measure was overall survival. A total of 410 patients was randomised to an initial recruitment target of 330.

DMC role

The DMC (known as the trial monitoring committee) was planned to monitor the conduct and progress of the trial. The DMC was not independent. Indeed, the data monitoring was initially performed by the trial statistician on a 6-monthly basis. If any of these interim looks at the data were statistically significant, they were to be discussed with the study coordinator and possibly with the main clinicians participating in the trial. The DMC was formed later in the trial.

Data

The following table summarises the accumulating data for the trial.

Timing	Gp	Survival									First progression	
		Events			Hormones			Chemotherapy			Horm	Chemo
		Acc	Prg	Dth	p	HR	95% CI	p	HR	95% CI	p	p
Apr. 1982	All	175	35	10	NS	–	–	≈ 0.05	–	–	NS	≈ 0.05
Mar. 1983	All	264	81	39	0.65	0.87	0.46 to 1.62	0.08	0.57	0.31 to 1.08	0.13	0.0002
Oct. 1983	All	319	99	62	0.58	0.87	0.53 to 1.43	0.02	0.56	0.34 to 0.92	0.04	0.0000
Apr. 1984	LA	346	96	57	0.46	0.82	0.49 to 1.38	0.01	0.50	0.30 to 0.85	0.14	0.0001
Apr. 1984	All	346	125	–	–	–	–	–	–	–	0.02	0.0001
Nov. 1984	LA	385	120	72	0.36	0.80	0.51 to 1.28	0.009	0.54	0.34 to 0.86	0.03	0.0000
May 1985	LA	399	138	86	0.16	0.75	0.49 to 1.13	0.004	0.53	0.35 to 0.82	0.04	0.0000
Mar. 1988	All	410	264	202	0.06	0.77	0.58 to 1.02	0.23	0.84	0.64 to 1.12	0.001	0.009

Acc, accrual; Chemo, chemotherapy; CI, confidence interval; Dth, death; Gp, group analysis (All, all patients; LA, locally advanced patients); Horm, hormone therapy; HR, hazard ratio; ns, not significant; p, p-value; Prg, progression.

Considerations

The summaries of each interim look at the data are as follows:

April 1982: continue recruitment

March 1983: data sent to study coordinator

October 1983: data discussed by DMC – continue recruitment

April 1984: continue (although accrual was by now slower)

November 1984: continue

May 1985: close trial because of slow accrual (except for an apex positive subgroup)

March 1988: final trial results published. The results were much changed in both comparisons: the effect of chemotherapy was no longer statistically significant; in contrast, the benefit to hormone therapy had become more convincing.

Consequences

Accrual had continued, although at decreasing rates, despite interim results. The final results were quite different to the immature results.

paper disagreed, “arguing that a steering committee cannot steer appropriately without access to such information”.

The release of unblinded data to sponsors is generally precluded by the consensus that they do not attend the closed session. A DMC may consider the release of blinded data to sponsors in rare circumstances.⁸ By contrast, one group³² has suggested that “in an industry-sponsored trial, an employee of the sponsor must have access to unblinded information so that the sponsor can report any serious adverse event to authorities”. Of course, the recommendation to continue a trial provides some information about what the trial does not (yet) show.³³ (See question 12 about releasing data for systematic reviews.)

Who outside the DMC should see or be informed about the decisions that are reached?

In the UK, the DMC usually makes recommendations to the trial’s steering committee. In practice, a recommendation to cease recruitment is effected by unblinding the steering committee to the latest efficacy and safety data on which such a recommendation was based. In most cases the steering committee will follow the recommendation of the DMC, but on occasion they will not (see examples in Chapter 6). Using this approach, it is for the steering committee, not the DMC, to decide to whom the trial results should be released, although the DMC may have a say (see question 14 for consideration of whether the DMC is advisory or executive and question 20 for who the DMC reports to).

Should the committee destroy their papers after the meeting?

Some authors have recommended that, to aid confidentiality, all confidential material should be collected (by the analysis statistician, or some other member of the coordinating centre, if they are allowed to handle this information) at the end of the DMC meeting.^{31,70} However, it is not uncommon for DMCs to monitor results over time and this requires access to earlier reports.

Question 9: What are the optimal practical arrangements for interim analysis and data monitoring?

Frequency and timing of DMC meetings

The frequency and timing of monitoring vary

according to context, are guided by the trial design and should be specified in the protocol.³⁴ The arguments for a first organisational meeting to review the protocol, establish procedure and agree terms of reference before starting enrolment¹⁹ or, if not, before the first interim analyses have been discussed previously (see question 4). The frequency of subsequent meetings depends on how quickly information on primary outcomes accumulates. Some monitoring plans use ‘information time’ (proportion of primary end-points or observed accrual) rather than calendar time to define the frequency of meetings. Although the former may be more efficient for interim analyses of the primary outcome, the latter is more practicable as meetings can then be scheduled well in advance. Earlier DMC meetings focus on monitoring safety and trial conduct because information on efficacy usually accumulates at a slower rate early in the trial. Many commentators suggest that biannual meetings appear to be more than adequate for most trials.^{31,50,51} Safety concerns or trends in efficacy data may lead to additional or unplanned interim analyses.¹⁵

Means of communication and other logistical aspects

The choice of dates and other logistical aspects of DMC meetings are the responsibility of the sponsor or the coordinating centre with input from the DMC, particularly in regard to scheduling and specific requirements.³¹ Currently, DMCs could use three modes of communication: face-to-face meetings, teleconferences and written correspondence (by mail or e-mail).

It is generally agreed that face-to-face meetings are the most effective way for committee members to communicate, as they facilitate adequate discussion.¹⁹ They are necessary when reviewing complex data or when data are at a crucial stage and important decisions are to be made.³⁴ They have also been recommended for the initial meeting, particularly when members may not be familiar with each other.^{51,54} One would presume that face-to-face meetings are also easier when the committee is international and does not share a first language (an example of this is presented in Chapter 6 *Case Study B*, p. 111). However, with the heavy demand on people with DMC experience, face-to-face meetings are sometimes difficult to arrange and are more time consuming.

With regard to time, teleconferences are more efficient and easier to arrange at short notice, but they allow less effective interaction between

members than face-to-face meetings. They are particularly useful for shorter meetings of small committees whose members are already familiar with one another. Little has been written on these issues in the published literature, but these topics are considered further in Chapters 3 and 5.

Written correspondence between members is considered the least satisfactory mode of communication and should be limited to administrative issues (e.g. circulation of minutes).

George⁴³ recommended that “Members who fail to attend two consecutive meetings (including conference calls) may be replaced”, but that it “wouldn’t be at the discretion of other DMC members”.

Question 10: What sort of training or preparation should DMC members have?

Although it is generally accepted that experience of clinical trials and knowledge of the disease area of the trial are essential for members¹⁸ (see also question 6), little has been written as to how individuals should gain suitable experience to serve as DMC members. Similarly, little has been published as to whether any formal training is required.

At present, when novice members are appointed to a DMC there are two ways in which they may be trained, which are not mutually exclusive. Following the first method, they “become apprentices who rely on the oral tradition to learn the rituals”, with the more experienced members acting “... like the caravans of yore, passing information from one society to another”.¹⁷ The tendency in North American cooperative groups is to have large committees that monitor a portfolio of trials. Therefore, when new, inexperienced people attend they are mixed in with those who are already experienced; this cannot happen so easily in smaller committees. Indeed, “It is good practice to include some experienced members on every [DMC]. A new committee should not be constructed entirely from inexperienced members, even if they are all experts” in their field.⁸⁰ But there is disagreement as to how many experienced members are needed to pass on knowledge and traditions orally.

There is agreement that the chairperson should be a more experienced member. “Clinical trial experience by all members of the [DMC] is highly

desirable, but prior experience of serving on a [DMC] by the [DMC] Chair is essential.”⁶⁴

The second training method advocates that potential or new DMC members turn to published case studies because these are “our best source of understanding the strengths and weaknesses of various monitoring and analysis strategies in practice and of informing current and potential data-monitoring committee members about situations they may face in their evaluations of trials ...”.²³ There is no widely available list of case studies to consider. Ten short case studies from the published literature are presented in boxes throughout this chapter; and four detailed case studies are presented in Chapter 6. However, interesting though these case studies may be, it is questionable whether case studies worthy of publication are truly representative of typical DMC functioning.

There has been a call for professional certification for DMC members in the belief that this would increase the transparency of the decision-making process,⁸¹ but even this paper did not suggest who would be providing the training leading to certification.

Perhaps training is needed not just for DMC members, but also for those who a DMC serves. In one paper, there was concern “that relatively few of the investigators are very cognisant of the board’s activities, and we have discussed the possibility of ‘educational outreach’. Sessions at upcoming meetings of the clinical trials groups are being planned to clarify for investigators the purpose of a [DMC], to present the operating procedures, and to permit board members to respond to any questions the investigators may have”.⁸

As discussed in question 6, many committees appoint a member who already has training in biomedical ethics,⁵³ but no published opinions were found as to whether all DMC members should undergo some training in ethics.

Question 11: What material should be available to a DMC?

Who produces it?

There are mixed views on whether the trial statistician or an independent statistician should act as the analysis statistician and produce the analyses for the DMC to consider. One article¹² implies that the DMC should perform the

analyses. The arguments in favour of using an independent statistician are that it retains the principle of keeping blind all those involved (in any way) with the trial, and prevents placing the trial statistician in a difficult position – that of knowing the current results, and interacting regularly with the other investigators in the trial. This is the current view of the FDA: “... the integrity of the trial is best protected when the statistician preparing unblinded data for the DMC is external to the sponsor ...”.³⁶ (Further discussion of this issue is presented by Ellenberg and colleagues.¹⁹)

However, a powerful argument that the trial statistician should perform the analyses is that to analyse a dataset requires knowledge of the disease, the trial and detailed aspects of data collection.^{15,55} Without this background it is easy to make many (and sometimes simple) errors in the analysis. This holds even if the trial statistician provides all the data for the analysis to be performed by the independent statistician, because discrepancies may only be spotted once the analysis has been performed. Thus, in most circumstances, it is the trial statistician who produces the analysis. Analysis of the data and preparation of the report are not then the responsibility of the DMC statistician.⁴⁸

What should be produced?

Buyse⁷³ presents a basic generic table for possible evaluations to be made to the DMC. *Table 5* is an amended version of this table, supplemented by extra aspects that may be useful. This could be used as a template for producing reports to

DMCs. Many authors emphasise the importance of providing comprehensive, but digestible information to the DMC.^{22,45} This must usually be done in the form of summary tables and statistics and, wherever possible and appropriate, by using graphical summaries. It is unrealistic to expect a DMC to plough through individual patient records,⁴² except perhaps at very early stages for certain key outcome measures, such as unexpected SAEs.²² It is often useful to agree the template for the report at the start or soon after the beginning of the trial. An argument for waiting until there are some data is that it can be difficult to make sense of empty (shell) tables.²²

The DMC, after appropriate discussion, should be able to ask for extra analyses to be performed (at any time) or further data to be collected during the course of the trial,⁶⁴ to enable it to carry out its primary responsibilities. The analyses should be based on up-to-date data.^{42,46}

Allied to this framework, it is often useful to set out an interim analysis plan,³¹ which will have the above framework and many of the components of a final analysis plan. The interim analysis plan should be seen and agreed by the DMC before the start of the trial or early on in the trial (see question 2).

Two reports are often prepared: one for the open session and one for the closed session.³¹ The open session report may be a subset of the closed session report or entirely separate (see question 8). The length of reports will depend on the context of the trial, perhaps between four and 200 pages:

TABLE 5 Possible evaluations to be made to the DMC (adapted from Buyse⁷³)

General area of evaluation	Specific evaluation	Session
Evaluation of trial procedures	Adequacy of record forms to capture the intended data	Open
	Procedures and arrangements for data processing and handling	Open
Evaluation of trial data	General monitoring of the trial	Open
	Date of freeze of the data set	Open
	Patient accrual and description	Open
	Patient exclusions	Closed
	Quality of data	Open
	Completeness of follow-up	Open
	Compliance to treatment	Closed
Evaluation of interim statistical analyses	Safety analyses	Closed
	Efficacy analyses	Closed
Evaluation of trial context	Interpretation of interim results	Closed
	Results from other individual trials	Open
	Meta-analyses	Closed
	Liaison with other groups or DMCs	Closed

somewhere between would be “reasonably satisfactory in context”.⁵⁵

An important issue is up-to-date information on the outcome measures. Fleming and DeMets suggest that, “In order to maximise available information and reduce the risk that subsequent data updates would substantively alter analysis conclusions, nearly current follow-up should be available on all patients. ... Decisions about early termination should be delayed if available data do not provide nearly current follow-up on almost all patients.”³⁹

Should the DMC be masked?

One aspect that has received some attention is whether the DMC should be masked in the sense of not knowing which trial group has received which treatment. In the report the treatments would just be labelled, for example, with A and B (see question 8). Some argue that such masking prevents the DMC from reaching premature conclusions from early trends.⁸² Masking also helps if the report finds its way into the wrong hands, and offers some protection against leaks.⁵⁴ In practice, masking data can be difficult because surrogate markers and adverse events often give the allocation away, but in these situations masking can be maintained by having different treatment codings for different aspects of the data.⁵⁴ This may be practically complicated and open to error. If the DMC is masked then it is usual to allow them to remove the masking at any time,⁷² although the same author feared that once imposed, the masking tended to become permanent because “the request [for unblinding] comes to be seen as heralding recommendations for changing the protocol”. However, as Pocock and Furberg⁵⁴ point out, many experienced DMC members believe that only the presentation of unmasked data allows a DMC to consider risk/benefit issues competently and efficiently and to integrate the often complex patterns of safety and efficacy issues more carefully. It has also been emphasised that recommendations for a change to the trial protocol are not usually independent of the direction of the effect. In such situations it is unreasonable to ask the DMC to behave as if it were indifferent to the direction of any emerging difference.⁷² In particular, in most trials, more evidence is required to stop a trial because of a benefit for new treatment than because of harm.

Further, it has been argued that masking undermines the value of the DMC discussion because much is conditional on knowing the

allocation. This causes too many ‘what if’ situations, and complicates the conduct of further analyses to examine the stability of any result.⁷² Finally, it has been pointed out²⁹ that it is difficult to imagine that masking could improve patient safety. Thus, unblinded data are more commonly presented to the DMC. Whichever approach is adopted, the options are best discussed with the DMC at its first meeting.

Should information be available before the meeting or only during the meeting?

Most authors generally agree that DMC members need some time to consider the information in a report⁴⁶ and thus should receive a report at least 2 weeks before the meeting.⁷⁰ A secure and expedited delivery system should be used.³¹

Should external evidence be included and how?

There is general agreement that external evidence should be considered by the DMC.⁸³ It has been argued that this would be best done in the form of a systematic review (which may or may not include a meta-analysis),⁸³ with considerable emphasis on the need for following the principles of a good systematic review. This can be a major undertaking; it is unrealistic to expect the DMC members to perform this review. The trial team is likely to be best placed to collect and summarise this external data for the DMC. Whether the trial data and external evidence should be formally combined in some manner depends on many issues, including the similarity of the trials being included. Most of the issues are similar to those faced in any systematic review. The added difficulty with preliminary data from the ongoing trials is that it is not clear what point and interval estimates of effect should be included. As indicated in the statistics section (see Appendix 1), for a trial that has stopped early these estimates of effect are more likely to be overestimates, or underestimates, depending on the reason for stopping. It has been suggested that Bayesian methods may be a solution to this problem.⁸⁴ Nevertheless, it has been argued that formal combination of the accumulating results from the trial and external evidence should not be done, or done with considerable caution⁸³ (*Case Study 2*).

Are there specific issues related to type of outcome?

In some trials outcome measures are reviewed (or confirmed) independently (often blind to the treatment assignment) to ensure that they are assessed objectively and systematically. This may

CASE STUDY 2 *Impact of external data together with interim data, leading to early stopping for harm*

Trial

CARET (Beta-Carotene and Retinol Efficacy Trial).^{85,86} This was a US-based National Cancer Institute (NCI)-sponsored double-blind, placebo-controlled, randomised trial for patients who were at risk of lung cancer owing to previous asbestos exposure or smoking. Patients were randomised between β -carotene plus vitamin A and placebo. The primary outcome measure was the incidence of lung cancer. The trial was powered to detect a 22% reduction or a 24% increase in the primary outcome measure with 110,000 person-years of follow-up (approximately 18,000 subjects required). Pilot studies were run between 1983 and 1988, and the main trial recruited between 1988 and 1995. Overall, 18,314 patients were accrued. A similar trial, the ATBC (alpha-tocopherol and beta-carotene) Cancer Prevention Trial,⁸⁷ was run concurrently.

DMC role

The DMC (known as the independent safety and end-points monitoring committee) consisted of five named members with unspecified positions. Their remit was to review accruing data. "The prespecified monitoring policy for stopping the trial ... was based on O'Brien & Fleming boundaries ..." of $\alpha = 0.0006$ for the first interim analysis and $\alpha = 0.007$ for the second interim analysis.

Data

Initially, the data was shown in a blinded fashion, although this was later stopped by the DMC: "When the results of the ATBC Cancer Prevention Trial became available, the committee reviewed the results of the first interim analysis and requested that the blinding [of the CARET trial] be ended." At the second interim analysis (December 1995), 2420 end-point events had been reported (1446 cancers, 974 deaths). The cumulative incidence of lung cancer was higher in the active treatment arm than the placebo arm; relative risk = 1.28 (95% CI 1.05 to 1.57, $p = 0.02$).

Considerations

"The 2nd interim analysis led [the] safety and endpoints monitoring committee and steering committee to recognise the extremely limited prospect of a favourable overall effect, as well as the possibility of true adverse effects. The decision to stop the intervention was made by the steering committee on January 11, 1996. It is possible that the excess mortality in the active-treatment group may have vanished or become statistically insignificant with completion of the intended intervention period plus several years of follow-up; such reversals of findings have occurred both in the course of a single large randomised trial and in subsequent randomised trials of the same agent or class of agents. However, it was impossible to ignore the results of the ATBC Cancer Prevention Study in deciding whether to stop the active-intervention phase." The ATBC trial, a prevention study with nearly 30,000 patients, had unexpectedly shown an increase in tumours at several major sites.

Consequences

The trial was stopped early by the steering committee. There were no systemic toxicities, due in a large part to external data. A further trial of vitamin A alone was discussed, but it was considered impractical.

Comments

It was a mix of trial data and external data that led to this trial stopping. The format in which the external data were presented or incorporated is not clear.

produce a timelag between 'unclean' (unconfirmed) assessments and 'clean' (confirmed) assessments. Pocock and Furberg⁵⁴ noted that:

"All available data should be included in the interim report for the [DMC], regardless of what has been adjudicated to date. This is a fundamental requirement. The 'clean' data should be shown separately, but possible decisions should inevitably be based on the totality of information available, whereas the reduced reliability of unadjudicated events is also taken into account. When the amount of unclean data is large, the situation is especially complex. One successful approach to such a case involves evaluating the relationship between the unadjudicated, or unclean, data and the final data for the patients for whom both types are available. This relationship may then be used to predict the results that would have

been found had all the data been clean at the time of presentation."

Slow reporting and validation of data in a trial may mean that interim analyses are based on old data, inhibiting the DMC from performing their role effectively. A partial solution suggested by Bolland and Whitehead⁵⁶ is for data relevant to formal safety monitoring procedure to be collected separately from baseline and other trial data, which may speed the whole process for these data elements.

Should there be interaction with other DMCs?

Interaction between DMCs that are monitoring similar trials is generally regarded as useful, in

principle.^{27,88} However, the practicalities of such interaction, including timing of reports, meetings and relevant information is difficult.⁸⁸ Perhaps more importantly, this sharing erodes the independence of each trial, and thus prevents 'independent confirmation' of results; such independence is an important, basic tenet of the scientific method.⁸³ Other difficulties are that interaction between the DMC, those preparing the report and the trial investigators is important in making any major decisions and this would be difficult or impossible in a model where DMCs are sharing confidential data.⁸⁸ In the absence of such interaction it is entirely possible that one DMC may misinterpret or overinterpret a written report.⁸⁸ A closely allied difficulty is that it is not clear what should happen if the DMCs disagree, especially if the DMCs are representing different communities (e.g. the trials are in different countries). It is likely that it would be difficult to include the trial investigators in any decisions made. As a consequence, sharing of data is rarely done in practice. For similar reasons, it is generally not recommended that the same individual serves on two parallel DMCs of two independent similar trials⁸⁸ (see question 7).

There are some suggestions (e.g. Yusuf¹¹) that safety data, especially those data relating to unexpected SAEs, are appropriate exceptions to the generally held beliefs. The situation may be slightly different, again, if one or more of the trials has closed, but is not yet published. These data may be easier to make available to the DMCs of other ongoing trials.⁸⁸

Should trial investigators be available to the DMC?

It is very useful to have some of the investigators (including the PI) at the open session of the DMC meeting in some form⁴⁵ (see question 8). This allows both the DMC and trial investigators to ask questions of each other, which can lead to a very useful interaction.

Baseline comparability

There is general agreement that the DMC should establish that any observed differences in outcomes are not due to imbalances in patient characteristics before recommending termination of a clinical trial because of efficacy, futility or toxicity.^{80,89} As the DMC will often be considering a relatively small amount of data, imbalances may be more likely than in large trials that have achieved their accrual target. It is, therefore, important that in such situations analyses are performed adjusting for possible imbalances. The

adjusted analyses to be performed should be prespecified in the statistical analysis plan.

Question 12: Who should own the interim data and analyses?

Little has been written in the published literature used in this review on ownership of interim analyses (13 related quotes were identified in ten of the sources). There are discussions beyond the scope of this report as to who owns the trial data overall. Indeed, it has been written that "pharmaceutical companies and some other sponsors of clinical research tend to think that because they have paid for a piece of work they own the data and are entitled to decide what should be published and in what form. This view ignores the rights of the participants in the study, the investigators and the organisations or institutions in which the work has been done".⁹⁰

It may be fair to assume that whoever owns the overall dataset (whoever that may be, in reality) and therefore the interim data, owns the interim analyses. However, it is accepted, in principle, that it is the DMC that is responsible for the interpretation of the interim data and for providing guidance based upon these data. Therefore, some may argue that it is the DMC's position to decide and guide on (see question 14 on whether the DMC should be advisory or executive) who else should see the interim results. There is some suggestion that the choice as to whether interim analyses are released to a trial committee for the purposes of planning a new trial should be made by the DMC.⁴⁵ Furthermore, these authors encourage sharing only if the trial is closed to new accrual and all patients have completed protocol therapy.

Contrary to this, in many cases the DMC are not allowed to keep the reports beyond the timeframe of the DMC meeting^{31,70} (see question 8): if they are not sufficiently in control of the data to keep it beyond the meeting, how can they be best placed to make conclusions on who else should see the data? This responsibility may then fall to the steering committee, if such an independent body exists, which would pass judgement without ever being made privy to the interim results. Similarly, "the responsibility for publishing findings is considered to belong to the study sponsor, the study's Executive Committee or publication committee, and the principal investigators".⁴¹ Therefore, the responsibility as to where interim data should go may not fall under the remit of the DMC.

In some circumstances, especially with regard to the release of unblinded comparative data on primary end-points from trials involving unlicensed products, it may be the FDA (or appropriate national equivalent) that assumes responsibility at the interim data stage.⁹¹

Question 11 deals further with the incorporation of data from more than one trial. A meta-analysis may be the more efficient way to combine such information, but the practicalities are likely to prove difficult.⁸⁸

Question 13: Should non-comparative analyses (which are ‘administrative’ and not separated by treatment arm) be carried out?

Little discussion of this topic has been revealed in the articles identified for this review. There is some debate about the actual nature of ‘administrative’ analyses. The most widely accepted definition of such analyses would be the evaluation of “factors that could affect the integrity of the trial but that can be assessed without revealing relative efficacy [or safety] results”.³⁹ However, the purposes of the administrative analysis may be wider than this and beyond the immediacy of the trial per se (e.g. planning for future trials).

There are four main ways in the literature in which the data could be presented without comparing primary outcomes:

- control arm data only
- active arm data only
- pooled overall trial data
- data by trial arm on non-outcome variables only (including baseline characteristics).

The ‘control arm only’ form may be considered for a number of reasons. By viewing ‘control arm only’ data, it is possible to check whether the accruing data are broadly in line with the anticipated data with regard to event rates or proportions of event-free subjects at a given time. The initial sample size calculation should have been designed based on historical (trial or non-trial) data on similar patients receiving the control arm treatment. Administrative interim analyses of this nature allow one to check whether the accruing control arm data deviate from these original assumptions; since any deviation would affect the power and the necessary sample size of the trial. This is commonly accepted as permissible.⁴⁵

Control arm only and active arm only data may be used separately for planning purposes of further drug development trials. However, these data generally “must be interpreted cautiously due to small sample sizes”.²⁰ Using the interim data on the experimental treatment to plan a new efficacy trial may be seen as rather presumptuous, but may be appropriate for safety trials.

As with control arm only data, pooled overall data may be presented to the wider community (or at least the participating clinicians) to keep interest in the trial: such data show participants that a trial is moving towards its goals.⁵⁴ However, while they may be easier to prepare, pooled data may be overly interpreted by participants. For example, a low overall event rate could be due to a less beneficial treatment, a lower risk population than anticipated, poor estimations of control arm data at the planning stage or chance, but may be interrupted as showing benefit of the intervention.

Administrative analyses may be defined as ones that rarely concern early termination.⁴² During trials with late-occurring or slow-accruing events or slow trial accrual it is still useful to convene the DMC since there is more to monitoring a trial than just monitoring the accumulating outcome data (see question 3 for further discussion of the responsibilities of the DMC).

One may wish to compare baseline characteristics between treatment groups to ensure that they are balanced. One may also check compliance with treatment.³⁹ A minority view is that administrative analyses should show data by treatment (e.g. survival curves), but not perform any formal test (discussed by Freidlin and colleagues²⁴).

Administrative analyses may consider other factors than the accruing trial data:¹²

- cost of the trial
- accrual (e.g. if lower than anticipated)
- trial design (e.g. if faulty or obsolete)
- quality of data collection
- loss to follow-up.

This information is similar to that which may be presented to a steering committee, should one exist, as such matters are likely to fall under its responsibility.

Although administrative analyses need “not affect the type I or II errors regarding the primary hypotheses”,³⁹ there is a need to document that the analyses were performed. “The need to

carefully control the dissemination of information resulting from interim analyses performed for administrative reasons is as necessary as information obtained from formal interim analyses.”²⁰

Question 14: Is the DMC advisory (to make recommendations) or executive (to make decisions)?

There is general agreement among commentators, which is also reflected in practice, that regardless of trial context, the DMC role should be advisory to the steering committee, lead investigators, sponsors or sponsor’s representative: whoever would be ultimately responsible for all aspects of the design, conduct and reporting of the trial.^{13,37,40,50} “As the trial is not organised by the data monitoring committee, its responsibility should be confined to recommendations to the organisers rather than decisions.”⁴⁸

A rather exceptional view that the DMC should have more than an advisory role is expressed by Korn and Simon: “Although the study investigators have the primary responsibility to suggest and make changes ..., we believe that the DMC should have a voice in any major change to the trial design. ... Although the DMC should make the decision, the input of the study investigators is obviously crucial.”⁷⁸ One of the arguments put forward for this view is that the trial organisers may have a real or apparent conflict of interest when considering a major change in the design or conduct of the trial, such as early termination.

Although the accepted wisdom is that the role of the DMC is advisory, its recommendations concerning certain types of decisions will generally prevail (Brown⁹²). For example, if a DMC recommends early termination of the trial on grounds of efficacy or safety, it would be unusual, although not impossible, for the organisers not to accept such a recommendation; for example, the Alpha trial⁹³ (see question 22).

Question 15: What decisions and recommendations should be open to the DMC?

This section considers the actual recommendations that may be made by a DMC. These may be formally agreed and presented in the DMC charter (see question 3). Some of the

recommendations will be guided by formal statistical analysis, which is briefly considered in question 17 and in further detail in Appendix 1.

Possible recommendations open to the DMC will vary according to the timing of a given meeting, that is, whether the meeting is taking place before, during or after the recruitment phase of the trial. Below are described the possible recommendations proposed as appropriate to a meeting at each of these times.

Meetings before the trial

In view of the DMC’s role to ensure that the trial comes to a valid conclusion, recommendations can include:

- improving design following review of the protocol^{19,31}
- improving procedures for quality assurance.¹⁹

Meetings while the trial is in progress

In trials with prolonged treatment and follow-up, meetings can be separated into three stages:²⁴

A: while patients are still being randomised: stopping accrual does not necessarily mean release of data, but in practice they will often go together.⁴⁰

B: after randomisation is closed, but while treatment is continuing

C: during the follow-up phase: where the recommendation is for release of trial data.

Freidlin and colleagues²⁴ emphasise that in situations A and B potential data will be lost, and there will be a concomitant decision whether to recommend release of data or await further follow-up. In situation C, and sometimes in situations A and B, there is an opportunity for additional analyses following further follow-up.

In each of situations A–C, three major recommendations are open to the DMC.^{15,22,31} These are detailed below.

The trial should stop completely or partially

To ensure the safety of trial participants, the DMC may recommend the trial stop because of safety concerns. The following reasons have been suggested by many sources^{8,19,73} (*Case Study 3*).

- Apparent benefit of active treatment on primary outcome: “A DMC, guided by a pre-specified statistical monitoring plan, will be charged with recommending early termination on the basis of

CASE STUDY 3 Early stopping for efficacy in a prognostically stratified protocol for leukaemia with no DMC credited**Trial**

CLL 80:⁹⁴ this was a Phase III RCT in chronic lymphocytic leukaemia (CLL) conducted in France and sponsored by Société Française d'Hématologie. Four treatment arms were compared using a risk-stratified approach to treatment, i.e. each patient was randomised between two treatments, but specifically which two treatments depended on their prognostic score:

- comparison X: a watching policy versus one cycle of chlorambucil
- comparison Y: one cycle of chlorambucil versus 12 cycles of COP (vincristine, prednisolone and cyclophosphamide)
- comparison Z: 12 cycles of COP versus 12 cycles of CHOP (COP + adriamycin).

Between May 1982 and May 1985 the trial recruited 850 patients to a 985 patient target (which was to include 282 patients in comparison Y and 89 patients in comparison Z). The primary end-point was overall survival.

DMC role

No DMC is named or credited in the paper. However, the trial followed a group sequential design (DeMets and Ware)⁹⁵ with five interim analyses of $\alpha = 0.017$.

Data

Trial accrual was quicker than anticipated. In the first year, 180 patients were recruited, whereas only 100 had been expected. Therefore, the sample size was revised upwards to 1170 and the first interim analysis was deferred until the original sample size had been met. Interim analyses appeared to have only included patients randomised 9 months before the interim analysis data (reference date).

Meeting	Time	Comparison X	Comparison Y	Comparison Z
First analysis	Feb. 1985 (ref. May 1984)	$n = 445, \chi^2 = 0.58$	$n = 219, \chi^2 = 0.92$	$n = 58, \chi^2 = 9.56$
Second analysis	Sept. 1985 (ref. Jan. 1984)	$n = 453, \chi^2 = 0.86$	$n = 223, \chi^2 = 0.11$	$n = 59, \chi^2 = 9.14$

Considerations

At the meeting in February 1985, the interim results of comparison Z were considered conclusive and the comparison was closed. All patients in comparison Z were then to be given CHOP. Based on this information, a new trial was designed for all patient groups, a date was set for the second interim analysis (January 1986) and the trial was closed to patient entry in May 1985 ($n = 985$).

Consequences

The trial closed early, clinical practice was changed and a new trial of CHOP was initiated for comparison Y patients.

Comments

The entire trial closed to recruitment early following the results of the interim analyses of one of the three trial comparisons. There is no mention of either a DMC or who took responsibility for trial closure.

a positive result only when the data are truly compelling and the risk of a false positive conclusion is low.”³⁶

- Apparent benefit of control on primary outcome: a particularly difficult situation arises when the active treatment appears inferior to the control. DeMets and colleagues³⁴ describe the difficulties in dealing with this “agonising negative trend” (*Case Study 4*).
- Concerns with safety outcomes (primary or secondary): monitoring adverse events is usually not based on a formal statistical procedure, and is particularly important when the events may arise from the disease being treated rather than from the treatment itself; in this case, precise attribution of cause is difficult and monitoring must necessarily involve unblinded comparisons.^{36,41}

Further reasons for stopping arise primarily for reasons of efficacy rather than safety, although it could be considered that continuing a trial for no good reason was itself an unethical, if not an actively unsafe, activity. Reasons can include the following.

- Small chance of eventually showing benefit: “‘Futility’ is the term used to describe the result in a superiority trial when there is no longer a reasonable chance that the null hypothesis can be disproved.”⁸
- Convincing evidence of equivalence or non-inferiority, in a trial with this objective: in this situation the objective of the trial has been achieved and, although no harm may come to participants in continuing, it may be considered inappropriate to expend resources and subject

CASE STUDY 4 Independent DMC stopping recruitment leading to early reporting of trial due to harm**Trial**

MRC LU16:⁹⁶ this was a randomised controlled trial of chemotherapy for small cell lung cancer (SCLC) requiring palliation. The trial treatments were four cycles of either (a) a standard intravenous (IV) regimens (etoposide + vincristine or cyclophosphamide + doxorubicin + vincristine) or (b) oral etoposide (50 mg, twice daily for 10 days). The trial was UK based and sponsored by the UK MRC with support from Bristol-Myers-Squibb. The primary outcome was the palliation of major symptoms 3 months after randomisation. "In this trial, equivalence in the primary endpoint between treatment groups was considered acceptable, provided that it was achieved without increased risk of toxicity of a clinically important survival penalty, because oral etoposide is so much easier to administer than IV chemotherapy." Between September 1992 and September 1995 the trial recruited 339 patients towards a target of 450 patients.

DMC role

The DMC (known as the data monitoring committee) was planned to review the trial's progress. No details on DMC membership are given in the publication. The DMC had no formal rules for stopping the trial.

Data

The published paper⁹⁶ focuses on the data shown to DMC:

Data		Oral etoposide	Standard IV
Tumour response (first 3 months)	Complete response	12/119 (10%)	24/133 (18%)
	Partial response	43/119 (34%)	44/133 (33%)
Survival	Deaths	111/171 (65%)	95/168 (56%)
	Median survival	130 days	183 days
	Hazard ratio	1.35 (95% CI 1.03 to 1.79)	
	Alive at 6 months	35%	49%
	Alive at 1 year	11%	13%

Considerations

The DMC "recommended that intake be stopped, because the interim analysis showed that although the palliative effects of treatment were similar in the treatment groups, there was increased haematological toxicity and significantly worse survival in the oral etoposide group". They also recommended "publication of the interim findings because of the widespread use of single-drug oral etoposide in the treatment of SCLC".

Consequences

"Intake was closed in September, 1995, as soon as the DMC recommendation had been received" and the interim results were submitted for publication soon after wards.

Comments

Based on the interim analyses the DMC recommended action to prevent further harm to patients both within and outside the trial.

patients to the uncertainty of an experiment. A superiority trial may also conclude 'equivalence', but generally one would expect the issue of futility to have already been addressed (*Case Study 5*).

- Lack of feasibility of trial coming to a sound conclusion: this could be due, for example, to quality considerations of the trial, lack of trial support, slow recruitment, drug supply problems (e.g. drug supplies run out). Termination of the trial for these practical issues is an important possible decision of the DMC.^{8,13,71,80}

The DMC may also recommend that only a part of the trial should be stopped for the following reasons.

- Stopping randomisation in a subgroup for one of the reasons given above: particular care must be taken over the multiple testing of hypothesis in many subsets, and the resulting possibility of a type I error.
- Stopping randomisation in one arm of the trial for one of the reasons given above: this may be particularly appropriate in factorial designs⁷³ (*Case Study 6*), but again statistical issues of multiple comparisons need to be carefully addressed.

All these decisions may not be based solely on the trial data:

- External evidence convincing: strong evidence from other trials may lead to termination in spite of equivocal results from the trial itself.

CASE STUDY 5 Early stopping in an equivalence trial based on a secondary outcome measure**Trial**

This trial was a randomised comparison of pumactant and poractant alfa for treatment of respiratory distress syndrome in neonates born at 25–29 weeks of gestation.⁹⁷ The trial was UK based and funded/sponsored by Britannia Pharmaceuticals, Serono Laboratories (UK) Ltd, the Community Foundation, Tiny Lives Fund and the Liverpool Newborn appeal. Between May 1998 and December 1999, 207 patients (target 482 patients) were randomised between two UK standard surfactant treatments: (a) pumactant, a synthetic surfactant, and (b) poractant alfa, a porcine-derived surfactant. The primary outcome measure was the cost consequences of treatment based on the number of days spent in high-dependency care.

DMC role

The DMC (known as the data safety and monitoring committee) was to “meet after about half of the neonates had been recruited”. No details are given about the membership of the DMC. There were “no formal rules for stopping the trial because the decision would depend on outcomes relating to safety and deaths, as well as clinical efficacy”.

Data

The DMC met in December 1999. “The committee, unaware of treatment assignment, noted an unexpected and highly significant difference in predischARGE mortality that was not explained by differences in gestational age or sex”

Outcome measure	Poractant alfa	Pumactant	OR (95%CI)	p-Value
Neonatal mortality	11/99 (11%)	25/100 (25%)	0.38 (0.17 to 0.81)	0.011
PredischARGE mortality	14/99 (14%)	31/100 (31%)	0.37 (0.18 to 0.74)	0.004

OR, odds ratio.

Consideration

The DMC, which was blinded to the treatment allocation, “recommended that the trial be stopped” based on the secondary outcome measure.

Consequence

Following the DMC recommendation, “the trial coordinators stopped recruitment”.

Comment

Based on a secondary outcome measure, the DMC acted to prevent further patients receiving an inferior treatment.

In all decisions to stop, the DMC will generally be expected to make recommendations concerning the release or reporting of the data. It has been emphasised that the potential impact of publication should be taken into account.^{31,88}

The trial should continue with modifications

As described in question 3, the DMC’s duties can include monitoring data quality, accrual, protocol compliance, patient evaluability and representativeness of trial to target population.^{11,13,15,19,37} This can involve a substantial administrative responsibility.¹¹ To improve the quality of the trial and the safety of participants the DMC may make a wide range of recommendations,¹⁹ which may include one or more of the following.

- Protocol changes: this could involve adjustments in treatments, changing eligibility criteria, and so on, to improve the quality of the trial.⁷³
- Terminate a particular clinic/centre: this will generally be due to suspected quality problems or low recruitment.¹¹
- Increased surveillance of specific adverse events: this would arise if suspicion arises that a certain type of adverse event is not being adequately detected.^{9,13,22}
- Additional interim analyses: if the interim data are suggestive of a trend, the DMC may recommend additional meetings and analyses. However, Matthews⁹⁸ points out that this can cause problems with certain types of statistical stopping procedures that are based around analyses at fixed points.
- Extending recruitment or follow-up time: a recommendation for ‘late continuation’ may arise through initial underestimation of the necessary sample size, or “for any sensible reason other than the results observed so far”.^{73,78} However, some, for example Whitehead,⁵¹ have claimed that since a sample size review does not involve treatment comparison it “does not relate to the activities

of the [DMC]”. Ellenberg and colleagues¹⁹ suggest pre-establishing a criterion for triggering sample size revision that is not based on comparative data.

- Amendment of the alternative hypothesis due to high accrual rates: Korn and Simon⁷⁸ suggest that changing the alternative hypothesis (e.g. to detect more reliably a smaller difference in efficacy) may be reasonable provided that the new alternative is still of interest and unblinded data will not have influenced the decision. The trial would still have to be monitored appropriately.
- Current and future participants should be informed of newly identified risks: this possibility is mentioned by the FDA’s draft guidance.³⁶
- Additional data analyses to be presented to DMC: it is plausible that the DMC will require additional information in view of indicative data.²⁵

The trial should continue without modification

The DMC will often issue a short report simply stating that the trial should continue as planned. However, it may still be asked to make recommendations concerning additional aspects of the trial, which may include the following.

- Approve ancillary studies: for example, assess the need for ancillary studies or additional secondary questions.⁸⁰
- Deal with requests for data:⁸⁰ however, it has been stated that “members should avoid any temptation to create problems and issues which are unimportant for the sake of being seen to be doing something”.²²

Meetings after the end of the trial

The DMC can contribute to determining when the data may be released^{37,40} (*Case Study 7*). However, Korn and Simon⁷⁸ say that “the decision on when the final analysis should be performed is best left to the study investigators” (see question 23 for consideration of the DMC’s involvement in publications).

General recommendations from DMCs

DMCs are trying to deal with the triple aims of safeguarding participant safety, preserving the trial’s integrity and ensuring reliable results for the wider clinical community.¹⁹ Therefore, it seems reasonable that “the committee will feel free to recommend any course of action that enhances the safety and quality of the trial”.⁸⁰

Question 16: How should the decisions or recommendations be reached within the DMC?

As discussed above, question 15 about the DMC’s decisions and recommendations can range from continuation of the trial as designed to early termination. These decisions are based on the monitoring plan and are taken after discussion of a detailed report on the progress of the trial, including interim analysis of available data. The meetings should be conducted in such a way as to facilitate effective discussion of the progress report and any other issues raised by the investigators and/or the sponsor.²⁶

A useful approach adopted by many DMCs is to divide the meeting into sessions including at least one open and one closed session (see question 8 for the practicalities of DMC meetings). The open session provides a forum of interaction between the DMC and the trial leadership where issues of concern to the investigators can be brought to light. It is also an opportunity for the DMC members to question the investigators about any general issues that merit clarification. The closed session is restricted to the DMC members and others whom the DMC chooses to invite (e.g. the analysis statistician).

The DMCs of some large trialist groups review several trials during each meeting. Therefore, to facilitate discussion, they assign two designated members (a clinician and a statistician) as primary reviewers for each trial that the DMC is monitoring.¹⁹ The primary reviewers introduce the trial report during the closed session and lead the discussion of important issues raised by the report during both closed and open sessions.

Process of decision-making

It has been suggested that, ideally all important DMC decisions should be reached by consensus rather than by majority vote.^{13,16} However, on occasions, arriving at a resolution of a difficult issue may require a vote, and so it is recommended by some that the DMC should have an odd number of members.¹³ Some DMCs allow the chair a casting vote to cover the eventuality of equal votes.¹⁵ It has been recommended that the process of decision-making should be laid out in advance (e.g. DMC charter), including, for example, when a DMC is quorate for decision-making¹⁹ (see question 3 and *Table 33*).

CASE STUDY 6 *Partial early stopping of a factorial trial with formal monitoring of an adverse outcome measure and use of a combined measure***Trial**

Women's Health Initiative (WHI) Clinical Trial.^{99,100} This is a large, double-blind, placebo-controlled trial with additional factorial randomisations and is sponsored by the US National Institutes of Health (NIH). The trial considers postmenopausal health with a primary outcome measure of coronary heart disease (CHD) incidence, with primary breast cancer as the primary adverse outcome measure. Women with a previous history of hysterectomy were randomised between oestrogen and placebo; and women with no history of hysterectomy were randomised between oestrogen plus progestin and placebo. Additional factorial randomisations of diet-control versus no intervention (for women aged 50–79 years only) and calcium+vitamin D versus no intervention were also included. From 1993 onwards the trial recruited over 16,600 women towards a 27,500 target (recruitment to the trial was ongoing at time of this report in 2002).

DMC role

The DMC (known as the WHI data and safety monitoring board) was to “ensure study subjects’ safety and to make provision for timely trial termination and reporting”. Formal monitoring began in autumn 1997 using O’Brien–Fleming boundaries (1979). Adverse effects boundaries were “further adjusted with a Bonferroni correction for the 7 major outcomes other than breast cancer that were specifically monitored ...”. With regard to membership, the “Board includes twelve outstanding medical researchers with expertise in aging, behavioral science, cancer, cardiology, ethics, gynecology, nutrition, osteoporosis, statistics, and women’s health” (data from www.whi.org).

Data

Five interim analyses had been completed by late 1999 and “... the [DMC] observed small but consistent early adverse effects in cardiovascular outcomes and in the global index. None of the disease-specific boundaries had been crossed. In the spring of 2000 and again in the spring of 2001, at the direction of the [DMC], hormonal trial participants were given information indicating that increases in MI [myocardial infarction], stroke, and PE/DVT [pulmonary embolism/deep vein thrombosis] had been observed and that the trial continued because the balance of risks and benefits remained uncertain.

“In reviewing the data for the 10th interim analyses on 31st May 2002, the [DMC] found that the adverse effects in cardiovascular diseases persisted, although these results were still within the monitoring boundaries. However, the design-specified weighted log-rank test statistic for breast cancer ($z = -3.19$) crossed the designated boundary ($z = -2.32$) and the global index was supportive of a finding of overall harm.”

Considerations

“On the basis of these data [31 May 2002], the [DMC] concluded that the evidence for breast cancer harm, along with evidence for some increase in CHD, stroke, and PE, outweighed the evidence of benefit for fractures and possible benefit for colon cancer over the average 5.2-year follow-up period. Therefore, the [DMC] recommended early stopping of the estrogen plus progestin component of the trial.”

Consequences

An attempt was made to develop feasible stopping rules for use on secondary outcome measures.

Comments

This is an example where the DMC recommended partial closure of a trial on the basis of harm.

Question 17: What should be the role of formal statistical methods in DMCs?

It is widely accepted that because the results of comparative analyses of efficacy and safety outcomes based on early interim data are inherently unstable, early termination of the trial based on these data requires much stronger evidence than the usual 5% significance level. Various methods of monitoring accumulating data, including sequential and group sequential boundaries, have been developed. However, there is almost unanimous agreement among experts that these boundaries should be considered as guidelines for considering early stopping, rather than as rules.^{34,39,71,78,101} (*Case Studies 8 and 9*).

Before recommending termination of a clinical trial because of efficacy, futility or toxicity, the DMC should establish that any observed differences in outcomes are not due to imbalances in patient characteristics.⁷ Large imbalances can occur when small numbers of individuals have been entered into the trial.

Further issues beyond any formal statistics that have been identified for taking into consideration include:

- overall balance between risk and benefit
- internal consistency of the results (for several outcomes and within subgroups)
- external consistency with what is already known about the disease and the treatment in question

CASE STUDY 7 Early reporting of a trial showing benefit after accrual was completed**Trial**

BHAT (Beta-blocker Heart Attack Trial):¹⁰² This was a four-arm, double-blind, placebo-controlled trial conducted in the USA and sponsored by the National Heart, Lung and Blood Institute. The trial compared a β -blocker, propranolol, with placebo in patients with previous MI. The primary outcome measure was survival. Between June 1978 and October 1980 the trial recruited 3837 patients towards an unspecified target, with follow-up due until a common date of June 1982.

DMC role

The DMC (known as the [independent] policy and data monitoring board) received trial results semi-annually “during [the] trial for evidence of potential harm or early benefit of propranolol with the aim of terminating the study if the data so warranted”. The DMC had 14 members comprised of physicians, biostatisticians and an ethicist, of whom seven were full voting members.

Data

The DMC reviewed data during and after the accrual period.

Timing	Normalised log-rank statistic (mortality)
May 1979	1.68
October 1979	2.24
March 1980	2.37
October 1980	2.30
April 1981	2.34
October 1981	2.82 ^a

^a O'Brien and Fleming boundary would have been crossed here.

Considerations

At the October 1981 review the mortality was 9.5% (183 deaths) in the placebo group, and 7% (135) in the propranolol group, which would have met the stopping rule. “After a thorough evaluation of the issues ... the Board recommended that the BHAT be terminated and the results disseminated promptly.”

Consequences

The trial was terminated 9 months early because “(1) the two groups were considered comparable; (2) the patients complied reasonably well with the protocol; (3) no unanticipated side effects were observed; (4) the observed treatment benefit was judged significant and likely to remain so during the 9 months remaining in the trial; (5) little additional information would be gained from continued follow-up; (6) results were consistent over subgroups and by cause-specific mortality”.

Comments

“... the BHAT results were statistically ‘significant,’ and not likely to change during an additional 9 months of follow-up ...”. The results were “quite consistent with those of two other recently reported large-scale clinical trials ...”. Therefore, the DMC allowed the trials results to be disseminated earlier than expected.

- the impact of early stopping, including whether and how the results would influence clinical practice.

Thus, the decision of early stopping is partly subjective and is based on both statistical and non-statistical considerations.

Another statistical method used to guide decision-making by some DMCs involves the notion of conditional power, that is, the likelihood, given current interim data, that a beneficial effect of the treatment under consideration would be detected if the trial were to continue as planned. However, the wisdom of stopping a trial based on futility (low conditional power) is open to debate.⁵⁵

Although some extreme views question the wisdom of making public any stopping boundaries at the outset of the trial,⁵⁵ it is generally agreed that specification and publication of guidelines for early termination provide a necessary framework from which the DMC can make informed decisions. (Further discussion of the statistical issues relating to DMCs is presented in Appendix 1.)

Question 18: Should specific trial designs influence the proceedings?

Different trial designs will have an effect on the statistical monitoring procedure and the range of

CASE STUDY 8 DMC recommended continuation, aided by a stopping boundary; results changed over time**Trial**

CPCRA ddl/ddC trial.¹⁰³ This RCT was sponsored by Terry Bein Community Programs for Clinical Research on AIDS (CPCRA). It was a US-based RCT of dideoxyinosine (ddl) and dideoxycytidine (ddC) in AIDS patients who were intolerant to, or had failed, zidovudine. Neither treatment could be considered as standard. It was initially designed to check for major differences between the research arms. However, one of the treatments (ddl) was changed to being considered as the standard treatment by the DMC after the drug received a monotherapy licence from the FDA while the trial was ongoing. The primary outcome measure was first disease progression or death. Between December 1990 and September 1991 the trial recruited successfully to its 467 patient target (set so as to observe 243 primary outcome events).

DMC role

The DMC (known as the data and safety monitoring board [of the National Institute of Allergy and Infectious Diseases]) was to monitor "... randomised clinical trials in the context of life-threatening diseases ... on an ongoing basis If early data provide convincing evidence of a superior efficacy/safety profile for one of the treatment, then early trial termination would satisfy important ethical requirements and save valuable resource and time". The DMC was to monitor the trial using Lan and DeMets¹⁰⁴ implementation of O'Brien and Fleming's guidelines.¹⁰⁵

Data

Analysis	Date	Prg or death		Death		RR (Prg or death)	
		ddl	ddC	ddl	ddC		
Meeting 1	02 May 1991	Administrative meeting only, no data shown					
Meeting 2	29 Aug. 1991	19	39	6	12	2.1, $p = 0.009$	
Meeting 3	08 Nov. 1991	50	66	18	22	NA	
Meeting 4	13 Feb. 1992	77	91	28	34	NA	
Meeting 5	21 Aug. 1992	130	130	73	66	NA	
Final results	20 Sept. 1992	157	152	100	88	0.93 (95% CI 0.74 to 1.18)	

RR, relative risk; NA, not applicable.

Considerations

In each of the first four meetings the DMC recommended continuation of the trial. This was despite the interim results presented at the second meeting. "Aided by the conservative O'Brien–Fleming guideline [0.001] and by careful consideration of all available information, the [DMC] judged these early results to be inconclusive and recommended continuation of the trial." At the final meeting the DMC concluded that the trial should "end as planned on September 20, 1992, since the planned number of events (243) has been achieved".

Consequences

The DMC did not stop the trial in the early stages, despite the small p -value. "If the trial results from the August, 1991, interim analysis had been broadly disseminated, it is quite likely that widespread prejudgment about the superiority of ddl would have occurred, preventing continuation of the trial and eliminating the opportunity to obtain the much more reliable and strikingly different assessments about the relative efficacy"

Comments

The guidance of DMC was beneficial to the trial in preventing a premature end to the trial due to a random high. Indeed, eventually the trial results did not demonstrate a difference between the trial arms.

options open to the DMC. Some specific examples cited in the literature are listed below:

- New treatment versus established treatment or placebo: it has been suggested that "Asymmetric boundaries should be used, because one is only interested in establishing superiority of the experimental arm",²⁴ leading to "less stringent statistical criteria for negative trends".³⁴
- One treatment is more "toxic, invasive, protracted, or much more expensive": again, it is argued that asymmetric boundaries may be more appropriate.²⁴
- Outcome measures: care must be taken over early stopping owing to the doubts about non-proportionality of hazard rates of the outcome measures with increased data: "early experience with little follow-up may not be reflective of the complete survival curves".²⁴ Examples provided by Ellenberg and colleagues¹⁹ show that the focus of attention may depend on context: sometimes the interest is in short-term outcomes, such as after a myocardial infarction, and sometimes in long-term outcomes, such as in arthritis studies.¹⁹

- Equivalence studies: active control equivalence Studies require particular care, as poor compliance in such trials may lead to misleading claims of equivalence. It is suggested that a particularly high-quality 'blue-ribbon' DMC is required in this context.⁶⁰ "Monitoring for non-compliance or sloppiness is perhaps even more important in equivalence trials than in superiority [non-inferiority] trials."⁸
- Multiple arms: this has been discussed in the context of factorial studies⁷³ and multiple experimental arms that may be dropped in turn.¹⁰⁶
- Multiple outcomes: alternative trial designs and consideration by the DMC of composite measures may be appropriate.¹⁰⁷
- Cluster RCTs: "The broad issues ... also apply generally to cluster randomised trials. Efficacy monitoring in accordance with a predetermined plan, however, does not seem to be a common feature of most cluster randomisation trials. This is at least partly because the theoretical underpinnings of standard data-dependent stopping plans invariably assume individual randomisation, while methods applicable to cluster randomisation trials have yet to be widely adopted"¹⁰⁸

Question 19: How should ethical issues be handled in DMCs?

Ethical issues are at the heart of the DMC's existence and operations.^{41,55} However, the way in which these issues are handled should also reflect the perspectives of the trial investigators. "The DMC should therefore not approach the ethical problems solely from their own personal perspectives, but rather should try to envisage the attitude that the investigators would adopt if they were fully informed about the data."⁵⁵

Unlike ethics committees (LRECs and MRECs in the UK, or IRBs in North America), whose remit is aimed almost exclusively towards the protection of the interests of the trial participants (individual ethics), DMCs also have ethical responsibilities to future patients (collective ethics). However, most commentators agree that the DMC's primary responsibility is to protect the rights and safety of patients in the trial. "The fundamental charges to those responsible for trial monitoring should have the following prioritisation: a) to safeguard the interests of the study participant; b) to preserve the trial's integrity and credibility; and c) to facilitate the availability of timely as well as reliable findings to the broader clinical community."¹⁹

Ethical issues and interim monitoring

The degree to which individual ethics should override considerations of collective ethics continues to be a subject of debate. This varies between committees and is generally reflected in the DMC terms of reference and detailed monitoring plans (see question 3). Various elements of monitoring plans work in favour of one or the other of these two ethical perspectives. Thus, close monitoring of adverse events and guidelines that allow stopping of the trial on less conclusive evidence of harm than of benefit favours individual ethics, possibly at the expense of collective ethics. However, it is commonly argued that a decision to stop the trial should be taken as soon as there is sufficient evidence of a difference in efficacy between the randomised arms, so as to minimise the number of individuals who would otherwise be exposed to an inferior treatment. This can be argued in terms of either individual or collective ethics, but conservatism in the stopping rule would tend to favour collective ethics.

Armitage, in Parmar¹⁰⁹ argues that this view may be too simplistic:

"I don't think it's necessary to see this conflict between conservatism or radicalism in stopping as an issue of collective versus individual ethics. The collective/individual business is whether one regards the interest of the immediate individual patient as paramount or whether one thinks the general population's interest is paramount. You can take an individual ethics point of view and still be quite reluctant to stop merely because a particular difference is significant at a certain level. The reasons for that are that there are very many aspects to a clinical trial, rather than just the significance of one particular outcome variable, very many outcome variables, the future progress of the disease as well as the immediate situation, and so on. I think it's entirely consistent with the individual ethics point of view, for instance, as held by Bradford Hill, to say, 'Let's just hold our horses and see what's going to happen in the future', before we decide what is really in the interest of this individual patient."

Many authors have strongly emphasised the importance of taking into account the extent to which a trial's results will influence clinical opinion.^{8,24,34} This is made explicit in stopping guidelines for, say ISIS-4, which state that the trial should only stop if there is both proof of benefit beyond reasonable doubt and "evidence that might reasonably be expected to influence materially the patient management of the many clinicians who are already aware of the results of the other main trials".⁷³ Such a perspective

naturally leads to an ethical debate concerning the duty to future patients.⁴⁸ The overall view appears to be that DMCs certainly should be fully aware of the consequences of their deliberations and their duty to both the participants and future patients to ensure the trial's conclusions are as valuable as possible.

An extreme view that can be argued for in terms of individual ethics is to make the results of interim analyses publicly available to patients and investigators. However, most authors strongly recommend that interim findings should not be released, since such practice may undermine the integrity of the trial^{88,110} and prevent its completion.

Relationship between DMCs and IRBs

In the USA, IRBs are responsible for reviewing the trial protocol, patient information, informed consent and trial procedures from the perspective of safeguarding the interests of the trial participants. During the conduct of the trial, they receive reports of unexpected SAEs, but they do not review unblinded interim data. "The involvement of an IRB alone, without a DSMC [DMC], may be sufficient in a trial that involves a single institution, especially when a mechanism is established for the significant involvement of a subcommittee or a particular individual. Most local IRBs, however, lack the expertise to monitor multicenter trials or lack sufficient time for the intensive work required in such cases."¹³

Little is written on how IRBs relate to the DMC, and, in practice, there is usually no direct communication between IRBs and the DMC. However, some IRBs regularly receive interim DMC reports (as presented at open sessions) through the sponsor.

Question 20: What should DMCs do with their decisions or recommendations?

It is generally agreed that the recommendations or decisions should be transmitted efficiently, accurately and responsibly to the appropriate bodies (e.g. the sponsor, a steering committee or the investigators).^{13,32}

Who should the DMC report to?

Models where the DMC reports to the sponsors and to the investigators (in the form of a

representative committee, such as an executive or a steering committee) have both been used.³² However, if the DMC is advisory (rather than executive) then to ensure that conflicts of interest do not dominate, it has been suggested that the DMC should report to the sponsor and trial investigators simultaneously.²⁹ In the lead-up to a final decision there would be a discussion including both the investigators and sponsors, or their representatives. One model is that it is the sponsor who takes the final decision, because the legal obligation for safety of the participants falls to them.¹¹ Another is that it is a joint decision through a formal committee containing both the sponsor and investigators which is formed to receive such reports.¹¹³

It has been suggested that relevant regulatory authorities and appropriate ethics committees should be kept informed of progress of a trial, but that such authorities should not be involved in any decision for early termination.^{8,38}

Should the DMC be advisory or executive?

Most authors propose that the DMC should be advisory rather than executive, especially as the trial is not organised and coordinated by the DMC.^{48,73} (For further discussion, see question 14.)

What form should the report take?

It is generally agreed that unless there are concerns about the conduct of the trial, a carefully worded, brief, written statement from the DMC chair about the importance of continuing the trial, avoiding any indication of evolving treatment differences, provides the best communication.^{31,45} This may be supplemented by oral communication to the PI.⁵⁴

If the DMC is advisory, any report recommending a change or amendment to the trial should contain sufficient information for the investigators and sponsors to consider the basis for the recommendation for themselves. In contrast, if the DMC is executive, then the data supporting any recommended change may best not be released. This is because there may be advantages for the closing stages of the trial to be conducted without knowledge of what the outcome of the interim analyses had been, beyond that the plan for the trial has been changed.²²

The DMC should also feel free to formally comment on other 'open' aspects of the trial, such as recruitment and data quality, in its report.

CASE STUDY 9 DMC not following guidance of a stopping rule**Trial**

This was an RCT in pressure sore prevention¹¹¹ sponsored by Northern & Yorkshire Regional Research Committee. The trial, run in the UK, followed a double triangular sequential design.¹¹² Between 1994 and 1996 patients hospitalised for surgery were randomised between a standard mattress and a gel bed during their operation. The trial recruited 446 patients. No recruitment target was reported, owing to the sequential design, but it is stated that a fixed sample size design would have required 1085 patients.

DMC role

The DMC (known as the data monitoring committee) was “to oversee the monitoring of the trial”. The analyses were planned at approximately 200 patients then every 100 patients (at 6 months, then 3 monthly). The DMC was comprised of “a statistician, a representative of the NHS purchasing organisation who was also a member of the funding committee, and a nurse researcher”. The member of the funding committee was present because the funding committee was uneasy about the flexible nature of the sample size.

Data

The data shown to the DMC was as follows:

Analysis	Date	Accrual	Variance	Z-value	Comment
Interim analysis 1	27 June 1995	181	6.6	7.6	Outside boundary
Interim analysis 2	22 Jan. 1996	293	8.1	6.7	Inside boundary
Interim analysis 3	30 May 1996	399	11.6	9.9	Outside boundary
Final analysis	05 June 1996	446	12.9	10.2	Outside boundary

Considerations

At the first interim analyses the DMC recommended continuation of the trial despite the statistic being outside the stopping boundary. “Contrary to initial beliefs of the trial investigators and the data monitoring committee when designing the study, members felt there was an overwhelming need for a larger definitive trial ...” plus there were additional concerns over the end-point’s subjectivity and differences in pressure sore rate between participating centres.

Indeed, by the second interim analysis the sore rate had dropped and the statistic was back inside the boundary. Continuation was recommended. By the third interim analysis there was judged to be a sufficiently large number of patients. “The DMC decided that patient randomisation should be suspended and the data for all patients should be analysed.”

Consequences

The trial was therefore stopped after 446 patients had been randomised when the result was judged to be clear. The final results were consistent with this interim result.

Comments

The DMC guided the trial past the stopping rule to enable the trial to become sufficiently large to be more convincing to the clinical community. In addition, the sequential design was shown to be practicable.

Are minutes of the meetings or notes of decisions made? If so, by whom and how detailed?

There is almost unanimous agreement that formal minutes of both open and closed sessions of the DMC are important for both documenting decisions and actions, and also for documenting the major points in discussion, reasons for decisions and information required for the next meeting.⁷⁰ Packer and colleagues provide a useful checklist suggesting that any minutes should at least follow minimal principles.³² The checklist is adapted here.

- Who attended the meeting and was the meeting quorate? (Note that no definitions for a quorate DMC were found in the included articles.)
- Who knew what and when? It is important to know, for example, whether any changes to the trial are being recommended in light of, or blind to, the current results.
- The records should include copies of all analyses that have been used to support the committee’s decisions; and also include all material reviewed by the DMC. In particular, clear documentation of the events leading to a recommendation by the DMC may be critical to the acceptance of the recommendations.
- A general sense of the DMC’s discussions, along with careful discussion of its decisions, should be documented. There should be limited attribution of statements to specific individuals, but if a DMC member has a specific expertise or a unique view the minutes should reflect this contribution.

- The DMC should make the minutes of any open session available to the trial leadership as soon as possible, whereas the minutes from the closed session should be kept archived until the end of the trial.

It should be remembered that any documents prepared for or by the DMC may be scrutinised subsequently by relevant interested parties.

The drafting of any minutes can involve a considerable amount of work, and the individual(s) appointed for this task should be identified at the time the DMC is formed. To ensure that a single individual is not overburdened, it is helpful if the minute-drafters are not heavily involved in the detailed deliberations of the DMC, and thus it has been suggested that members of the statistical coordinating centre fulfil this role, with the members of the DMC commenting on and signing off the minutes of the meeting.⁷⁰ However, if the statistical coordinating centre is not party to all discussions, for example closed/executive sessions, then other models will have to be adopted, perhaps with a member of the statistical centre minuting those sections of the meeting that they attend (see question 8) and a member of the DMC (such as the chair or an appointed executive secretary) being responsible for the minutes of the other sessions. This may be a considerable burden for these individuals, and thought should be given as to whether it is feasible; it may be appropriate to provide some support for this activity.⁵⁴ Sometimes it may be feasible to tape meetings,⁵⁴ although it is not easy to access these records if needed later.

Whichever model is adopted, it is important that the approach to minute-taking and individuals involved should be specified at the start of the trial. Further, all individuals involved should know and agree with the role set out for them.

Question 21: What should be done in 'difficult' situations?

Although the DMC will have a set of regular prespecified meetings, there needs to be an option for the DMC to meet at relatively short notice, for example if information emerges from other trials.¹⁶ Those outside the DMC can review external information as well as the DMC, but only the DMC can assess the external information in the light of the information from the trial. In these situations the DMC may need to provide more detailed comments on the issues raised.⁸⁸

There may sometimes be considerable external pressure on a DMC, usually to stop a trial. One may envisage occasions in which a sponsor may pressure DMC members to reveal interim results. In these and similar situations, an independent DMC is important. Hampton⁴⁷ insists that, in connection with drug company sponsorship, the DMC should be comprised of "strong individuals who insist on meeting regularly and who will not bow to company pressures". He goes on to state that "only a strong [DMC] can protect [the sponsor from stock market forces] by allowing them honestly to claim that they do not know trial results".

It has been suggested that information regarding the DMC members should remain confidential during the trial.⁵² Although this may be helpful when there is external pressure, this approach may be counterproductive in most circumstances. Also, in many cases, it is the sponsor that nominates DMC members (see question 6) and this approach would have to be reconsidered if the DMC members were to be unknown to the sponsor. Subtle pressures from sponsors during meetings can be relieved by the use of closed sessions (see question 8).

Pressure may also arise from the media. For example, Packer and colleagues³² describe "a particularly troublesome example, [where] members of the press frequented the venue of [DMC] meetings of the Global Utilisation of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-1) trial¹¹⁴ in an attempt to acquire some preview of the results of the study". The sensationalism surrounding the trial led to DMC members and their families being at risk of harassment and intrusive public scrutiny. Conflict may arise with the steering committee on occasion if a DMC recommendation is not followed. Further details of such circumstances are given in question 22.

Indeed, circumstances can be made more difficult if disagreements are made public. For example, Packer and colleagues³² describe the Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited to Very Unstable Signs and Symptoms (PRISM-PLUS) trial.¹¹⁵ The DMC recommended stopping one of the three study arms when it observed a high relative risk of death among individuals in one of the treated groups. Despite agreement from the sponsor, the PI disagreed and publicly expressed the opinion that the arm in question had been stopped inappropriately.

Question 22: Should some DMC decisions be considered to be ‘errors’?

“If a trial is erroneously stopped early, the reputation of a promising new treatment may forever be tarnished. If a premature claim of treatment superiority is not subsequently accepted as convincing, then another trial may be required. Even worse, no further trials may be done, leaving a potentially valuable treatment in limbo. However, a [DMC] cannot wait until trends become so convincing that no-one would ever challenge them.”³⁴ It is clear that decisions are generally difficult to make and there are rarely second chances to make or even reverse a decision. It is further recognised that “less experienced [DMC]s may sometimes overreact to favourable as well as unfavourable data trends”.⁵⁴

“Legitimate differences of opinion can and often do occur regarding the interpretation of trial data [amongst DMC members], and the criteria that should be used to approve, alter, or terminate a study sometimes require considerable discussion.”¹³ But differences of opinion need not be problematic providing there is adequate group discussion and that the DMC reaches a considered conclusion.

It is difficult to judge whether DMCs have made good or poor decisions, since these decisions are, by their nature, subjective. Determining whether a DMC’s recommendation was erroneous may be possible in hindsight in some situations by comparing later (final, published) data with the data presented to the DMC. For example, the Physician’s Health Study¹¹⁶ was stopped by the DMC with a relative risk reduction for myocardial infarction of 45%. The final, clean data demonstrated a 30% relative risk reduction; this is still a substantial improvement, but not quite of the same magnitude.

The DMC may be considered to have made an erroneous recommendation if, as a result:^{12,34,89}

- the trial is stopped early for a benefit which subsequently disappears
- the trial is stopped early for a benefit which subsequently diminishes so that the results are not sufficiently compelling to the regulatory or licensing bodies or to the clinical community
- the trial continues in an attempt to demonstrate a potential benefit despite a serious toxicity trend; if the benefit does not materialise,

further patients would have been exposed to a serious risk of harm.

Yusuf¹¹ suggested systematic documentation of every controversial decision, and suggests that when there are difficulties, all the criteria for the decisions, together with the names of the members of the DMC, should be published. However, such an approach may be counterproductive in the long term, as it may deter individuals from joining DMCs.

DMCs generally make recommendations rather than decisions (see question 14). In these circumstances, the body to which the DMC reports (see question 20) would make decisions based on the DMC recommendations. It is theoretically possible then that erroneous decisions may be made by the decision-making body despite non-erroneous recommendations from the DMC. But are DMC recommendations ever overruled? Not very often, it would seem (although see *Case Study 10* for an example). George⁴³ reported a survey of North American cooperative trials groups and only one of 11 responding groups knew of any trial where a DMC’s decision to terminate or modify a trial had been overruled. The DMC is usually in a unique position with regard to data: anyone who challenges their recommendations would, at least initially, have to do so without being privy to the interim data. Indeed, if the trial steering committee (TSC) or sponsor disagrees with the committee then “In the absence of ethical issues the sponsor might freely override a [DMC] decision for early termination”.⁵² Where the investigators do not choose to follow the course of action suggested by the DMC it can lead to a great deal of friction, and sometimes the resignation of DMC members.^{19,80} It has been suggested that “a [DMC] charter should contain an ‘escalation clause’ for resolving differences of opinion”.³²

If the TSC, sponsor or coordinators were seriously concerned about a recommendation of the DMC they could instead “convene another committee”.¹¹⁹ For example, Packer and colleagues³² suggest that “an ad-hoc Executive Committee with an odd number of participants should be charged with resolving the dispute. In recent industry-sponsored trials, the Executive Committee has consisted of two sponsor representatives, two Steering Committee representatives, and an independent third party agreed by both groups”. Such independent resolution is helpful and can prevent conflicts escalating. A more general approach for

CASE STUDY 10 *DMC's recommendation to continue a trial overruled by the steering committee*

Trial

Department of Veteran's Affairs Cooperative Study of Steroid Therapy for Systemic Sepsis¹¹⁷

This was a US based, double-blind, randomised, placebo-controlled, trial that was sponsored by the Department of Veterans Affairs. Patients with systemic sepsis were randomised between steroids and placebo. The primary outcome measure was mortality. Between 1983 and 1986 the trial recruited 223 patients towards a 276 patient target.

DMC role

The DMC (known as the data monitoring board) was to monitor the progress of the study annually. It was formed from "outside experts not involved in the conduct of the study". For monitoring purposes, the DMC accepted the recommended closed sequential plan based on Armitage.¹¹⁸

Data

The DMC met twice. No efficacy data were presented at the first meeting. At the second meeting in 1985 the sequential boundary of no difference in mortality between the two treatment groups was reached for all patients. Contrasting with this, "a 75% reduction in mortality with steroid therapy was observed in the small subgroup of 51 patients with gram-negative bacteremia".

Considerations

At the first meeting "71 patients had been enrolled and of these 60% had gram-negative sepsis and only 23% had gram-negative septicemia. Therefore, the [DMC] recommended that the study be modified to assess the effect of therapy in all patients with sepsis and in those with gram-negative infections. The [DMC] made this decision without knowledge of the observed effect of treatment." At the second meeting the DMC again "recommended that the trial be continued to evaluate the emerging trend".

Consequences

Contrary to the DMC's recommendations the trial was halted by the responsible committee: "... at the scheduled midpoint review of the trial by the Cooperative Studies Evaluation Committee [CSEC], the Committee opted to terminate the trial because steroid therapy did not reduce mortality in all patients with sepsis. The CSEC also viewed the gram-negative trend as more apparent than real because it was based on a total of only 8 deaths ...".

The DMC was not invited to the CSEC meeting at which study representatives had presented the accumulating data to the CSEC. The DMC appealed and met with the CSEC. To prevent an escalation of the conflict between the two committees, two anonymous independent reviewers passed verdict and agreed with the CSEC that the trial should close because the stated objective had been met.

Comments

The DMC recommendation was overruled because the clinicians were sufficiently convinced by the data. It is unclear why the clinicians and CSEC were reviewing trial data at this stage. Independent adjudication was used to resolve the conflict.

implementing the model suggested by Packer is for the DMC to routinely report to a committee with a degree of independence (see question 7). In practice such independent resolution has produced conclusions both supporting and contradicting the original DMC position.

According to some commentators DMC recommendations are less likely to be interpreted as contentious (and, therefore, less likely to be overruled) if some of the trial staff are present at the meeting. This way the "advice or recommendation takes into account the concerns of the people who have to accept the advice ...". This is a "consensus building process rather than a totally independent decision".¹²⁰ This consensus decreases tension between groups and allows them to reach the best possible decision. "It may be that completion of data collection reveals that the stopping criteria had not been reached.

Sometimes, re-opening the trial may be an option. More usually it will be too late."²²

Practically, the sponsor may be less likely to overturn a recommendation to stop the trial rather than one to continue: a recommendation of continuation is subject to further administrative considerations by the steering committee or sponsor; for example, if the DMC recommends continuation based on clinical data, the sponsor may choose to stop the trial because of practical issues such as accrual rates or funding (see question 13).

The participating clinicians may also effectively overturn a recommendation by the DMC to continue by refusing to randomise further patients into the trial. This is only likely if, for some reason, unblinded interim data had been released to the participants. This has been a more common occurrence in the past⁸⁹ (see *Case Study 1*).

So, who is liable for the recommendations?
According to Herson,⁶⁰

“In terms of liability insurance coverage, [DMC] members lie in a ‘no man’s land’ between the sponsor’s liability insurance and the liability insurance from the institutions/firms where the [DMC] members are employed. It is doubtful that [DMC] members could be protected by the insurance policies at their home institutions for these extramural activities, but sponsors are reluctant to include [DMC] members on their policies because it could compromise the independence of these boards. At the moment [1993], this issue is being avoided through ‘hold harmless’ clauses in the agreements between sponsors and [DMC] members. [DMC] members are, however, not protected from direct lawsuits from patients and their families. ... more work must be done in this area if pharmaceutical firms expect qualified people to serve on their [DMC]s.”

As serving on DMCs is largely a voluntary activity, this approach could lead to large numbers of individuals refusing to accept invitations to sit on DMCs. Indeed, Meier in Yusuf had disagreed on the DMC’s liability: “It is the people who are responsible for the trial who ultimately will make the decision” and it is they who are legally responsible.¹¹

Question 23: What should the DMC’s role be concerning publications?

Few authors have addressed the question of the DMC’s role concerning publication of the trial results (32 quotes from 19 sources).

The DMC should have developed a deep understanding of the data from several discussions over a period of time, and will generally have had more time to think about the results than the investigators.⁵⁴ As noted under question 3, a meeting at the end of the trial offers a valuable opportunity for members of the DMC to share their thoughts with the investigators (and/or sponsor, as appropriate). The data may have changed since they were last seen by the DMC, especially if recruitment was terminated with many enrolled patients still waiting for outcome assessment. Such discussions would naturally focus on the interpretation of the data and thus may lead to some input into the development of a manuscript for publication. However, members of a DMC should not be co-authors of the primary trial publications, which would conflict with their independent status.¹⁹ Involvement of the DMC in

post-trial discussions would help to avoid the rare situation of DMC members publicising their disagreement with the published interpretation.⁵⁴

Several authors have commented on the ethical principle that the results of the trial should be published whatever they are.^{41,54,92} Some have suggested that ensuring publication is one role of the DMC.⁵⁴ Further, Pocock and Furberg⁵⁴ suggested that as “the conscience of the trial, the [DMC] should assume the responsibility for publication of trial results if the trial mechanism fails”.⁵⁴ It is unclear whether and how this could be achieved in practice. In the UK MRC model, this role is assumed by the steering committee.⁵⁹ A minority view is that the DMC should decide when the trial results should be published,³⁵ although in effect the DMC may make this decision during the course of the trial if and when they recommend that the trial stops recruiting.

Regardless of the involvement of the DMC in developing the manuscript, a particular issue is the way in which the activities of the DMC are described in the publication.¹⁷ As well as mentioning that there was a DMC (and naming the individuals), it is desirable that the publication includes a summary of the process of data monitoring³⁹ (Chapters 4 and 5 present more detailed surveys on this issue). The DMC should approve the wording of such text, and should have the opportunity to ensure that their views “are not misrepresented to the public”.⁵⁴ More generally, some authors suggest that the DMC should review the whole manuscript,^{16,54} to “ensure that publication is ... unbiased and correct”.¹²¹

Subsequent literature

Important publications appeared after the formal interactive searches had been undertaken for this systematic review. A recent book¹⁹ on DMCs covers a wide range of issues illustrated by numerous examples, and in particular sets out the need for a charter to describe the roles and responsibilities of a DMC. An issue of *Controlled Clinical Trials* in February 2003 featured a number of case studies and commentaries on DMCs. These included a number of ‘difficult decisions’ (see question 21). First, where a DMC was unable to reach a decision and an NCI committee stepped in to recommend stopping the trial;¹²² second, where a DMC wanted to continue but was overruled by a sponsor who stopped the trial;¹²³ and third, where there was a large commercial impact of stopping a trial:¹²⁴ “With the benefit of hindsight, there are

certain organizational and procedural issues that would have been better to resolve early on, such as rules regarding absentee voting in the [DMC], to which body the [DMC] should report officially, which body had the power to accept or reject the [DMC]'s recommendation, and the timing and general content of dissemination of different kinds of results." With increased use of DMCs in industry trials, it is vital that a DMC charter should address such issues before the trial commences.

A final example concerns the dangers of stopping early following an early positive finding that eventually evaporated:¹²⁵ "It is important that [DMC]s hold their nerve and consider all aspects thoroughly and, if they do not consider the interim analysis provides 'proof beyond reasonable doubt', then they should recommend that the trial continue."

Conclusions

This chapter provided a summary of the published literature on many aspects of DMCs that serve RCTs. The systematic review was, by nature, a systematic collection of data pertaining to DMCs. The a priori formulation of 23 key questions (and associated subquestions) provided a valuable framework around which to extract data, and synthesise summaries of the key topics. This methodology was useful and is recommended to others undertaking similar reviews. The structuring allowed information to be assimilated on many aspects of DMCs. It demonstrated a paucity of writing, and perhaps therefore of thought, in many of these areas.

Chapter 3

Review of small group processes relevant to data monitoring committees

Introduction

Background

The decision that a DMC reaches can have major implications for the trial participants and for current and future patients, as well as for the researchers and sponsors of the trial. Hence, the quality of the decision reached by a DMC is crucial. Concern has been raised in the literature that a DMC may make a 'mistaken' decision because of the ways in which the decision is reached, rather than any deficit in formal terms of reference.

Decision-making can be a complex process and is considered to be one of the most important tasks undertaken by groups. However, groups do not always make 'good' decisions and the current literature is not conclusive on how best to improve performance. Most of what we do know is based on studies within cognitive, social and organisational psychology, sociology and management sciences.

Aim

The aim of this chapter is to review systematically the social scientific literature to achieve three objectives:

- to identify factors that make errors more or less likely in small (less than 20 members), task-orientated, decision-making groups
- to consider the implications of these factors for data monitoring committees
- to make recommendations for the construction and process of future DMCs and to identify areas in which further work is needed.

Methods

Scope of material used

The empirical literature on small group processes is extensive and has been regularly reviewed.^{126,127} The aim of this review was to identify factors that make errors more or less likely in small decision-making groups (similar to DMCs), and

not to review systematically all of the literature on small group processes. To ensure that the factors we identified were based on robust evidence, the literature search focused primarily on high-quality reviews of empirical studies. This had implications for the search and ascertainment of the literature, and the final inclusion criteria were reached in an iterative manner as the search progressed.

The review drew on a similar body of psychological literature to that which informed an issue of *Health Technology Assessment*¹²⁸ on the use of consensus methods in the development of clinical guidelines. Using comparable methods a search strategy was developed to include issues that were not addressed in that report or that were of specific relevance to DMCs.

Selection of databases

It was initially decided to search 12 relevant bibliographic databases. However, a pilot search found that ABI Inform, IBSS and Westlaw (databases covering business and law studies) did not yield sufficient numbers of relevant articles.

Details of the nine electronic databases that were searched and the periods covered are summarised in Appendix 5. A full description of the keywords and terms searched is presented in Appendix 6.

Other methods of identifying articles

As each section of this review chapter was written, further relevant articles were found by reviewing the bibliographies of included articles and from the personal knowledge of the authors and external advisors.

The study excluded reviews of group dynamics or group processes in small groups other than task-orientated, decision-making groups (e.g. psychotherapy groups, focus groups), animal studies and reviews published in languages other than English (owing to time and translation restrictions).

Search strategy

The review strategy focused primarily on:

- reviews of empirical studies of small group processes and decision errors in small, task-orientated decision-making groups in laboratory settings, published between 1950 and 2001
- reviews of empirical studies of small group processes and decision errors in naturally occurring groups (e.g. juries, committees), published between 1950 and 2001.

A secondary search of the same databases was undertaken to identify any key empirical papers in areas not covered by reviews or that may have been published too recently to be included in reviews. This search aimed to identify empirical studies of the relationship between group processes and decision-making in small, task-orientated groups in laboratory settings, published between 1990 and 2001, and empirical studies of group processes and decision-making in naturally occurring groups (e.g. juries, committees), published between 1990 and 2001.

A total of 3194 review articles was identified. The abstracts of all of these articles were obtained and assessed by two reviewers as ‘possibly relevant’, ‘uncertain’ and ‘not relevant’. In total, 57 review articles were assessed as relevant and included in the review (see Appendix 7). Only four of these were included in the review undertaken by Murphy and colleagues.¹²⁸

A total of 1277 ‘possible relevant’ empirical abstracts was identified, of which 224 reported findings of interest. The majority of these studies reported material that had already been included in reviews. After further assessment, none of these articles was considered to be of good quality, or relevant to DMCs and therefore not included (Figure 2).

Handling of references

A total of 3194 review article references was retrieved electronically from the electronic databases, and downloaded into the bibliographic software, Reference Manager (Reference Manager 9.5N; ISI ResearchSoft, Carlsbad, CA, USA).

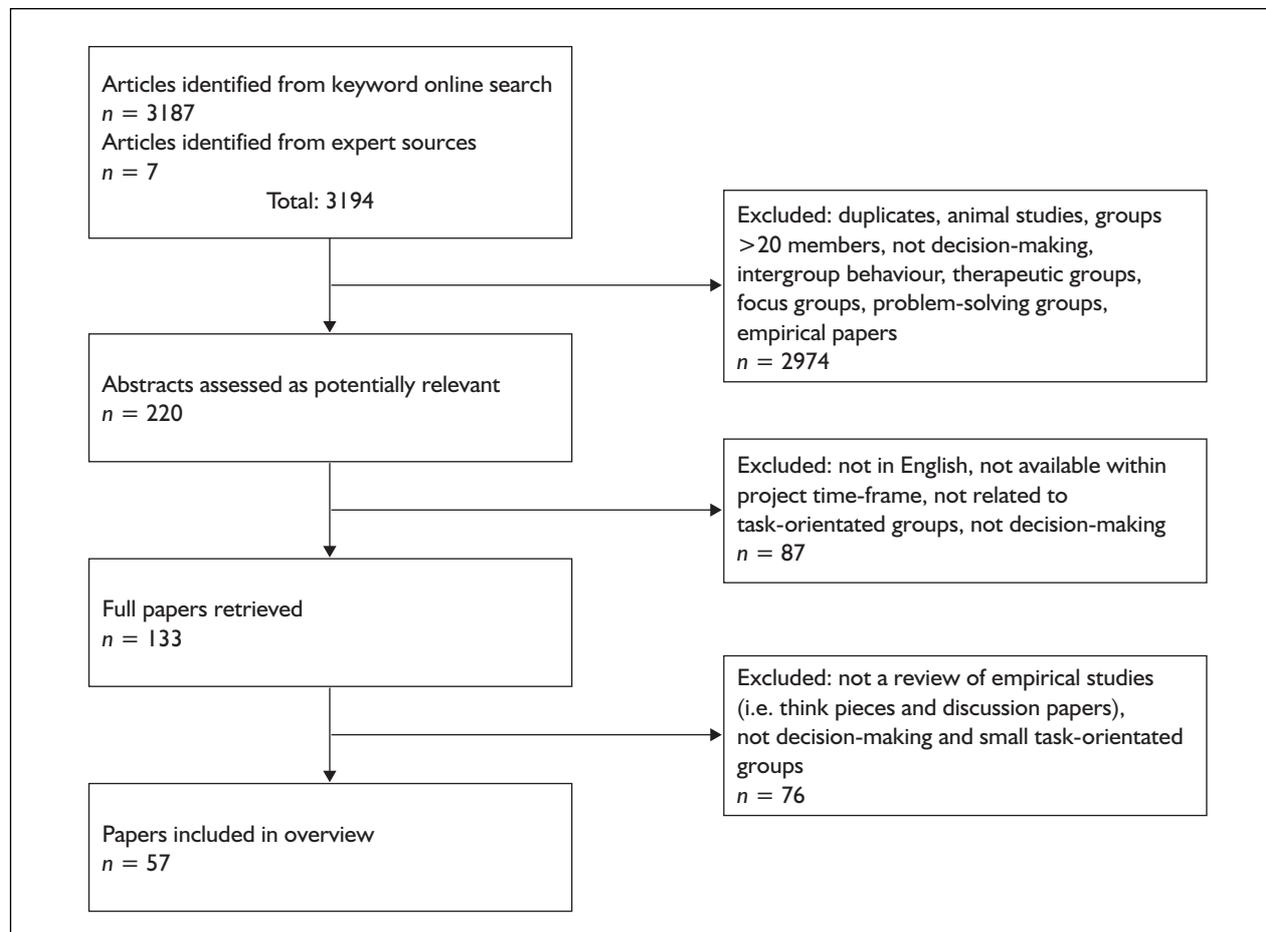


FIGURE 2 Exclusions at each stage of the small group processes review

Assessment of references

After downloading into Reference Manager, an initial screening of references was undertaken by one researcher. Titles, keywords and abstracts of all references were assessed and classified into 'possibly relevant', 'uncertain' or 'not relevant'. Thereafter, two researchers fully assessed all the abstracts to ensure consistency and agreement of categorisation.

For all the 133 'possibly relevant' references, copies of the original articles were sought so they could be read in full. Some articles were unavailable within the time-frame of the project, and owing to the cost of interlibrary loans, some articles were not requested if the abstract indicated that it would provide, at best, low-level evidence about a topic already covered. On this basis it was also decided to exclude one non-English article as translation would have been costly. Therefore, seven 'possibly relevant' articles were not obtained.

Of the remaining 126 'possibly relevant' reviews, each full article was initially assessed for its relevance by one reviewer. Some articles, despite having promising titles and abstracts, turned out to be of poor content and/or quality and were disregarded as irrelevant. Both reviewers read and assessed any articles that were 'uncertain'. This procedure ensured that no 'possibly relevant' articles were disregarded without double-checking. Samples of 'not relevant' reviews were checked by a second reviewer to ensure that no 'possibly relevant' article was disregarded. In addition, certain articles thought to be particularly important were tagged 'key article'. A total of 57 reviews was finally agreed for inclusion in the review (see Appendix 8).

Each full article accepted for inclusion in the review was fully assessed by two reviewers and the relevant information extracted onto a data extraction form (see Appendix 9); this summarised the research question, type of review, methodology, decision-making activities, and structural and psychological processes.

Synthesis

The synthesis strategy for structuring the review was guided by a heuristic input–process–output model of small group behaviour and decision-making, as shown in *Figure 3*. This was not an exhaustive model, but provided a useful structure of the key variables emerging from the literature. Once specific group processes had been identified, the extracted data were coded and analysed using NVivo, a qualitative software package, to assist with analysis. Two reviewers assessed the coded extracts to ensure that all relevant data were appropriately and consistently coded. Following this, extracts were imported to NVivo software, where each data set was coded. Coded data sets were then subjected to a process of critical, iterative analysis by two reviewers, in which an interpretation was evaluated against the data and discarded or modified until a consistent interpretation was reached.

Results: error and bias in decision-making

Overview of the literature

Small groups can be involved in a wide range of decision-making tasks, and evidence indicates that both the process of decision-making and its outcome are influenced by the type of task a

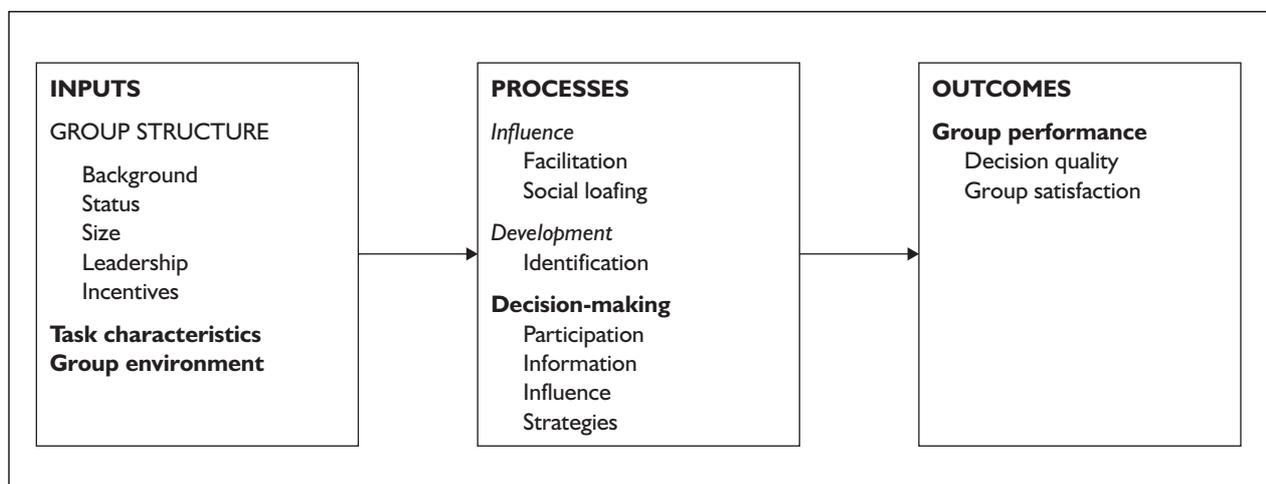


FIGURE 3 A heuristic input–process–output model of small group decision-making¹²⁹

group is working on.¹²⁷ The majority of the literature on small groups is concerned with four types of decision-making task. These are generating plans, solving problems with correct answers (intellective tasks or problem-solving tasks), deciding issues with no right answers (judgemental tasks or choice-dilemma tasks) and resolving conflicts of viewpoint.¹³⁰ Perhaps unsurprisingly, the largest body of research is concerned with experimental studies of artificially created groups (usually comprised of students) engaged in intellective tasks. A DMC can be considered a small group of individuals with varying expertise charged with the task of considering the interim data from a trial and deciding whether or not it should continue. This is a task that does not have a demonstrably correct answer, but which requires consideration of evidence, assessment of risk and the achievement of a consensus view to make a group decision. In McGrath's schema, it equates most closely to a judgemental or choice-dilemma task.

To identify factors that may influence the quality of the decision made by a DMC, this chapter will give greatest weight to findings from studies of groups engaged in judgemental and choice-dilemma tasks. In particular, studies of real-life groups, such as juries or political decision-making groups, will be considered. Evidence from studies of groups engaged in other types of decision-making task will be considered, but accorded less weight in making recommendations for DMC procedures.

Error and bias in small group decision-making

The key concern for this review is identification of factors that make errors in decision-making more likely. How have decision errors been defined in the literature on small groups? Jones and Roelofsma¹³¹ draw on Reason's¹³² definition of error to make a clear distinction between errors and biases in small group (or team) decision-making. They propose that a decision error refers to 'those occasions when the team's decision-making activities fail to achieve its intended outcome'.¹³¹ From this perspective, a DMC decision would be considered to be an error either if current trial participants were exposed to harm from the experimental drug or procedure, or if future patients were unable to benefit from it.

A decision bias is defined as "a team decision-making behaviour that deviates from what

normative decision-making models imply".¹³¹ Normative decision-making models (e.g. Subjectively Expected Utility theory)¹³³ allow a mathematical calculation of the 'correct' decision for an individual (or group) based on a knowledge of their pre-existing values (or utilities) and the likelihood that particular choices will satisfy these preferences. A bias is said to occur when the decision reached in reality differs from that which should be reached according to the theory. Several common biases have been identified in group decision-making.¹³⁴ A bias may not necessarily result in the failure to achieve an intended outcome; hence it is not in itself an error, but it may be responsible for one.

Measuring error and bias in small group decision-making research

The majority of research on errors and biases in decision-making is concerned with intellective (or problem-solving) tasks, in which small groups are asked to reach a decision about the solution to a problem with a known answer. A typical example is the horse-trading task.¹³⁵ In this task, groups are told that a man has bought a horse for \$60 and sold it for \$70. Then he bought it back for \$80 and again sold it for \$90. They are then asked to decide how much money the man made in the horse-trading business (\$20). Typically, experimental studies systematically investigate the effect of structural factors, leadership style, and so on, on the proportion of occasions on which groups solve these types of problem correctly. In addition, some studies consider the impact of manipulated variables on features of the decision-making process using these tasks, for example, the time taken to reach a decision or the number of alternative solutions considered.

Errors and biases are more difficult to quantify in studies of judgemental tasks or dilemmas. In these studies, four broad approaches can be identified: assessment of the process of decision-making, comparison of group decisions with aggregated individual decisions, post hoc assessment of the decision by the group members, and post hoc assessment of the decision by 'expert' panels or public opinion.¹³⁶

Errors and biases in the process of decision-making are usually assessed by reference to the classical assumption that decision-making should proceed through a series of stages.^{137,138} The detailed description of these stages varies between authors, but there are generally assumed to be three or four basic stages. In the simplest version,

the three stages are described as problem identification, alternative generation, and evaluation and choice.¹²⁷ Matsatsinis and Samaras¹³⁹ describe four stages of initialisation, preference elicitation, group preference aggregation and conflict resolution. In the initialisation stage, the group's objectives are established and decision alternatives are determined. Individuals then state their preferences on the decision alternatives. In the third stage, some sort of synthesising mechanism (formal or informal) is used to reach a tentative collective decision. Finally, in the conflict-resolution stage, this collective decision is evaluated and an effort is made to reach consensus or reduce the degree of conflict between opinions, through information exchange or problem reconsideration. The preferred and rejected alternatives are re-examined and a final decision is reached. From this perspective, the quality of the output that a group produces is influenced predominantly by the extent to which all of these stages are successfully achieved. A group may make a poor decision because it failed to conceptualise the problem properly, because it failed to identify or consider all of the decision alternatives, because it failed to synthesise all of the preferences into a collective decision, or because it failed to consider the implications of the initial decision or re-examine the alternatives. The most complete summary of potential defects in the decision-making process is found in Irving Janis's work on real-life decision fiascos (see next section). Janis identified seven symptoms of a defective decision-making process in judgemental-type tasks: incomplete survey of alternatives, incomplete survey of objectives, failure to re-examine preferred choice, failure to re-examine rejected alternatives, poor information search, selective bias in processing information, and failure to develop contingency plans. The existence of one or more of these symptoms is assumed to increase the likelihood that a decision will fail to achieve the objective that the group intended.

It is rare that an opportunity emerges to determine the 'correct' verdict in actual jury trials. For this reason, field studies of actual juries usually focus on procedural criteria that should theoretically be related to the accuracy of the verdict. These include: thorough review of the facts in evidence, accurate jury-level comprehension of the judge's instructions, active participation by all jurors, resolution of differences through discussion, and systematic matching of case facts to the criteria for various

verdict options.¹⁴⁰ The absence of any of these characteristics is assumed to increase the likelihood of an inaccurate or erroneous decision.

Results: factors associated with error or bias in decision-making on judgemental tasks

This section will consider evidence relating to factors that may influence the quality of the decision made by a DMC. A high-quality decision is one in which all of the stages of decision-making have been satisfied (see previous section), and the chance of error or bias is low. A poor quality decision is one in which one or more of the stages has not been successfully achieved, or one which shows symptoms of defective decision-making as defined by Janis (see above). As noted earlier, greatest weight will be given to findings from studies of groups engaged in judgemental and choice-dilemma tasks. In particular, studies of real-life groups, such as juries or political decision-making groups, will be considered. Evidence from studies of groups engaged in other types of decision-making tasks will be considered, but accorded less weight in making recommendations for DMC procedures. To reflect this weighting, this section will consider experimental studies of choice-dilemma tasks, studies of decision fiascos and jury decision-making, before summarising findings from studies in other areas of decision-making.

Experimental studies of choice-dilemma tasks

Choice shift and group polarisation

Stoner first described the phenomenon of group polarisation in 1961. He observed that people were more willing to advocate risky courses of action after taking part in a group discussion, and referred to this effect as the risky shift.¹⁴¹⁻¹⁴⁵ For example, on average, individuals may decide that someone should have heart surgery if the chances of an adverse outcome are 1 in 10. After group discussion the same individuals may decide that the operation should go ahead if the chance of an adverse outcome is 2 in 10. Subsequent research, largely in experimental settings using a series of 12 standard dilemmas known as the Choice-Dilemma Questionnaire (*Box 6*), has demonstrated that groups do not always shift towards risk. In some studies, groups were seen to shift towards caution. In other words, the phenomenon is one of a choice shift, and not necessarily a risky shift. The term group polarisation arose from the

BOX 6 An item from the Choice-Dilemma Questionnaire, developed by Kogan and Wallach (1964)¹⁴⁶

Mr B, a 45-year-old accountant, has recently been informed by his doctor that he has developed a serious heart ailment. The disease would be sufficiently serious to force Mr B to change many of his strongest life habits – reducing his workload, drastically changing his diet, giving up favourite leisure-time pursuits. The physician suggests that a delicate medical operation could be attempted which, if successful, would completely relieve the heart condition. But its success could not be assured, and in fact the operation might prove fatal.

Imagine that you are advising Mr B. Listed below are several probabilities or odds that the operation will be successful. Please check the lowest probability that you would consider acceptable for the operation to be performed.

- Place a check here if you think Mr B should not have the operation no matter what the probabilities.
- The chances are 9 in 10 that the operation will be a success
- The chances are 7 in 10 that the operation will be a success
- The chances are 5 in 10 that the operation will be a success
- The chances are 3 in 10 that the operation will be a success
- The chances are 1 in 10 that the operation will be a success

assumption that direction of the shift would always reflect the initial opinions of the group members.¹⁴¹ That is, if group members are initially tending to be cautious about a dilemma, then the outcome of the group discussion will be more cautious than the aggregated individual opinion. However, the direction of change is not always related to initial opinions in empirical studies, and choice shift has become the preferred description for the phenomenon.^{141,144} Choice shift following group discussion is a robust phenomenon, and research over the past 20 years has focused predominantly on the development and evaluation of theoretical explanations for it. Accounts of this literature can be found within the included reviews,^{127,142,144,145} but will not be discussed here.

In a meta-analysis of 14 articles (121 hypothesis tests) published between 1962 and 1992, BarNir¹⁴¹ reports a moderate to high choice shift effect size across a range of choice-dilemma questionnaire items. Several group characteristics that may moderate choice shift were considered, including group size, composition, individual differences, leadership style, discussion content and degree of prior acquaintance. BarNir draws the following conclusions.

- Larger groups and less well acquainted groups are more likely to shift to risk (conversely, smaller and well-acquainted groups are more likely to shift to caution).
- If risky behaviour is considered socially desirable, then the motivation to create a good impression in the presence of unfamiliar others may lead to a shift to risk in some groups.

- Expert groups (high knowledge) are more likely to shift to risk. Introducing intervention techniques that emphasise uncertainty or high stakes of consequences (e.g. devil's advocacy) may be a feasible technique for attenuating these effects.
- The same group may not display a consistent decision pattern over time, because choice shifts are moderated by the type of decision and by factors that change over time (knowledge and familiarity).

One of the factors that may influence the degree of choice shift in groups is the framing of the original problem.¹⁴³ Framing effects were first studied by Kahneman and Tversky.^{147,148} They presented people with dilemmas such as the following.

“Imagine that the US is preparing for the outbreak of an unusual disease, which is expected to kill 600 people. Two alternative programmes to combat the disease have been proposed. Assume that the exact scientific estimates of the consequences of the programmes are as follows:

- If programme A is adopted, 200 people will be saved.
- If programme B is adopted, there is a 1/3 probability that 600 people will be saved, and a 2/3 probability that no people will be saved.”

When presented with this problem, the majority of people (72%) choose the risk averse option – they prefer to save 200 lives for sure than gamble on saving more lives. However, when they changed the framing of the problem, different results occurred. People were presented with the same situation, but given the following choices.

- If programme C is adopted, 400 people will die.
- If programme D is adopted there is a 1/3 probability that nobody will die and a 2/3 probability that all 600 people will die.

These options are numerically identical to the previous ones, but framed in terms of lives lost rather than lives saved. When presented in this way, the majority of people (78%) choose the riskier option – they prefer to gamble on saving all 600 lives rather than be certain that 400 lives will be lost.

The evidence that framing affects individual decision-making is robust, and although relatively few studies have considered this possibility in group decision-making, those that have demonstrate the same effects.¹⁴³ That is, when a problem is presented in a positive frame (e.g. a new drug has a 50% success rate), the majority of groups will choose to avoid risks in deciding how to resolve the problem. In contrast, when a problem is presented in a negative frame (e.g. a new drug has a 50% failure rate), groups tend to choose a riskier solution to the problem. Despite the clear implications of framing, it has proved more difficult to identify circumstances that trigger groups to see their decision as a choice between losses (negative frame) or a choice between gains (positive frame). The extent to which groups have been historically involved with the problem and the degree of escalation of commitment to the decision have both been shown to be associated with negative framing (and riskier decision-making),¹⁴³ but there may be other important factors, as yet unidentified.

Majority and minority influence

We are all exposed to numerous attempts to influence our opinions every day. An extensive body of research considers the relationship between the number of people expressing a view or opinion and the level of attitude change.^{127,144,149,150} Do we always conform to a majority view, or can a minority be persuasive?

Empirical studies in this area began in the 1950s, with classic experiments in which naive participants were asked to make objective judgements (e.g. about the relative lengths of a pair of parallel lines).¹⁴⁹ The naive participants joined a group containing five other members (confederates of the experimenter) and were asked to make their judgements in public after hearing all of the other members express their view. In experiments such as these naive participants generally conform to the majority view expressed, even when that view is objectively incorrect.

Studies within this paradigm have demonstrated that the degree of conformity increases with the size, status and power of the majority.¹²⁷ Later research initiated by Moscovici and his colleagues using a similar paradigm has shown that minorities can be influential if they express a stable view and are consistent among themselves.^{149,150} Most of the studies conducted within this paradigm have investigated the influence of minority and majority opinions in non-interacting groups, and hence have limited direct relevance for DMCs. Findings from studies of majority and minority influence in groups that do interact are summarised below.

- When the majority of group members initially favour a particular position, this position is likely to determine the group's final decision. In addition, the size of the majority affects its ability to prevail.¹²⁷
- Although strong evidence for majority influence is found in decision-making groups, majorities do not always prevail. Majorities are more important on judgemental tasks, which lack demonstrably right answers, than on intellective tasks, which have such answers.¹²⁷ However, this pattern is modified for some choice tasks, especially in juries. In juries, acquittal requires less initial support than conviction to prevail.¹⁴⁴
- When a group is working on a judgemental task and status differences are large, the group decision rule changes from 'majority wins' to 'power wins'.¹²⁷
- Minorities have been shown to be influential in jury decision-making and group discussion of social problems.¹⁵⁰ There is strong support for the notion that a minority needs to be consistent to be influential.¹⁵⁰
- Double minorities, who differ from the majority in terms of both their expressed views and their ascribed category membership (e.g. gender, religion, skin colour), tend to be less influential.¹⁵⁰
- A majority has more direct and public influence than a minority (minorities tend to influence private judgements).¹⁴⁹

Experimental studies of moral reasoning

The majority of research on reasoning about moral dilemmas has been conducted by developmental psychologists, and has focused on understanding the processes of reasoning that individuals use as they progress through childhood and adolescence and into adulthood. There is relatively little research that investigates moral reasoning in groups, and only one of the identified articles reviewed experimental studies in

this area.¹⁵¹ As moral reasoning is central to the work of DMCs, the findings of this review will be described here in some detail.

Research on moral reasoning in psychology draws heavily on the work of Piaget¹⁵² and Kohlberg,¹⁵³ and has identified a sequence of developmental stages of moral reasoning (see Box 7). An individual progresses through these stages as his or her reasoning processes become more sophisticated. However, not all individuals progress through all of the stages, and even among those who do, adults do not always resolve moral dilemmas using the highest levels of reasoning. The level of reasoning used by an individual to solve a particular dilemma can be assessed using a standard psychometric instrument called the Defining Issues Test (DIT), which produces a score on a continuous scale of 'principled moral reasoning'. The higher the score on this instrument, the more likely that the

individual is using principled or postconventional morality in Kohlberg's scheme (Box 7).

Dukerich and colleagues¹⁵¹ review existing research using the DIT to investigate moral reasoning by groups, and present two experimental studies of their own. In these studies, participants (university students) were pretested using the DIT and then assigned to four-member groups. Each of the groups contained members with initial DIT scores in each of the four quartiles of the range of scores. One to two weeks after the pretesting, the groups were brought together and asked to discuss and resolve the three dilemmas presented in the DIT as a group. Following the tape-recorded group task, each participant completed another copy of the DIT (composed of different dilemmas) individually. The researchers conducted studies in which the groups were simply observed and manipulated a range of factors to investigate whether leadership style and the level of moral reasoning used by the

BOX 7 Kohlberg's stages of moral development

Level 1 Preconventional morality	Stage 1: Punishment and obedience orientation	The child decides what is wrong on the basis of being punished. Obedience is valued for its own sake, but the child obeys because adults have superior power
	Stage 2: Individualism, instrumental purpose and exchange	The child follows rules when it is in his/her immediate interest. What is good is what brings pleasant results. Right is also what is fair, what is an equal exchange, a deal, an agreement
Level 2 Conventional morality	Stage 3: Mutual interpersonal expectations, relationships and interpersonal conformity	The family or small group to which the child belongs becomes important. Moral actions are those that live up to others' expectations. 'Being good' becomes important for its own sake, and the child generally values trust, loyalty, respect, gratitude and keeping mutual relationships
	Stage 4: Social system and conscience (law and order)	A shift in focus from the young person's family and close groups to the larger society. Good is fulfilling duties one has agreed to. Laws are to be upheld except in extreme circumstances. Contributing to society is also seen as good
Level 3 Principled or postconventional morality	Stage 5: Social contract or utility and individual rights	Acting so as to achieve the 'greatest good for the greatest number'. The person is aware that there are different views and values, that values are relative. Laws and rules should be upheld in order to preserve the social order, but they can be changed. Still, there are some basic non-relative values, such as the importance of each person's life and liberty that should be upheld no matter what
	Stage 6: Universal ethical principles	The person develops and follows self-chosen ethical principles in determining what is right. Since laws usually conform to these principles, laws should be obeyed; but when there is a difference between law and conscience, conscience dominates. At this stage, the ethical principles followed are part of an articulated, integrated, carefully thought out and consistently followed system of values and principles ^a

Adapted from Kohlberg (1976).¹⁵³

^a Kohlberg (1978)¹⁵⁴ concedes that stage 6, if it exists at all, is extremely rare, and should perhaps only be applied to exceptional individuals, e.g. Martin Luther King and Mother Theresa.

leader have an effect on group performance. Their findings, based on their own studies and previous research, are summarised below.

- Task leadership is a dominant variable in this type of group decision-making task, regardless of how task leadership was operationalised. The reasoning level of the individuals who took on the leadership role had a major impact on the subsequent performance of the group and the individual members. Specifically, group performance suffered when the task leaders were less principled reasoning individuals (as measured by the DIT). Groups with more principled reasoning leaders either improved or stayed the same.
- Individual reasoning skills tend to increase after involvement in group discussion. However, the more principled reasoners appeared to experience a setback in reasoning skill after group discussion (possibly a transitory effect).
- Emergent leaders are just as likely to be low on reasoning skill as high. It cannot be assumed that more principled reasoning individuals will automatically assume leadership. Organisations may want to select leaders who are more principled reasoners, or to train influential members in moral reasoning.

Decision fiascos and groupthink

Background and history

Folk wisdom argues that 'two heads are better than one' when it comes to making decisions in complex situations. If that is so, then a group composed of particularly intelligent and knowledgeable people might be expected to make even better decisions. As Raven¹⁵⁵ puts it: "How then could one account for John F Kennedy's presidential advisory group, composed of the 'best and brightest', developing plans for the Bay of Pigs invasion of Cuba, frequently characterised as one of the most militarily disastrous and morally disgraceful ventures in American history?" This puzzle intrigued Janis and led him to apply his knowledge of the social psychology of groups to case studies of political decision fiascos (Table 6). On the basis of his analysis, he argued that the processes that generally make groups more effective (e.g. high morale, high cohesiveness, good leadership, excellent knowledge and experience) can in some circumstances lead to disastrous results. In some cases, he argued, a high level of morale and commitment to the group can result in a sense of moral superiority and a stronger tendency to conform to the majority within the group. He called this phenomenon groupthink, which proposes that this high cohesiveness and desire for

TABLE 6 Some case studies of groupthink

Study	Description	Summary of results
Janis (1972, 1982)	Bay of Pigs invasion of Cuba Invasion of North Korea Pearl Harbor Escalation of war in Vietnam Cuban missile crisis Making of the Marshall Plan Watergate crisis and cover-up	Identified antecedent conditions and symptoms of groupthink and defects of decision-making. Five cases show evidence of groupthink, two do not (Cuban missile crisis, Marshall plan)
Raven (1974, 1998)	Advisory groups associated with President Nixon involved in the planning that resulted in the Watergate fiasco and the cover-up afterwards	Sociometric analysis suggests evidence of groupthink with modified antecedents. The team lacked mutual respect, but consisted of two strongly competing factions, held together by loyalty to the President and a desire to be group members. Two antecedents (cohesiveness and insulation) and six symptoms present
Tetlock (1979)	Further analysis of Janis's original six case studies	Content analysis of public statements of key decision-makers. Found differences between decision-makers in groupthink and non-groupthink cases
Huseman and Drive (1979)	Decisions of professional investors in the stock market Decision by the Ford Motor Company to produce the Edsel Price-fixing conspiracy in the electrical industry during the 1950s	Decision-making groups in industry show signs of groupthink in decision fiasco situations. Two antecedents (cohesiveness and insulation) and five symptoms present

continued

TABLE 6 Some case studies of groupthink

Study	Description	Summary of results
Smith (1984)	US mission to rescue hostages in Iran	Showed all groupthink symptoms and four decision-making defects present. Antecedent conditions not examined
Hensley and Griffin (1986)	Decision in 1977 to build an addition to the Kent State University gymnasium on part of the area where students and Ohio National Guard members confronted each other before a fatal shooting in May 1970	Showed all antecedent conditions, seven out of eight groupthink symptoms (exception 'illusion of unanimity') and majority of defective decision symptoms present
Herek, Janis and Huth (1987)	19 US policy decisions about international crises, 1947–1973	Examined relationship between symptoms and decision outcomes. Concluded that when more symptoms are present, decisions are more likely to have adverse effects on US interests and to increase international conflict
McCauley (1989)	Reanalysis of cases described by Janis (1982)	Failed to find support for hypothesis that cohesion predicts occurrence of groupthink. Cohesion present in two out of six groupthink cases. Antecedents present in both groupthink and non-groupthink cases
Esser and Lindoerfer (1989)	Decision to launch the space shuttle Challenger in 1986. Challenger exploded 73 seconds after launch, killing all seven astronauts on board, and becoming the worst spaceflight disaster in US history	Quantitative analysis using coded statements from investigative report. Conclude that the decision to launch involved groupthink
Hart (1990)	Iran Contra affair	Three antecedents present (cohesiveness, insulation, leadership) and all eight symptoms
Moorhead, Ference and Neck (1991)	Challenger disaster	Analysed the level I Flight Readiness Review meetings over 2 days before the decision to launch. Three antecedents (cohesiveness, leadership, insulation), eight groupthink symptoms and a majority of defective decision symptoms were present
Neck and Moorhead (1992)	Jury deliberations in the trial of USA vs John DeLorean	Five antecedents present, but groupthink did not occur owing to the moderating impact of methodical decision-making procedures
Tetlock, Peterson, McGuire, Chang and Feld (1992)	Janis's seven cases Decision to rescue the crew of the Mayaguez Iran hostage rescue Nazi appeasement decision of Chamberlain cabinet	Confirmed Janis's five groupthink cases. Classified Nazi appeasement as groupthink, but not Mayaguez or Iran hostage rescue Found strong link between symptoms and defective decision-making. Weak links between cohesiveness and symptoms
Esser (1995)	Challenger	Six antecedents, five symptoms and seven defects in decision-making present

This table is an adaptation of tables within Raven 1998,¹⁵⁵ Neck 1995,¹⁵⁶ Esser 1998,¹⁵⁷ Moorhead 1991,¹⁵⁸ Park 1990,¹⁵⁹ and Wekselberg 1996.¹⁶⁰

unanimity can override the group's ability to appraise alternative courses of action and result in poor-quality decision-making and decision errors.¹⁶⁰ He then went on to develop a model describing the antecedents, symptoms and consequences of groupthink (summarised in *Figure 4*).

The concept of groupthink has a strong intuitive appeal and has triggered a substantial body of empirical research, including both case studies of decision fiascos and empirical studies of groupthink hypotheses.^{155-157,162,163} Case-analytical research includes studies that aim to describe groupthink and identify situations in which it has

occurred or may be likely to occur. These studies involve the retrospective application of groupthink hypotheses to reported decision fiascos (usually based on content analysis of archival data and press reports), and tend to consider all aspects of the model. They have largely been used to develop the theory and generate hypotheses, rather than to test relationships between components of the theory.¹⁵⁷ However, some studies do investigate whether the hypothesised antecedents of groupthink are present in groups showing symptoms of groupthink, or broadly to test the relationship between symptoms of groupthink and defects in decision quality (see *Table 6* for details).

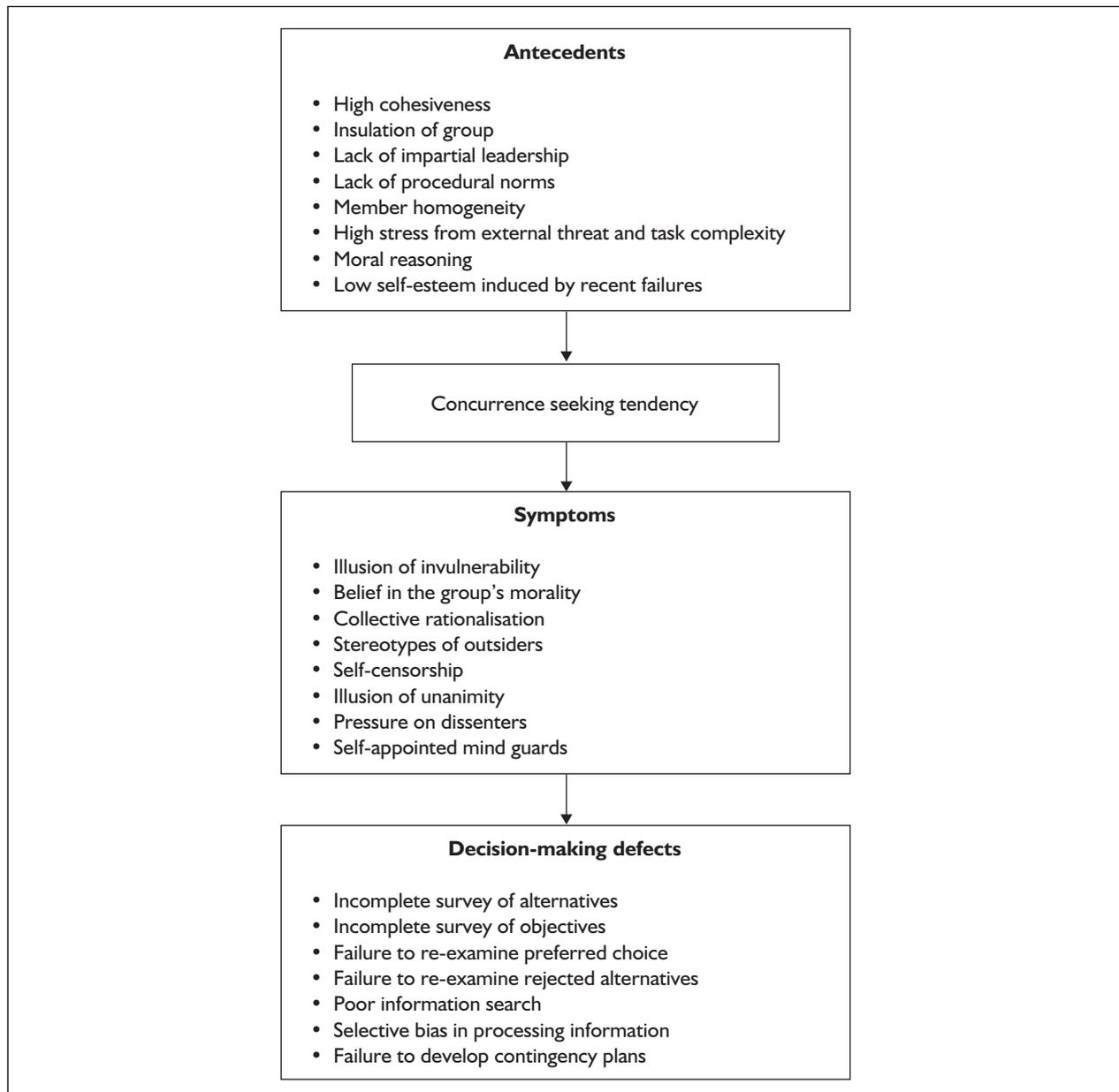


FIGURE 4 The groupthink model (adapted from Janis and Mann, 1977¹⁶¹)

Empirical studies deal with experimental tests of specific groupthink hypotheses in a laboratory setting using groups constructed for the purpose of the study (usually composed of undergraduate students). While case studies tend to provide evidence for the existence of groupthink and some support for the hypothesised links between antecedents, symptoms and decision quality, experimental studies generally fail to, and empirical support for the full groupthink model is weak.^{156,157,159,160,163,164} Indeed, some authors argue that the concept of groupthink is weak both theoretically and empirically and should be abandoned, despite its popular appeal.¹⁶⁰ Others feel that the model continues to have a heuristic value and merits further research,¹⁵⁷ or use it as a basis for more comprehensive models of group decision-making.^{163,164} The model serves a useful function for this chapter in identifying variables that may impair the quality of decision-making (the hypothesised antecedents of groupthink). The evidence relating to each of these is summarised here.

Antecedents of groupthink

High cohesiveness

Group cohesion is the central variable in the groupthink model and is the most widely studied variable in experimental studies. Cohesiveness is generally thought of in terms of group members having strong positive feelings towards one another (or the group). However, research suggests that cohesiveness is a multifaceted construct that has both task and interpersonal dimensions.^{155,165} Task-based cohesion occurs when there is a shared commitment to goals or tasks of the group. Interpersonal cohesion is based on personal relationships, the prestige associated with membership of the group itself, and regard for and dependence on the leader of the group. Some case studies have suggested that aspects of cohesiveness that are unrelated to the personal relationships of group members can be more important in determining cohesiveness in some settings (e.g. in the Nixon group associated with the Watergate fiasco).¹⁵⁵

A meta-analysis of nine experimental studies (17 hypothesis tests, involving 1382 participants), found a small and non-significant effect of cohesiveness on decision quality overall.¹⁶² However, relationships were found between cohesiveness and decision quality in certain circumstances. When other antecedent conditions are set up to promote groupthink, high cohesiveness impairs decision quality (small but significant effect, three hypothesis tests). When conditions are set up to thwart groupthink, high

cohesiveness enhances decision-making (six hypothesis tests, significant but small effect). When other antecedent conditions are not explicitly eliminated or exaggerated, decision quality increases as a function of cohesiveness when cohesiveness involves more 'commitment to task'. Decision quality decreases as a function of cohesiveness when cohesiveness involves more 'interpersonal attraction'. In addition, there is a significant effect of group size on the relationship between cohesiveness and decision quality. Cohesiveness tends to impair decision quality as group size increases.¹⁶²

Overall, reviews summarising both case studies and experimental research conclude that group cohesiveness, either alone or in combination with other factors, has little effect on groupthink or decision quality.^{157,159,160,163,164}

Insulation of group

The problems that may occur when a group is insulated from expert information and external scrutiny were highlighted by Janis, and insulation has emerged as a key antecedent of groupthink in several case studies.¹⁵⁷ The reviews included in this chapter only identify one experimental study of insulation,^{157,159} which found partial support for the theory. Insulated groups generated fewer alternative decisions (a decision-making defect), but contrary to the theory, they felt more vulnerable and were more likely to seek expert advice than non-insulated groups. In summary, it is currently unclear whether group insulation is an important factor in determining decision quality.

Lack of impartial leadership

An overly directive leadership style is hypothesised to be another key antecedent of defective decision-making, and has been investigated in several empirical studies. Overall, laboratory studies tend to support this hypothesis,¹⁵⁷ with a few exceptions.¹⁵⁹ Groups with directive leaders (who state their preferred decision early) tend to suggest fewer alternatives and report more self-censorship, and are more likely to acquiesce to the leader's preferred decision.^{157,159}

Lack of methodical decision-making procedures

Four studies have examined the effect of adopting clear methodical procedures of information search and appraisal on decision quality. Three provide some support for the hypothesis, while one found that the presence or absence of these procedures has no effect on decision quality.^{157,159} The effect of these procedures seems to be particularly important in cohesive groups. Highly cohesive

groups without adequate decision procedures are less likely to agree and make poorer decisions than similar groups that take a more methodical approach.¹⁵⁷

Other factors

Janis describes four other potential antecedents of groupthink: high stress from external threat or task complexity, member homogeneity, moral reasoning ability and low self-esteem induced by recent failures. These have received less empirical attention than other factors, possibly because they have been less apparent in case studies. Threat, as operationalised in laboratory experiments, has rarely had any consequences for group decision-making outcomes or processes.¹⁶⁶ However, studies that manipulate the degree of accountability that group members have for the decision suggest that accountable groups tend to share influence in the decision-making process more evenly and are more likely to question procedures and objectives throughout the process, but have more difficulty in reaching agreement.¹⁵⁷ Studies have investigated the effects of member homogeneity and moral reasoning ability on decision quality, but not in relation to groupthink hypotheses, and these studies are discussed elsewhere (experimental studies of choice-dilemma tasks, above; findings from studies of decision-making on non-judgement tasks).

Studies of jury decision-making

Background to and history of jury decision-making research

Systematic research on juries began with the Chicago Jury Project, initiated in 1953. This was a large field study involving 3500 civil and criminal jury trials. One arm of the study collected survey data from judges, lawyers and ex-jurors. The other arm involved audiotaping real jury deliberations and experimental studies with mock juries. The invasion of jury privacy by audiotaping their deliberations raised a storm of protest about the ethics of the study, and ultimately led the US Congress to stop the project in 1955. Following this decision, federal government and most states banned access to the jury room, limiting the range of research that could be conducted with real juries.^{140,167} Since that time, research on jury decision-making has largely been confined to experimental studies of mock juries, interviews or surveys of real jurors after their deliberations and archival studies of real jury verdicts. In the 1990s, two large field studies of juries were initiated in the USA. The Capital Jury Project investigates jury decision-making in cases involving a possible death sentence across 15 states in the USA.

The Arizona Jury Reform study is a randomised controlled field trial to evaluate the effect of a decision by the Arizona Supreme Court to allow jurors to discuss evidence while a trial is still in progress. Preliminary findings from these studies are included in one of the reviews informing this chapter.¹⁴⁰ A systematic review of jury decision-making from 1955 to 1999¹⁴⁰ identified 206 empirical studies, 136 of which involved mock juries, 40 involved analysis of archival data from real juries, 14 described surveys of ex-jurors, 13 used field experiments or studies and three used a combination of methods.

Jury decision-making research is directly pertinent to DMCs because it is concerned primarily with identifying factors that may result in a miscarriage of justice. However, as noted earlier (see section 'Error and bias in small group decision-making', p. 52), it is rare that an opportunity emerges to determine the 'correct' verdict in jury research. Rather than attempt to identify factors that make errors more or less likely in jury decision-making, the majority of this research considers the effect of various factors on the likelihood of a particular verdict (usually a decision to convict in criminal cases or find a defendant liable in civil cases). A large number of such factors has been studied and reviewed.^{140,145,167,168} From these, 12 have been shown to have sizeable effects on jury decision outcomes: definitions of key legal terms, verdict/sentence options, trial structure, juror-defendant demographic similarity, jury personality composition, jury attitude composition, defendant criminal history, strength of evidence, pretrial publicity, inadmissible evidence, case type (for civil trials) and initial juror verdict preference distribution. Some topics not included in this list are associated with small yet reliable effects (e.g. jury size), mixed results suggestive of higher order interactions (e.g. juror experience, decision rule, expert testimony) or potential effects that require more research to draw firm conclusions (e.g. juror note-taking, juror question-asking, defendant appearance, plaintiff characteristics, deliberation style, foreperson effects on damage awards).¹⁴⁰ Many of these factors are unlikely to be pertinent in DMCs. In the following sections, evidence relating to those factors that do appear relevant will be summarised. This evidence has been divided into two categories: factors relating to the deliberation process and non-deliberation factors.

The deliberation process

Foreperson effects

Choosing a foreperson is an initial task for most juries, and one that tends to be achieved quickly

and with little discussion. The elected foreperson tends to be the person who happens (or has chosen) to be seated at the head of the table and is more likely to be male, better educated and an experienced juror. The person selected as foreperson is usually one of the first people to speak and often the first member to mention the need for a foreperson. Once selected, forepersons speak more during the deliberation (around 25–30% of the time on average) and influence the speaking time and order in which other members speak. Hence, forepersons are in a position to influence the quality of the decision-making process. The influence of forepersons has only been studied in civil cases. In these cases they are disproportionately influential in determining the size of financial damages awarded, but do not appear to unduly influence the verdict about liability.¹⁴⁰

Deliberation content

Several studies have examined the content of jury deliberations through video- or audio-taping mock jury discussions or through postdeliberation interviews with real jurors. Findings from these studies are difficult to synthesise because they have tended to use study-specific coding schemes. However, these studies do demonstrate that juries spend most of their time talking about the facts of the case and the expressed preferences of members. Several studies have demonstrated that deliberation variables can help to explain why jury verdicts do not always match the initial preferences of jurors. In particular, these studies suggest that the content of discussion is particularly important early in the deliberation process and before any votes or straw polls have been taken. Once a vote has been taken and members are aware of the relative sizes (and characteristics) of pro-conviction and pro-acquittal factions, the content of discussion appears to be less influential than pressures to conform.¹⁴⁰

Deliberation style

Observations of jury discussions have identified two main types of approach that juries can take in reaching their verdict. These have been called the verdict-driven style and the evidence-driven style. Juries adopting a verdict-driven style take a vote (or straw poll) early in the proceedings and then focus their discussion around the verdict options. Evidence-driven juries postpone the first vote until after extensive discussion of the evidence and structure their discussion around a systematic evaluation of the evidence. These two styles occur equally often in studies of real juries. One study of mock juries manipulated this variable by asking

jurors to adopt a particular style of deliberation and found that deliberation style can affect jury verdicts. Juries using a verdict-driven style were more likely to find a defendant liable in a civil case in which liability depended on meeting both of two legal criteria, but less likely to return a verdict of liability when either of the two criteria was sufficient. The opposite was found in juries using an evidence-driven style.¹⁴⁰

Straw polls

Most juries undertake repeated straw polls or votes during the deliberation process. These are usually public expressions of the current verdict preference of individual jurors, but some juries undertake private votes. The frequency and format of straw polls affect the deliberation process and are key factors in changing the verdict preferences of individual jurors. Juries that undertake frequent and regular polls take longer over their deliberations, but are more likely to reach a decision. Secret votes are associated with rapid changes of juror opinion in the early stages of deliberation, but less opinion change in the later stages. Public votes show the opposite effect: jurors are less likely to change their expressed opinion early in the discussion, but more likely to change their minds later. The format of voting makes little difference to the final verdict if the evidence in the case is clear. When cases are close, however, six-person juries are more likely to reach a decision if they vote in public, with the opposite being true of 12-person juries.

Non-deliberation factors

Jury size

In the 1970s, some relaxation of the traditional requirement for a 12-member jury led to large body of research on effects of jury size. Most of these studies compared six-member with 12-member juries, although some included eight-member juries. A meta-analysis of these studies shows that jury size has little if any effect on the nature of the verdict reached or on the likelihood that juries will reach a 'correct' verdict (i.e. one that matches the verdict chosen by the majority of the population).^{140,165} Smaller juries are less likely to include members of minority groups, recall less evidence, deliberate more quickly and less thoroughly, and less likely to reach a verdict.^{140,167,168} Six-member juries award larger damages in civil cases.^{140,168}

Decision rule

Juries may be asked to return a verdict on the basis of either a unanimous or a majority decision (usually a two-thirds majority). These different

decision rules usually result in the same verdict in mock jury experiments.^{140,167,168} Some studies show that a unanimous decision rule results in 'hung juries' more often than a majority decision rule. Juries operating under a unanimity rule deliberate for longer and spend more time discussing legal definitions of verdict categories.¹⁶⁸ Juries operating under a majority decision rule tend to stop deliberating once a quorum is reached and use fewer straw polls of opinion. As a consequence, they tend to reach a verdict more often and more quickly.¹⁴⁰

Standard of proof

The prosecution may be required to demonstrate the guilt of the defendant (or case of the plaintiff) beyond a reasonable doubt (the strictest standard of proof), on the basis of clear and convincing evidence, or on the basis of the preponderance of evidence. In experimental studies, the proportion of verdicts favouring the plaintiff decreases significantly as the standard of proof becomes stricter.^{140,160} In addition, the wording used to convey the standard of proof has a substantial effect on jury verdicts. For example, higher acquittal rates are found when reasonable doubt is defined broadly as any conceivable doubt.¹⁴⁰

Demographic characteristics

A considerable body of research has examined the possibility that social and demographic characteristics of jurors can predict their verdict preferences. Much of this work has evaluated the effects of selecting jury members on the basis of personal characteristics ('scientific jury selection' procedure) on jury verdicts. These studies show that few if any juror characteristics can predict individual juror verdict preferences.^{140,168} However, jury demographic factors interact with defendant characteristics and the strength of evidence presented to produce a bias in favour or against defendants who are similar to jury members in some salient respect (e.g. gender, age, ethnicity). When the evidence against a defendant is weak or ambiguous, juries that are demographically similar tend to be lenient. When the evidence against a defendant is clear, however, demographically similar juries tend to be harsher.¹⁴⁰ Jurors who have prior experience of jury service tend to be more pro-conviction and influential than novice jurors. They also appear to evaluate the evidence in the light of their previous experience, which may bias their views towards the current defendant.¹⁴⁰

Personality and attitudes

Juror attitudes do not predict jury verdicts. However, juries that contain a high proportion of

members who obtain high scores on measures of authoritarian or dogmatic personality traits are more likely to convict a defendant and tend to impose longer sentences. It should be borne in mind that these findings are based on studies of mock juries. The effect of authoritarian personality on real jury verdicts has not yet been examined.¹⁴⁰ There is some evidence (two studies) to suggest that the level of jurors' moral reasoning (defined according to Kohlberg's theory, see *Box 7*) influences jury verdicts. Juries composed of members with higher levels of moral reasoning are more likely to find a defendant non-liable in a civil case. Mixed juries or juries consisting of more members with a lower level of moral reasoning are more likely to fail to reach a decision or award damages to the plaintiff. This may occur because jurors with higher levels of moral reasoning are more dominant during discussion.¹⁴⁰

Strength of evidence

The strength of evidence presented is one of the primary determinants of jury verdicts. Strength of evidence refers to the quantity and quality of evidence presented by the prosecution (or plaintiff) during a trial. In experimental studies it is manipulated in a variety of ways, e.g. by varying eyewitness identification of the defendant, the number of testifying witnesses and the presence of additional evidence such as polygraph data. Juries that hear evidence that is strong, either in quality or in quantity, are more likely to return a guilty verdict and are more likely to convict in error. Across studies, conviction rates range from 24% when the evidence presented is weak to 70% when the evidence presented is strong. Overall, the effects of strength of evidence are large and robust, but the extent to which these effects interact with (or are moderated by) other biasing factors is not yet known.¹⁴⁰

Pretrial publicity

Folk wisdom suggests that negative pretrial publicity may bias jury members, and experimental studies support this. A meta-analysis of 44 studies found an average correlation of $r = 0.16$ between negative pretrial publicity and judgements of guilt among non-deliberating mock jury members.¹⁶⁹ Only five studies have investigated the effect of pretrial publicity on juries (rather than jurors), but their findings suggest a consistent bias. Four of the studies suggest a consistent impact of negative pretrial publicity, while one found that the impact is moderated by the strength of evidence presented. When the prosecution's case was weak, the bias associated with negative pretrial publicity

disappeared after jury deliberation. When the prosecution case was stronger, jury deliberation increased the likelihood that a guilty verdict would be returned. Hence, it seems that in the presence of strong evidence, the bias that jurors feel towards a guilty verdict is not reduced by the deliberation of the jury, and may even be enhanced by it.¹⁴⁰

Inadmissible evidence

Jury verdicts are strongly influenced by inadmissible evidence. Even when judges give clear instructions to ignore this type of evidence, jurors do consider information that appears to be relevant. This effect is particularly strong when the inadmissible evidence supports the defendant's case. The effect of inadmissible evidence is reduced for more serious charges and if jurors are presented with information challenging the credibility of the inadmissible material. The impact of inadmissible evidence on jury verdicts is less than the effect on juror preferences, and jury deliberation can ameliorate its effects; but majority processes can also increase the effects (depending on the predeliberation juror verdict preference distribution, see below).^{140,168}

Initial juror verdict preference distribution

Jurors develop their own verdict preferences as they hear the trial evidence and before they enter into discussion with the other jurors. The judgement they reach is best explained by a 'story' model of decision-making, rather than models that imply a mathematical weighting and integration of information.^{140,168} That is, jurors appear to organise trial evidence into a plausible story about the defendant. They then attempt to match the story to the possible verdicts until they find a verdict that provides the best fit. They then enter into jury deliberations with an initial verdict preference in mind.

Findings from the Chicago Jury Project and from numerous mock jury studies provide compelling evidence that the verdict favoured by the majority of jurors before deliberation will be the final verdict in 90% of cases. In other words, the majority view tends to prevail in jury decision-making. Juries in which opinions are evenly split before deliberations begin tend to acquit a defendant or fail to reach a decision. Meta-analytical reviews support a strong majority effect, but also show an asymmetrical leniency bias favouring acquittal. So, for example, a two-thirds majority favouring guilt will result in a guilty verdict in 67% of cases, but a two-thirds majority supporting acquittal will result in a not guilty verdict in 94% of cases. In a 12-member jury, if

seven or fewer jurors initially favour conviction, the jury will probably acquit. If ten or more jurors favour conviction, the jury will probably convict. If eight or nine jurors favour conviction, the result is unpredictable.^{140,167,168}

Findings from studies of decision-making on non-judgement tasks

The general literature on group performance and decision-making is extensive and has been reviewed regularly (e.g. Levine and Moreland^{126,127}). In this section, key factors that are associated with group performance or decision quality are described. However, it should be borne in mind that the studies reviewed here are concerned with tasks that do not necessarily resemble those undertaken by DMCs.

Group composition

Heterogeneity within groups (in terms of demographics, education, personality or initial opinion) has a generally negative effect on group dynamics.^{127,170} This seems to be due to an increase in miscommunications and misunderstandings resulting in greater potential for interpersonal conflict and feelings of isolation and alienation. Findings are mixed with regard to whether the overall effects of heterogeneity on performance are positive or negative, however.¹⁷⁰ Indeed, a few recent studies focus on the paradoxical effects of heterogeneity, noting the occurrence of both positive and negative effects.¹⁷⁰ There is a consensus that the relationship between composition and performance is a complex one, precluding the identification of broad and stable generalisations.¹⁷⁰

Heterogeneity often increases conflict in groups, which might be presumed to have a negative impact on performance. This is not the case, however, and several researchers have found that conflict and argument can actually improve decision-making and problem-solving effectiveness.¹⁷⁰ One reason for this may be that conflict increases the likelihood that a range of alternatives will be proposed and discussed, improving the decision-making process. It is also the case that groups can learn to manage the effects of having a diverse membership. Two sets of tactics are generally effective. Negative effects can be managed by controlling conflicts between members; for example, by educating them about their similarities and differences, encouraging tolerance and improving social skills. In addition, positive effects can be created by making structural changes to simulate diversity (of opinions); for example, by assigning members to

act as ‘devil’s advocate’, adopting stricter decision-making norms or introducing occasional consultants.¹²⁷

Group size

Having more members increases the reliability of group judgement, but may cause coordination problems. The effects of group size on decision-making are subtle and difficult to detect. It seems likely that below six participants, reliability will decline quite rapidly, while above 12 improvements in reliability will be subject to diminishing returns.^{127,128}

Leadership

Many reviews have found that the role of the leader can be a crucial variable in a group context, which may have important consequences for group decision processes and outcomes.^{127,158,163,171}

Overall, empirical studies have yielded relatively consistent evidence that groups with directive leaders use less of the available information, suggest fewer solutions and rate their leaders as more influential in the decision process than groups with non-directive leaders.^{129,157,171} A directive style leader who states his or her opinion in a forceful way is less likely to foster the discussion of divergent opinions and hence may reduce the likelihood of reaching a good decision.¹²⁸ It is important to note, however, that most of the research in this area is concerned with the type of leader who must lead a group, in the sense of being ‘the boss’, and not with the type of leader who is chairing or facilitating a meeting. Very little is known about the effects of facilitation or chairing on group decision-making, or which aspects of these roles are important.¹²⁸ However, as Murphy and colleagues conclude, it seems likely that this key role will influence group decision-making and the quality of the decision made.¹²⁸

Incentives

Research into the effect of incentives has been concerned overwhelmingly with the relationship between different ‘pay-for-performance’ systems and either productivity or employee satisfaction.¹⁷² Empirical research into group incentive schemes has focused largely on the effects of distributing rewards equally or differentially among the group members. Findings in this area are complex and appear to be influenced strongly by the nature of the task and the details of the incentive scheme. Broadly speaking, differentially divided rewards appear to be as effective as or occasionally more effective than equally divided rewards.¹⁷² However, differential division of rewards can cause individuals to block other members of the group

(e.g. by not sharing important information) rather than help other members on some types of task. If blocking is a possibility, then equal division of rewards leads to better performance.¹⁷³

In DMCs, sharing of information and generation of alternative decisions would be considered to be signs of a better decision process, and might be associated with higher quality decisions. Applying these findings would imply that an equal division of rewards within the group should result in better decision processes (because it may avoid blocking).

Presence of others

It is well established that the mere presence of other people may either facilitate or inhibit individual performance, depending on the nature of the task and the degree of expertise that the individual has.¹⁷⁴ Reviews of the social facilitation literature are inconsistent, however, as to the effect of the presence of others on performance within groups.¹²⁹ However, effects thought to occur in the presence of other people include apprehension due to group judgement or evaluation, cognitive or physical conflict as a result of being distracted by other group members, increased effort to make a good impression and an increase in conforming to group norms.¹⁷⁴ One phenomenon that affects group performance is known as ‘social loafing’. This describes the tendency of individuals to expend less effort when working in a group context compared with working alone. Although a robust phenomenon, it is not always inevitable.¹²⁷ It has been suggested that increasing the visibility and attractiveness of the task and value of members’ contributions may go some way to reducing social loafing.^{126,127,129} In addition, an individual’s attitude towards the group and task is considered to predispose their motivation in the decision situation.¹⁷⁵

Communication

Although the study of communication in decision-making groups has grown considerably over the past 70 years, it would appear there is not enough clear evidence of how communication affects group decision-making.¹⁷⁶ Further, there have been no studies on how communication processes serve to detract from or enhance the quality of decisions that should be reached with a group’s potential.¹⁷⁷ However, it is suggested that groups are more efficient if there is active communication between members, preferably face-to-face so that they can communicate directly with everyone in the group.¹⁷⁸ Although there may be a lack of strong evidence of the impact of communication, it would appear communication is an important

variable when analysing how group members learn and provide cognitive stimulation.¹⁷⁷

Participation

Member participation is an important part of the decision-making process, with much known about its potential consequences.^{175,176} Empirical results consistently support the notion that participation and influence are highly associated and that a group's decision is more likely to reflect the opinion of those members who have participated more.^{128,180,181} In a new group, inequalities in participation evolve quickly, with members perceived as having higher task ability being encouraged to participate more.¹⁸² As a result of their additional contributions and perceived task performance, they are more influential towards the group decision.¹⁸¹ Gill and colleagues, in their review of antecedents to member participation within small groups, suggest that participation is influenced by factors such as self-esteem, attitudes towards the tasks, perceived attitudes of other group members and group atmosphere.¹⁷⁵ However, more research is needed to understand how other more complex variables may interact on the decision-making process.

The size of the group has been shown to affect disparities in participation. Larger groups tend to result in less participation from group members, with disparities being minimised in smaller groups.^{162,180} However, it is not clear which behaviours increase the quantity or quality of participation in groups.¹⁷⁵ In terms of gender role effects on group participation, it has been reported that males tend to be much more verbally active, dominating discussions.¹²⁹

Although equality of participation is expected to lead to higher member satisfaction and improved decision quality, it is likely to result in increased time needed to reach a decision and possibly create greater conflict within the group.¹⁷⁹ However, as already stated, although it is commonly assumed that conflict has a negative effect on decision-making, several studies have revealed that certain types of conflict may improve the decision-making.^{170,183} Conflict is a common part of the group experience, and may serve different functions depending on the stage of group development. In particular, task-related conflict has been demonstrated to have a positive effect, especially in groups that encourage openness.¹⁸³

Presentation of information

The way in which information is presented to a group may influence individuals' judgement in a

variety of ways that are important when reaching a decision.^{128,164} Central to this notion is the prospect theory, which describes how the risk-taking behaviour is dependent on whether the decision is positively or negatively framed (see section 'Choice shift and group polarisation', p. 53). Related to this point, Whyte¹⁶⁴ suggests that framing may have been an important contributing factor in groupthink. He argues that in the fiascos studied by Janis the decision-making group framed its decision as a choice between definite loss and potentially greater loss. The framing of the decision in such a negative domain consequently influenced and contributed to a risk-seeking tendency by the decision group. As to what type of information is influential, the few studies that have been reported suggest that novel information may have the most impact on influencing opinions.^{128,142}

Efforts to understand the impact of information on decision-making groups often highlight the role of information exchange among members.¹²⁷ Good information exchange combined with careful consideration of all the information can potentially lead to better decisions by a group.^{180,181} The failure of group members to exchange information has been a major component of the groupthink phenomenon on defective decision-making.¹²⁶ In addition, the possibility of a faulty or inaccurate information base has negative consequences for the decision outcome.¹²⁶

Results: effects of formal and informal decision-making procedures on decision process and quality

Various formal and informal strategies have been suggested for helping groups to reach consensus and improve their decision-making performance. Examples include informal strategies such as brainstorming and devil's advocacy, as well as more formal strategies, such as computational schemes or electronic decision support systems. The effectiveness of these approaches is thoroughly reviewed in the recent HTA report on consensus methods in guideline development groups,¹²⁸ and hence this literature will not be discussed in detail here. This review concluded that formal methods of developing consensus (e.g. Delphi technique, nominal group technique) perform at least as well as, and often better than informal methods. There is insufficient evidence to know whether any one formal method is better than any other.¹²⁸

Informal decision-making procedures

Informal decision support procedures are generally intended to improve the process of decision-making, either by increasing the number of alternative decisions that are considered or by enhancing the evaluation of different options. Two commonly recommended techniques are brainstorming and devil's advocacy.

Brainstorming is a popular technique that encourages members to suggest large numbers of ideas without evaluation or judgement from other group members.^{126,127} Despite its popularity, empirical data reveal that brainstorming is not particularly productive, and may in fact be harmful.¹²⁷ Brainstorming groups consistently produce fewer ideas and poorer quality ideas than either individuals working alone or groups engaged in free discussion.^{127,184}

Devil's advocacy is a technique whereby one of the group members deliberately criticises and attempts to question all that is wrong with a plan or decision, expounding the reasons as to why the plan should be rejected.¹⁸³ Research suggests that devil's advocacy may reduce the quality of performance in circumstances where tasks are well understood and non-complex. However, when the devil's advocate questions valid assumptions, it may lead to these assumptions being rejected and thus lead to defective decision-making.¹⁸³ It is considered that devil's advocacy is most beneficial in group decision-making when the decision involves high uncertainty but enough information.¹⁸⁵

Electronic group decision support systems

Electronic group decision support systems (GDSSs) act as a facilitation technique that can influence group structure and procedures. According to the literature, there is evidence that groups using GDSS technologies make higher quality decision; however, decisions will take longer to reach and it is unclear as to what effect these technologies have on members' satisfaction.¹⁷⁹ GDSS provides groups with varying levels of technological support depending on the group and task type. Its use facilitates anonymous exchange, which supports an open discussion, thus making it easier for group members to present their ideas or solutions to the group.¹⁷¹ Simultaneously being able to input ideas and opinions is a creative process leading to a rich source of ideas, which should encourage broader, more active participation.¹⁷¹

In GDSS, anonymity is regarded as a tool to reduce the impact of the group over its members

and this is a key factor to improved decision-making.¹⁸⁶ Although anonymity has frequently been isolated as an important variable in determining the effects of GDSS, there has been no systematic review to date.¹⁸⁶ The results on the impact of computer-mediated communication on group performance are inconclusive.¹⁸⁶ However, it is suggested that compared with males, females are more likely to be affected by the absence or lack of non-verbal communication during computer-mediated groups.¹⁸⁷

Traditionally, research has focused on comparing electronically mediated groups with face-to-face groups. However, it has been shown that electronically supported groups processes are different from non-computer-assisted groups and these differences interact with other factors such as the task and its impact on group effectiveness.¹⁸⁸ Overall, the weight of evidence suggests that GDSS increases equalisation of participation and decreases domination by some individuals. The equalising effects of GDSS are attributable to simultaneous participation and anonymity.^{171,179}

Implications and recommendations for DMCs

This section will consider the implications of the evidence described in this chapter by summarising the findings in relation to ten of the 23 questions about DMCs outlined in Chapter 1 (see *Box 1*). The greatest weight will be given to evidence drawn from studies of groups engaged in judgemental and choice-dilemma tasks, especially juries and political decision-making groups. Throughout this section, reference will be made to effects on the outcome of the decision-making process (decision outcome) and effects on the process of decision-making (decision quality).

What should the membership of a DMC be? (Question 6)

Size

The relationship between group size and both decision quality and decision outcome has been widely researched. This research suggests that size has very little impact on the decision made, but may affect the quality of the decision-making process. For example, jury sizes ranging between six and 12 members have little effect on the verdict itself, but larger juries are more likely to include a wider range of opinions, which tends to improve the process of decision-making. However, there is a point at which size may begin to have a negative impact on the process of decision-making

because members may be more reluctant to express their views in a larger group or because conflicts occur between the opinions expressed. A bias towards riskier decision-making may also occur in larger expert groups, such as DMCs. Murphy and colleagues¹²⁸ recommend an optimum size of six to 12 members for guideline development groups, and this also seems appropriate for DMCs.

Membership

There is a limited pool of potential DMC membership because members are generally expected to have a good understanding (and experience) of trial design and statistics. The mechanisms by which members are selected from this pool for a particular DMC are obscure (see Chapter 2); however, there is very little available research to guide decisions about how DMC members should be chosen or selected. It is clear that groups that include members with a range of opinions tend to make better quality decisions, provided that all members have a chance to participate in the discussion, and that any conflicts that arise are handled appropriately. Hence, selection methods that encourage a degree of diversity within the group should probably be recommended. Studies of jury selection suggest that formal methods of selection based on psychometric assessment of demographic characteristics and attitudes have few advantages. It seems unlikely that such methods would have a role in DMC member selection. Although none of the reviews included in this chapter considered the role or effects of consumer representatives in expert groups, it seems likely that if they add a different point of view and are able to participate fully in the discussion, they may improve the quality of the decision made.

Chair

Studies of juries and other small decision-making groups indicate that the person who chairs or leads the group can have important effects on both decision outcome and decision quality. Directive leaders who limit the range of views expressed can steer the discussion and hence the decision made. If there are large status differences among group members, then the decision tends to be the one preferred by the more powerful members (which generally includes the leader) rather than the majority. Defects in decision-making are more frequently observed if the group has partial and directive leadership. In addition, groups led by leaders with more experience (or expertise) in discussing ethical problems tend to make better quality decisions. All of these findings

suggest that DMCs should be chaired by experienced members, who have the skills to be impartial and can facilitate a full discussion of the issues.

How is independence to be maintained? (Question 7)

There is very little research concerned with the effects of the independence of groups (or group members) on decision outcome or quality. Jury research indicates that jurors tend to evaluate the evidence they hear in the light of their experience. If this is also the case in DMCs, then conflicts of interest may occur. None of these reviews considered the effects of declaring conflicts of interest on decision quality or outcome. Studies of decision fiascos suggest that groups that are accountable for their decisions tend to make better quality decisions. The effects of payment on groups have largely been studied in relation to productivity rather than decision-making, and their implications for DMCs are unclear.

Should the DMC deliberations be open or closed? (Question 8)

The presence of other people can have a significant effect on how we act, either improving our performance or inhibiting it. However, it is not clear what the implications of this are for whether DMC deliberations should be open or closed. DMC members whose deliberations are observed in an open meeting may be inhibited from expressing their views and more inclined to agree with the majority, as were the participants in Asch's conformity experiments.¹⁸⁹ This would clearly have a detrimental effect on decision quality. Alternatively, the presence of observers may serve to increase feelings of accountability and enhance decision quality. Further empirical work is required before clear recommendations can be made on this point.

What are the optimal practical arrangements for interim analysis and data monitoring? (Question 9)

Practical aspects such as the frequency and timing of meetings have not been studied in relation to decision quality or outcome. Communication has been studied more extensively, and findings in this area suggest that groups are more efficient if there is active communication between members, preferably face-to-face. The effects of telephone conferences on decision quality or outcome are not clear, but if they inhibit members from expressing their views then they may impair decision quality.

The effects of electronic communication have largely been considered in the context of electronic decision support systems. In this situation, members' contributions are anonymous, which supports an open discussion and may enhance decision quality. However, the effects of this form of communication on decision quality or outcome are currently unclear.

What sort of training or preparation should DMC members have? (Question 10)

Decision quality is generally enhanced if group leaders have the skills to facilitate a discussion, can manage conflict effectively and can be impartial. DMC chairs who do not already possess these skills may benefit from training. Similarly, an opportunity to participate in discussions of ethical dilemmas may be useful for some relatively inexperienced DMC chairs. All members of DMCs will require training if formal or methodical approaches to decision-making are adopted (e.g. GDSS).

What material should be available to a DMC? (Question 11)

Substantial empirical evidence supports the view that the way in which information is framed can have a significant impact on decision outcomes. Extrapolating from this evidence, it might be expected that DMCs will tend to avoid risks if they are only presented with information about the benefits of treatments, but will have a greater tolerance for risk if they are only given information about the costs or harms associated with different treatments. To avoid these biases, the material available to DMCs should contain full information about the benefits and harms of all the treatments under consideration.

Studies of juries have shown that the strength of evidence presented in terms of both quantity and quality is a major determinant of decision outcome. Juries that are presented with strong evidence are more likely to convict a defendant in error than juries that hear weaker evidence. For example, juries presented with statements from several witnesses are more likely to convict than juries that only hear evidence from one or two witnesses. If this applies equally to DMCs, then it might be expected that providing large quantities of detailed information (e.g. about secondary outcomes) would increase the chances of making a mistaken decision. In addition to this, jury decisions are clearly influenced by all of the information they are given, and not just the evidence that is directly relevant to the case. Again, if this occurs in DMCs, biases may occur if

too much information is provided about secondary outcomes or subsidiary hypotheses. Guidance about 'standard' data sets to be presented to DMCs, or restriction of DMC discussions to primary outcome data may help to reduce the risks of error associated with strong evidence or excess information.

Prior publicity about criminal or civil cases has a strong effect on juries and can cause significant bias. It is unlikely that most DMCs will have been exposed to media publicity about the trials they consider, although this may occur in some circumstances. However, care should be taken to avoid excessive publicity around trials that will be considered by DMCs.

How should the decisions or recommendations be reached within the DMC? (Question 16)

Criteria for guiding deliberations

It is not currently clear whether DMCs use legally defined standards of proof to guide their deliberations; that is, whether DMCs are required to decide that a trial should stop or continue beyond a reasonable doubt, or on the basis of clear and convincing evidence or on the basis of a preponderance of evidence. These differing legal standards of proof are associated with different decision outcomes in studies of juries. If different DMCs (or members within a DMC) use different standards (implicitly or explicitly) then significant inconsistencies and apparent biases may occur. To avoid this, guidance should be provided to DMCs about standards of proof, and the standard being used should be made explicit.

Process of decision-making

As already discussed (section 'What should the membership of a DMC be?', p. 67), the quality of decision-making is improved if a range of opinions is expressed and all members have an opportunity to participate in the discussion. Following discussion, a decision may be made on the basis of either a unanimous or a majority view. Jury studies indicate that the choice of decision rule (majority or unanimous) has little effect on the decision outcome, but does influence decision quality. Juries that are required to reach a unanimous decision discuss the case for longer and make greater efforts to resolve conflicting views. As a consequence, unanimous decisions are generally of a better quality. However, a unanimous decision rule is also more likely to result in a hung jury that is unable to reach a decision.

Decision-making groups may use votes or straw polls to gauge the range of views and/or to achieve a final decision. Jury studies indicate that the timing of these votes can alter both decision quality and decision outcomes. An early vote (or public expression of opinion) tends to limit the amount of discussion and increase the tendency of group members to conform to the majority view. A quick decision is generally achieved, but is of relatively poor quality. Frequent and regular votes during the deliberations prolong the proceedings, but increase the chances that the group will ultimately reach a unanimous verdict. Secret votes are useful early in the deliberations because they reduce the pressure to conform before a full discussion has been held. Later in the proceedings, public votes are more useful because they maximise the likelihood that individuals will consider changing their opinion. Overall, the use of voting is to be recommended so long as it follows a full discussion of all views.

Formal methods of achieving consensus in groups are generally as good as or better than informal methods, and may be useful in some DMCs. The technique of devil's advocacy, in which one or more members deliberately present a contradictory view to promote discussion, can be useful in improving decision quality if the decision involves a high degree of uncertainty or complex information, or if the group is homogeneous. GDSSs using electronic forms of communication increase participation by all members and reduce the risk that any one member will dominate the discussion. It is not currently clear whether these effects translate into benefits for decision quality or outcome.

How should ethical issues be handled in DMCs? (Question 19)

Discussion of ethical issues is the main business of DMCs. Evidence from these reviews suggests that DMC members (and especially the chair) should have some experience of discussing this type of issue (see Case Study A in Chapter 6).

What should be done in 'difficult' situations? (Question 21)

'Difficult' situations may occur because of unforeseen circumstances or external pressures. The limited available evidence suggests that these situations may have less impact on decision quality and outcome than might be expected. Difficult situations are likely to increase the likelihood of conflict between group members, which tends to improve the quality of decisions, providing that all opposing views are expressed and considered. Circumstances that limit the available time for discussion or make it more difficult for all members to participate (e.g. the need for meetings at short notice) could have a deleterious effect. In these circumstances, formal decision support techniques may be helpful. This may also be the case if unforeseen circumstances increase the complexity of the information that a DMC has to consider.

Should some DMC decisions be considered to be 'errors'? (Question 22)

Group decision errors can be defined as 'those occasions when the team's decision-making activities fail to achieve its intended outcome'.¹³¹ From this perspective, a DMC decision would be considered to be an error either if current trial participants were exposed to harm from the experimental drug or procedure, or if future patients were unable to benefit from it. It is rare that an opportunity emerges to determine the 'correct' decision in real-life decision-making groups. For this reason, field studies usually focus on procedural criteria that should theoretically be related to the accuracy of the decision. These include thorough review of the evidence, accurate comprehension of the instructions, active participation by all group members, resolution of differences through discussion and systematic matching of case facts to the criteria for various decision options.¹⁴⁰ The absence of any of these characteristics is assumed to increase the likelihood of an inaccurate or erroneous decision.

Chapter 4

Cross-sectional review of the reported use of data monitoring committees in the main published reports of randomised controlled trials

Introduction

This chapter reviews the information provided on DMCs in main published articles of a sample of RCTs in order to describe their use and reporting. Selected general and specialist medical journals were handsearched for the year 2000 to provide a cross-sectional picture. In addition, the general medical journals were handsearched for 1990 to allow a comparison across time for these journals.

Methods

Choice of journals for inclusion

The aim of this review was to be systematic but not exhaustive. A sample of RCTs was identified by searching selected general medical journals and specialist medical journals covering four disease areas in which many RCTs have been conducted: cardiology, infection and immunity, oncology and psychiatry. The higher impact journals relating to the chosen disease areas were identified from the 1999 *Journal Citation Report (Science Edition)*.¹⁹⁰ At least four journals that stated that their remit included reporting RCTs were selected for each disease area. Journals within each speciality, ranked by citation impact factor, were examined from the top of the list until the sample number of journals had been selected from each list (see below). Journals were excluded if the journal's remit did not include the publication of RCTs or the journal was US based and three higher ranked US-based journals had already been selected. This was to ensure that some non-US journals were included for each speciality.

For both oncology and psychiatry five journals were selected; although *Leukemia* (oncology) and *Neuropsychopharmacology* (psychiatry) aim to publish RCTs, in practice, they publish very few. The number of general medical journals was also increased to include the top six journals so that at least two were non-US based. *Table 7* shows the included journals and their 1999 impact factor scores.

Handsearching methods

Journals were handsearched to identify the main published report of RCTs in human subjects that intended to evaluate therapeutic or preventive healthcare interventions. The reported use of DMCs was estimated from the proportion of identified RCTs that explicitly mentioned the use of a DMC, although inevitably this is likely to be an underestimate of actual use.

A single researcher handsearched hard copies of each included journal for the year 2000 for reports of RCTs. The one exception was *Infection and Immunity*. After an unproductive and time-consuming search of the first two volumes of this journal, online searches were used to identify the few RCTs published in 2000. All sections of each identified article were searched for relevant information, including the Acknowledgements. After searching was completed, the same researcher checked a 20% random sample, stratified by year and journal category (general versus specific), for quality-control purposes.

Details for extraction

Details on the disease, trial treatments, planned and actual sample size, recruitment time and general design were collected (see Appendix 10). Information on the existence of a DMC and performing of interim analyses was collected separately; that is, it was not assumed that interim analyses were planned just because use of a DMC was reported or vice versa. If any details were not included in the main trial report earlier published papers on the trial referred to in the main report (e.g. papers on methodology and/or preliminary results) were examined, wherever possible.

Scope of searching

Although all selected journals were handsearched for eligible RCTs published in 2000, only the selected general medical journals were handsearched for 1990. Therefore, the RCTs identified in 2000 give a broad contemporary cross-section of the reported use of DMCs, whereas the comparison of 1990 and 2000 gives

TABLE 7 Details of included journals and reported DMC use in 2000

Journal category	Journal	Impact factor ^a	Trials with DMC reported	Total trials
General	<i>New England Journal of Medicine</i>	28.86	22 (35%)	62
	<i>Journal of the American Medical Association</i>	11.45	12 (24%)	49
	<i>Lancet</i>	10.20	28 (32%)	88
	<i>Annals of Internal Medicine</i>	10.10	5 (24%)	21
	<i>Archives of Internal Medicine</i>	6.71	3 (11%)	28
	<i>British Medical Journal</i>	5.14	0 (0%)	34
	General total		70 (25%)	282
Cardiology	<i>Circulation</i>	9.90	14 (23%)	60
	<i>Journal of the American College of Cardiology</i>	7.37	5 (12%)	41
	<i>Stroke</i>	5.54	7 (30%)	23
	<i>European Heart Journal</i>	3.21	6 (29%)	21
	Cardiology total		31 (21%)	145
Infection and Immunity	<i>AIDS</i>	6.93	5 (21%)	24
	<i>Journal of Infectious Diseases</i>	4.84	4 (19%)	21
	<i>Infection and Immunity</i>	4.18	1 (33%)	3
	<i>Journal of Antimicrobial Chemotherapy</i>	3.30	0 (0%)	8
	Infection total		10 (18%)	56
Oncology	<i>Journal of the National Cancer Institute</i>	12.95	0 (0%)	12
	<i>Journal of Clinical Oncology</i>	7.96	5 (8%)	60
	<i>Cancer</i>	3.63	1 (6%)	18
	<i>Leukemia</i>	3.56	1 (50%)	2
	<i>British Journal of Cancer</i>	3.28	1 (9%)	11
	Oncology total		8 (8%)	103
Psychiatry	<i>Archives of General Psychiatry</i>	10.95	0 (0%)	20
	<i>American Journal of Psychiatry</i>	6.34	0 (0%)	20
	<i>Neuropsychopharmacology</i>	4.86	0 (0%)	4
	<i>Journal of Clinical Psychiatry</i>	4.17	0 (0%)	21
	<i>British Journal of Psychiatry</i>	4.09	0 (0%)	11
	Psychiatry total		0 (0%)	76
General medical journals			70 (25%)	282
Specialist medical journals			50 (13%)	380
Overall total			120 (18%)	662

^a According to the 1999 Science Citation Index.¹⁹⁰

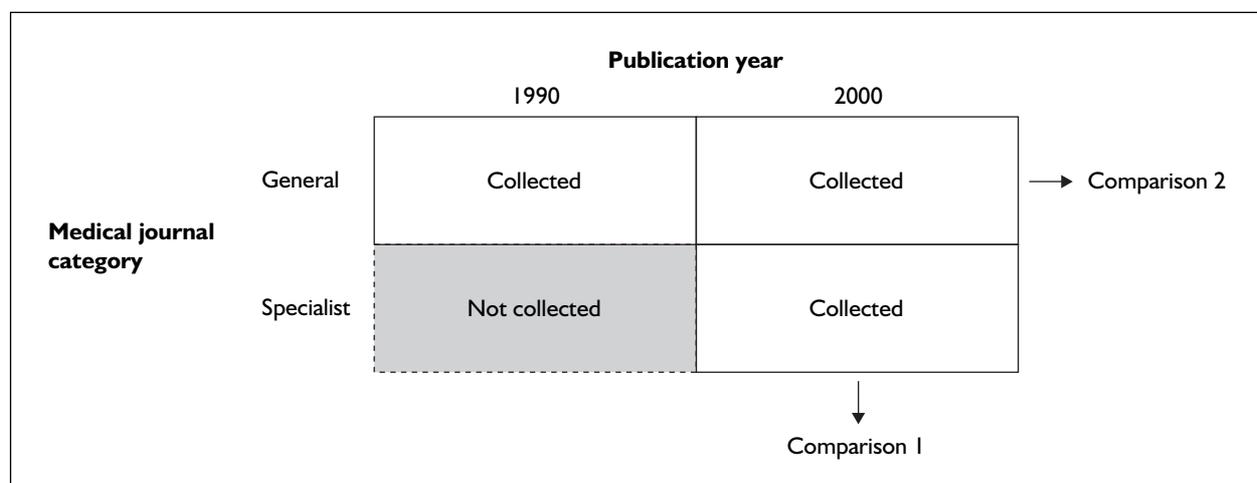


FIGURE 5 Study design: depiction of data collection cells. Comparison 1: cross-sectional review of reported DMC use in trials published in 2000 in general and specialist medical journals; comparison 2: repeated cross-sectional review of reported DMC use in trials published in 1990 and 2000 in general medical journals.

an indication of changes in conduct and/or reporting over a 10-year period in the general medical journals (*Figure 5*).

Analyses and categorisation

Data were collected and stored in a specially created database (MS Access 2000, version 9.0) with analyses performed using Stata (version 8.0, TX) and MS Excel (2000, version 9.0). To perform analyses on the continuous variables collected, such as the intended size of the trial, categorisation was performed. Category boundaries were chosen after data collection was complete to produce approximately evenly sized groups. Data categories were collapsed for inclusion in univariate and multivariate logistic regression models where the reported use of a DMC was the independent variable. Separate analyses were performed for the data relating to trials published in 2000 and for the data relating to trials published in the general medical journals. Variables were excluded from these two multivariate analyses if they greatly decreased the available sample size for the model.

Results

After approximately 150 hours of handsearching, 866 trials that met the inclusion criteria were identified. For 2000, 662 trials were identified and are included in the cross-sectional analysis (282 in general medical journals and 380 in specialist journals). For the comparison by year of publication in the general medical journals, 486 trials were identified, 204 in 1990 and 282 in 2000; these latter 282 articles appear in both of the comparisons reported (*Figure 5*).

Most articles did not report at least one item of data sought for this review. Indeed, the reports of only five (<1%) trials overall provided a complete set of the data, including details of interim analyses and the DMC (e.g. number of members, any formal stopping guideline).

Cross-sectional review of trials published in general and specialist medical journals in 2000

Trials and reporting

Of the 662 eligible trials identified in 2000, 120 (18%) explicitly reported the use of a DMC. Planned interim analyses were reported for 107 (16%) trials, and 77 (12%) reported use of both a DMC and planned interim analyses. Planned interim analyses were reported in 30/107 (28%) trials, but these made no explicit mention of a

DMC, and 41/120 (34%) of trials explicitly mentioned a DMC but made no explicit mention of planned interim analyses. In total, 156 (24%) trials mentioned either the use of a DMC or interim analyses (planned or unplanned) or both. In nine trials it was apparent that no DMC was involved in the trial and eight reported that interim analyses were neither planned nor performed.

In 2000, a DMC was reported more often in the general medical journals than in the specialist journals (*Table 7*): 70/282 (25%) versus 50/380 (13%). Excluding the journals with fewer than ten published trials, the journals with the highest proportion of trials reporting DMCs were *New England Journal of Medicine*, *The Lancet* and *Stroke*, in which DMCs were reported for approximately one-third of trials. None of the 76 trials published in psychiatry journals reported the use of a DMC.

Cardiology, oncology and psychiatry were the disease areas most commonly covered by the included trials (*Table 8*). Excluding the disease areas with fewer than ten published trials, the use of a DMC was reported most often in cardiology and HIV/AIDS trials. Only one of 29 psychiatry trials published in the general medical journals reported a DMC.

None of 21 trials of educational interventions reported the use of a DMC. The reported use of a DMC was higher in trials that had at least one arm using drug, placebo, vaccination or surgery (*Table 9*). Reporting of DMC use was more common for double-blind trials [73/296 (25%) if double-blind versus 47/363 (13%) if not; three unclear]. The reported use of DMCs was higher if a pharmaceutical company was involved in the trial in some way than if there was no involvement [74/305 (24%) versus 35/250 (14%)]. The levels of reported DMC use were similar (23–25%) over various levels of pharmaceutical company input: pharmaceutical company trial, full pharmaceutical company funding, partial pharmaceutical company funding and free/discounted drug supplies. No information regarding funding sources was given in 107 (16%) of the reports.

No evidence was found that the reported use of a DMC was related to the number of treatment arms (18%, 16% and 15% for two, three and more than three arms, respectively), but DMCs were more often reported for factorial trials than for non-factorial trials [8/18 (44%) versus 106/644 (16%)], although the factorial trials were generally larger. Of 15 trials identified as cluster-randomised, none

TABLE 8 Reported DMC use in trials published during 2000 by disease area^a

Disease area	General			Specialist		
	Total	DMC reported	(%)	Total ^b	DMC reported	(%)
Accident and Emergency	1	0	(0%)	NA ^b	–	–
AIDS/HIV	13	6	(46%)	33	6	(18%)
Arthritis	9	3	(33%)	NA ^b	–	–
Asthma	7	2	(29%)	NA ^b	–	–
Cardiology	52	23	(44%)	141	32	(23%)
Diabetes	5	0	(0%)	1 ^b	0	(0%)
Elderly	1	0	(0%)	NA ^b	–	–
Endocrine	3	0	(0%)	NA ^b	–	–
Gastroenterology	15	2	(13%)	NA ^b	–	–
Haemaotology	2	0	(0%)	NA ^b	–	–
Infection	29	6	(21%)	12	2	(17%)
Miscellaneous	6	1	(17%)	NA ^b	–	–
Neonatal	4	1	(25%)	NA ^b	–	–
Nephrology	6	0	(0%)	NA ^b	–	–
Neurology	10	2	(20%)	NA ^b	–	–
Nutrition	9	0	(0%)	NA ^b	–	–
Obstetrics and Gynaecology	6	2	(33%)	NA ^b	–	–
Oncology	22	6	(27%)	104	8	(8%)
Orthopaedics	5	2	(40%)	NA ^b	–	–
Osteoporosis	2	1	(50%)	NA ^b	–	–
Palliative	1	0	(0%)	NA ^b	–	–
Patient care	2	0	(0%)	NA ^b	–	–
Primary care	4	1	(25%)	NA ^b	–	–
Psychiatry	29	1	(3%)	77 ^b	0	(0%)
Respiration	21	7	(33%)	2 ^b	0	(0%)
Sexual health	2	0	(0%)	1 ^b	0	(0%)
Surgery	8	1	(13%)	NA ^b	–	–
Transplantation	3	2	(67%)	NA ^b	–	–
Vaccination	5	1	(20%)	8	2	(25%)
Total	282	70	(25%)	380	50	(13%)

^a It is intended that comparisons be made down columns or across rows, but not diagonally.

^b Many categories are not applicable (NA) and others have small numbers; the specialist journals selected were not expected to cover these areas in great depth, e.g. some trials published in the cardiology journals were classified under diabetes, nephrology and psychiatry.

TABLE 9 Reported DMC use by intervention evaluated in trials published during 2000

At least one arm containing:	Total ^a	DMC reported	(%)
Drug	447	99	(22%)
Placebo	241	61	(25%)
No treatment	127	14	(11%)
Surgery	37	9	(24%)
Education	21	0	(0%)
Image/scan	7	1	(14%)
Radiotherapy	13	1	(8%)
Vaccination	14	3	(21%)
Other ^b	165	15	(9%)

^a Categories are not mutually exclusive.

^b For example, follow-up scheduling, choice of carer, hormone therapy (separated here from drug treatment) and nutrition (including vitamin supplementation).

TABLE 10 Reported DMC use by size of trial in those published during 2000^a

Intended no. of participants	Actual no. of participants				Total
	< 100	100 to <500	500 to <1000	≥ 1000	
< 100	54 (7%)	9 (0%)	0 (0%)	0 (0%)	63 (6%)
100 to <500	5 (0%)	164 (16%)	7 (14%)	0 (0%)	176 (16%)
500 to <1000	0 (0%)	4 (50%)	38 (21%)	5 (20%)	47 (23%)
1000	0 (0%)	1 (100%)	4 (25%)	47 (74%)	52 (71%)
Missing	137 (5%)	131 (11%)	23 (17%)	33 (45%)	324 (12%)
Total	196 (6%)	309 (14%)	72 (19%)	85 (60%)	662 (18%)

^a Number of trials reporting DMC use/number of trials (% trials reporting DMC use).

explicitly reported use of a DMC. For only one of 37 cross-over trials was a DMC reported, perhaps reflecting their shorter duration and smaller size.

The trial size bore some relation to whether the trial would report a DMC. Both the intended and actual size of the trial were collected, where available. Almost half of the reports did not state the intended sample size [324/662 (49%)]. Only 51 trials intended to recruit at least 1000 participants, 24 of which were in cardiology. *Table 10* (rightmost column) shows that, as the intended size of a trial increased, so did the likelihood that it reports a DMC. A similar trend was seen when looking at the actual size of the trial (*Table 10*, bottom row). However, the actual number recruited may not reflect the number initially intended at the design stage, as trials may be stopped early or have their targets revised upwards during the accrual phase.

Multicentre trials were defined as having more than two participating sites. The use of a DMC was more frequently reported for multicentre trials than for single- or two-centre trials [106/401 (26%) versus 11/233 (5%); the number of centres was not reported in 28 trials], although this may be a reflection of the larger size of multicentre trials (median=315 participants, where known) over single- and two-centre trials (median=80 participants) and their longer duration.

Some commentators have suggested that DMCs are only required where survival is a primary end-point of the trial.^{13,23} A DMC was reported more often for those with survival end-points [15/49 (31%)] and event-free survival primary end-points [22/62 (35%)] than for trials where the primary end-point was not survival based [83/551 (15%)]. There is likely to be confounding here by the intended sample size: there was a trend towards

larger intended sample size in trials with a survival-based end-point ($\chi^2_{(3)} = 13.44, p = 0.004$). The majority of these trials with survival-based primary end-points were conducted in cancer [60/111 (54%)] and cardiology [34/111 (31%)].

Approximately half of the included trials recruited some or all participants from the USA; 232 (35%) trials from the USA only and 74 (11%) from the USA plus at least one other country. There was a higher rate of reporting of DMC use in trials involving the USA and at least one other country. However, trials involving the USA and other countries' trials tended to be larger, regardless of whether a DMC was reported (median 1685 patients with DMC reported and 353 if no DMC reported for trials with recruitment from the USA and other countries, versus 480 with a DMC reported and 150 if no DMC reported for other recruitment combinations).

Logistic regression models were constructed to look at the relative importance of 14 of the variables discussed above in predicting the reported use of a DMC. *Table 11* presents a summary of 14 univariate analyses and one multivariate analysis including the ten variables with adequate data. The more important explanatory variables in the multivariate analysis ($p < 0.1$) were increasing number of patients actually recruited, at least one arm involving a placebo, factorial design, survival-based primary end-point, multicentre trial, publication in a general medical journal and US involvement in the trial. The multivariate analysis was based on 519/662 (79%) articles where all of these variables were available. Those with full data were more often published in the general medical journals, were larger, contained a placebo arm, had multicentre recruitment and involved the USA than did trials that were excluded from the model because of missing values.

TABLE 11 Results from univariate and multivariate logistic regression models for trials published in general and specialist medical journals in 2000

Factors ^{a, b}	Univariate analyses				Multivariate analysis			
	n	OR	95% CI	p-Value ^c	n	OR	95% CI	p-Value ^c
Year 2000 data								
Actual sample size	662	2.811	2.262 to 3.494	<0.001	519	2.368	1.779 to 3.151	<0.001
Placebo involved	662	2.079	1.394 to 3.102	<0.001	519	2.246	1.286 to 3.924	0.004
Factorial design	662	3.800	1.467 to 9.843	0.006	519	5.780	1.680 to 19.889	0.005
Primary end-point	662	2.819	1.782 to 4.459	<0.001	519	2.391	1.245 to 4.591	0.009
Centres	604	6.272	3.284 to 11.977	<0.001	519	2.487	1.112 to 5.565	0.027
Journal category	662	0.459	0.307 to 0.686	<0.001	519	0.608	0.357 to 1.037	0.068
USA involvement	662	2.019	1.350 to 3.022	0.001	519	1.617	0.965 to 2.710	0.068
Drugs involved	662	2.628	1.590 to 4.344	<0.001	519	1.801	0.861 to 3.769	0.118
Cross-over design	660	0.121	0.016 to 0.894	0.038	519	0.317	0.038 to 2.676	0.291
Pharma involvement	555	1.968	1.264 to 3.064	0.003	519	0.906	0.487 to 1.687	0.756
Planned sample size	338	3.237	2.381 to 4.400	<0.001	NA ^d			
Recruitment length	381	0.929	0.661 to 1.307	0.672	NA ^d			
Follow-up length	405	1.833	1.300 to 2.584	0.001	NA ^d			
Primary analysis time	436	1.559	1.191 to 2.040	0.001	NA ^d			

^a Separate models were constructed for the year 2000 data and the general medical journals.

^b Planned and actual sample size: <100 (ref.), 100–499, 500–999, ≥ 1000 patients; Placebo involved: no placebo-based arm (ref.) versus at least one placebo-based arm; Factorial design: no (ref.) versus yes; Primary end-point: survival-based versus non-survival based (ref.); Centres: single centre (ref.) versus multicentre; Journal category: general medical (ref.) versus specialist medical; USA involvement: no involvement (ref.) versus some involvement (ref.); Drugs involved: no drug-based arm (ref.) versus at least one drug-based arm; Cross-over design: no (ref.) versus yes; Pharmaceutical company involvement: no involvement (ref.) versus some involvement; Recruitment length: <12 months (ref.), 12–60 months, >60 months; Follow-up length: <3 months (ref.), 3 months to 1 year, 1–5 years, >5 years; Primary analysis time: <3 months, 3 months to 1 year, 1–5 years, >5 years.

^c p-Value for test for interaction.

^d Not included in multivariate analysis owing to quantity of missing data.

n, number of trials with available data; OR, odds ratio; 95% CI, 95% confidence interval for odds ratio; Pharma, pharmaceutical company; ref., reference category.

Details of DMCs and interim analyses

Where interim analyses or DMC use were reported further details were extracted from the paper. For 2000, some data could be obtained for 150/156 trials reporting a DMC and/or interim analyses. Considering here the trials published in 2000 (see 2000 data in *Table 12*), the most commonly reported methods were from the frequentist ‘group sequential’ class of rules (e.g. O’Brien & Fleming) in both general medical and specialist journals. (For further details of these rules, see Appendix 1). For 92/150 trials (61%), these details were not provided.

Of these 150 trials, the planned number of analyses was reported explicitly for 51 (34%) trials and deduced in a further 29 (19%) trials (e.g. reported as ‘6-monthly’ or ‘at least five analyses’). The actual number of analyses was reported for 63 (42%) trials, with an indication of this number given in a further 22 (15%) trials. Where the planned and actual number of analyses were reported or indicated, these matched in 25/54

(46%) cases. Where the number of analyses did not match, 18/29 (62%) stopped early, whereas 11/25 (44%) stopped early where the numbers matched.

In the 120 trials where a DMC was reported, the size of the DMC was explicitly described in 72 (60%) trials. The number of members ranged from one to ten with a median of 4 overall (4 in specialist journals, 4.5 in general journals). In 43 cases (36%), the DMC was explicitly reported as being ‘independent’, although a definition of independence was rarely given (see Chapter 2, question 7).

Repeated cross-sectional review of trials published in general medical journals in 1990 and 2000**Trials and reporting**

In total, 204 eligible trials were identified from 1990 and 282 from 2000, an increase of 38% (*Table 13*). Much of the overall increase was accounted for by *The Lancet* and *Journal of the American Medical Association*. The number of trials

TABLE 12 Form of interim analyses guidelines reported by year of publication and by journal type

Methodology for interim analyses ^{a, b}	1990	2000	2000	Total
	General	General	Specialist	
Frequentist (group sequential)	5 (31%) ^c	13 (35%)	7 (33%)	25 (34%)
Frequentist (continuous)	5 (31%)	7 (19%)	6 (29%)	18 (24%)
Frequentist (informal)	4 (25%)	10 (27%)	3 (14%)	17 (23%)
Frequentist (group sequential) and decision theory	0 (0%)	1 (3%)	0 (0%)	1 (1%)
Bayesian	0 (0%)	0 (0%)	1 (5%)	1 (1%)
Other	1 (6%)	2 (5%)	1 (5%)	4 (5%)
None	1 (6%)	4 (11%)	3 (14%)	8 (11%)
Subtotal	16 –	37 –	21 –	74 –
Missing	13 (45%)	47 (56%)	45 (68%)	105 (59%)
Total	29 (100%)	84 (100%)	66 (100%)	179 (100%)

^a Further details on these categories can be found in Appendix 1.

^b The second and third columns report general medical journal data for 1990 and 2000 and the third and fourth columns compare the data for trials published in 2000 in the general and specialist journals.

^c Percentages are on subtotal of trials with non-missing data.

TABLE 13 Change between 1990 and 2000 in the total number of trials published in the general medical journals and the number of trials reporting DMC use

Journal	Total trials reported			Trials reporting DMC use		
	1990	2000	% Change ^a	1990	2000	Change in % ^b
<i>Ann Intern Med</i>	33	21	-36%	1 (3%)	5 (24%)	21%
<i>Archives Intern Med</i>	22	28	27%	0 (0%)	3 (11%)	11%
<i>BMJ</i>	25	34	36%	0 (0%)	0 (0%)	0%
<i>JAMA</i>	19	49	158%	1 (5%)	12 (24%)	19%
<i>Lancet</i>	40	88	120%	6 (15%)	28 (32%)	17%
<i>N Engl J Med</i>	65	62	-5%	13 (20%)	22 (35%)	12%
Total	204	282	38%	21 (10%)	70 (25%)	15%

^a Change in trials published between 1990 and 2000 as a percentage of trials published in 1990.

^b Change in percentage of trials reporting use of a DMC between 1990 and 2000.

reporting the use of a DMC increased from 21/204 (10%) in 1990 to 70/282 (25%) in 2000 (relative increase=141%, 95% CI 53 to 279%). Similarly, the reporting of planned interim analyses increased from 21 (10%) to 59 (21%). An increased proportion of trials reporting DMC use was seen in all journals, with the exception of the *British Medical Journal*, where no trials with DMCs were detected in either period (Table 13).

Differences between the type of trial published in 1990 and 2000 were investigated to see whether this could explain any of the increase in reporting: as noted, for year 2000 trials, longer follow-up and time to analysis were each associated with increased reporting of DMC use. Although the analysis times and follow-up lengths of the identified trials in the general medical journals in 1990 and 2000 were

very similar, the relation to reported DMC use was only seen in the 2000 data. With regard to other factors that could affect reporting, the proportion of double-blind trials [114/204 (56%) versus 135/282 (48%)], placebo-controlled trials [107/204 (52%) versus 130/282 (46%)] and cross-over trials [28/204 (14%) versus 13/282 (5%)] each decreased from 1990 to 2000, although the explicit reporting of the double-dummy approach increased [2/204 (1%) versus 13/282 (5%)]. Other than a slight decrease in placebo-controlled trials, the type of treatment comparison changed little over time, although the proportion of trials with three or more arms increased [45/204 (22%) versus 80/282 (28%)]. There was a small decrease [30/204 (15%) versus 21/282 (7%)] in the proportion of drug trials for which the nature of any pharmaceutical industry involvement was unclear.

TABLE 14 Number of trial participants by journal and year of publication in general medical journals

Journal	1990		2000	
	Median	Interquartile range	Median	Interquartile range
<i>Ann Intern Med</i>	50	(24–160)	194	(72–320)
<i>Arch Intern Med</i>	135	(60–303)	340.5	(138–791.5)
<i>BMJ</i>	97	(40–257)	134.5	(360–614)
<i>JAMA</i>	99	(18–229)	219	(138–1062)
<i>Lancet</i>	93	(60–484)	350.5	(125–837)
<i>N Engl J Med</i>	146	(60–404)	281	(100–683)
Overall	101.5	(41.5–315)	307	(120–751)

As discussed previously, for all journals in 2000 trial size was associated with the reporting of DMC. There were changes in factors related to trial size between 1990 and 2000 that may explain the increase in reported use of DMCs. For instance, the proportion of multicentre trials increased from 84/204 (41%) to 185/282 (66%). The intended number of participants was more frequently reported [62/204 (30%) versus 179/282 (63%)] where this information was available it was not apparent that the planned trial size had greatly increased, with the median planned size only increasing from 225 to 300 (data from 62 and 179 trials, respectively). The actual sample size was available for all trials. There was a larger increase in the median actual trial size from 1990 to 2000 (204 and 282 trials, respectively) (Table 14).

Logistic regression models were constructed to explore the relative importance of 15 variables listed above in predicting the reported use of a DMC. Table 15 presents a summary of 15 univariate analyses and one multivariate analysis including the ten variables with adequate data. The more important explanatory variables ($p < 0.1$) in the multivariate analysis were survival-based end-point, increasing number of patients actually recruited, multicentre trial, at least one arm involving a drug, at least one arm involving a placebo, US involvement in the trial and year of publication. The multivariate analysis was based on 413/486 (85%) articles where all of the variables were available. However, the multivariate analysis model included proportionately more trials that were published in 2000 and involved the USA than did trials that were excluded from the model because of missing values.

Details of DMCs and interim analyses

In total, 113 trials in the general medical journals reported the use of a DMC, planned interim analyses or both; 29/204 (14%) trials from 1990 and 84/282 (30%) trials from 2000. Details of

statistical stopping rules for interim analysis were less clearly reported in 2000 than in 1990 (Table 12, first and second data columns). The planned number of analyses was reported explicitly for five (17%) and 32 (38%) trials in 1990 and 2000, respectively, and deduced for a further six (21%) and 13 (15%) trials. Where the planned and actual number of analyses matched, 1/2 (50%) trials from 1990 and 8/15 (53%) trials from 2000 were stopped early.

In the 91 cases where a DMC was reported (21 from 1990, 70 from 2000) the size of the DMC was explicitly reported in 16 (76%) and 48 (69%) trials. The median number of DMC members was 3.5 (range one to ten) in 1990, and 4.5 (range one to ten) in 2000. The proportion of DMCs explicitly reported as independent increased from 5 (24%) in 1990 to 27 (39%) in 2000.

Nomenclature

The DMCs identified during this review had a variety of names (Table 16). The most common were data and safety monitoring board and data and safety monitoring committee. This may reflect the preponderance of USA-based trials. None of the reported DMCs used the UK MRC's current preferred choice of name, data monitoring and ethics committee,⁵⁹ although the naming policy was probably introduced too recently to have yet permeated into any published reports. Similarly, the names treatment effects monitoring committee (TEMC), the favoured name of some commentators¹⁸ and independent data monitoring committee (IDMC), as used by the ICH E9 guidelines,⁵⁷ were not detected.

Table 17 reports the frequency of keywords used in the names of the reported DMCs. Apart from board or committee, the most common words were monitoring, safety and data. Nineteen different names using only combinations of these words were found, representing 113/141 (80%) of the

TABLE 15 Results from univariate and multivariate logistic regression models for trials published in general medical journals in 1990 and 2000

Factors ^{a, b}	Univariate analyses				Multivariate analysis			
	n	OR	95% CI	p-Value ^c	n	OR	95% CI	p-Value ^c
General medical journals								
Primary end-point	486	8.772	4.804 to 16.017	<0.001	410	9.893	3.953 to 24.755	<0.001
Actual sample size	486	3.099	2.420 to 3.970	<0.001	410	2.468	1.757 to 3.467	<0.001
Centres	461	12.000	5.405 to 26.640	<0.001	410	3.538	1.361 to 9.196	0.010
Drugs involved	486	2.637	1.498 to 4.639	0.001	410	3.218	1.252 to 8.273	0.015
Placebo involved	486	1.769	1.118 to 2.798	0.015	410	2.080	1.038 to 4.169	0.039
USA involvement	486	2.128	1.317 to 3.438	0.002	410	1.996	1.034 to 3.852	0.039
Publication year	486	2.877	1.700 to 4.870	<0.001	410	1.972	0.940 to 4.140	0.073
Pharma involvement	435	1.887	1.151 to 3.096	0.012	410	0.615	0.276 to 1.372	0.235
Factorial design	486	2.718	0.962 to 7.681	0.059	410	1.347	0.211 to 8.605	0.753
Cross-over design	481	0.202	0.048 to 0.854	0.030	410	1.031	0.198 to 5.372	0.971
Planned sample size	241	2.860	2.056 to 3.979	<0.001	NA ^d			
Follow-up length	325	2.397	1.546 to 3.717	<0.001	NA ^d			
Primary analysis time	306	1.955	1.376 to 2.779	<0.001	NA ^d			
Recruitment length	286	1.279	0.841 to 1.943	0.250	NA ^d			
Cluster design	486	0.428	0.054 to 3.385	0.421	NA ^e			

^a Separate models were constructed for the year 2000 data and the general medical journals.

^b Primary end-point: survival-based versus non-survival based (ref.); Planned and actual sample size: < 100 (ref.), 100–499, 500–999, ≥ 1000 patients; Centres: single centre (ref.) versus multicentre; Drugs involved: no drug-based arm (ref.) versus at least one drug-based arm; Placebo involved: no placebo-based arm (ref.) versus at least one placebo-based arm; USA involvement: no involvement (ref.) versus some involvement (ref.); Publication year: 1990 (ref.) versus 2000; Pharmaceutical company involvement: no involvement (ref.) versus some involvement; Factorial design: no (ref.) versus yes; Cross-over design: no (ref.) versus yes; Follow-up length: <3 months (ref.), 3 months to 1 year, 1–5 years, >5 years; Primary analysis time: <3 months, 3 months to 1 year, 1–5 years, >5 years; Recruitment length: <12 months (ref.), 12–60 months, >60 months; Cluster design: not cluster RCT (ref.), cluster RCT.

^c p-Value for test for interaction.

^d Not included in multivariate analysis owing to quantity of missing data.

^e Not included in multivariate analysis because no cluster randomised trials with reported DMC use in year 2000 data. For abbreviations see Table 11.

reported DMCs, and only 28 (20%) DMCs used a word in the name other than these five words.

Five further trials reported the presence of some external monitoring: an independent safety monitor (two trials), an independent safety reviewer, a medical monitor and a study statistical consultant.

Discussion

Principal findings

DMCs were explicitly mentioned in a minority of main published reports of RCTs. Reported use of DMCs varied considerably by medical speciality and certain design features, aspects that are not independent. There were no reports of DMC use in psychiatry trials; this may reflect a judgement that DMCs are not necessary because such trials are typically small and short, and do not have survival-based primary end-points. There was a

relationship between trial size and reported DMC use, with larger trials more likely to report DMCs. However, this does not necessarily mean that larger trials use a DMC more often than smaller trials, but could indicate that they were more likely to report the use of a DMC when there was one; this would be possible if, for example, they tend to be awarded greater reporting space by journals.

The increased proportion of trials reporting DMC over the decade 1990 to 2000 probably reflects greater use of DMCs, although it may also be due to better reporting, or perhaps reflect a change in the nature of the trials being reported. Some improved reporting in 2000 may be due to the application of the Consolidated Standards of Reporting Trials (CONSORT) statement,¹⁹¹ which aims to improve the reporting of clinical trials in general, including the reporting of stopping rules. However, there remains considerable scope for better reporting of the way in which accumulating data in trials are monitored. This is reflected by

TABLE 16 Reporting names for DMC in review of trials

Reported DMC name	1990		2000		2000		Combined	
	General medical		General medical		Specialist			
Data and safety monitoring board	2	(10%)	21	(30%)	7	(14%)	30	(21%)
Data and safety monitoring committee	0	(0%)	7	(10%)	8	(16%)	15	(11%)
Data monitoring committee	3	(14%)	6	(9%)	3	(6%)	12	(9%)
Data safety and monitoring board	0	(0%)	5	(7%)	5	(10%)	10	(7%)
Data safety monitoring board	0	(0%)	6	(9%)	3	(6%)	9	(6%)
Data-monitoring committee	2	(10%)	4	(6%)	0	(0%)	6	(4%)
Safety committee	1	(5%)	1	(1%)	4	(8%)	6	(4%)
Data safety monitoring committee	0	(0%)	1	(1%)	3	(6%)	4	(3%)
Safety monitoring committee	0	(0%)	3	(4%)	1	(2%)	4	(3%)
Data monitoring and safety committee	1	(5%)	0	(0%)	1	(2%)	2	(1%)
Data monitoring board	1	(5%)	1	(1%)	0	(0%)	2	(1%)
Data safety and monitoring committee	0	(0%)	2	(3%)	0	(0%)	2	(1%)
Drug safety monitoring board	0	(0%)	2	(3%)	0	(0%)	2	(1%)
External safety and efficacy monitoring committee	0	(0%)	1	(1%)	1	(2%)	2	(1%)
Monitoring committee	1	(5%)	1	(1%)	0	(0%)	2	(1%)
Safety and data monitoring committee	2	(10%)	0	(0%)	0	(0%)	2	(1%)
Safety monitoring board	0	(0%)	1	(1%)	1	(2%)	2	(1%)
Ad hoc safety committee	1	(5%)	0	(0%)	0	(0%)	1	(1%)
Data efficacy and safety monitoring committee	0	(0%)	0	(0%)	1	(2%)	1	(1%)
Data safety and advisory board	0	(0%)	0	(0%)	1	(2%)	1	(1%)
Data-monitoring board	0	(0%)	0	(0%)	1	(2%)	1	(1%)
Ethical review committee	1	(5%)	0	(0%)	0	(0%)	1	(1%)
Ethics committee	1	(5%)	0	(0%)	0	(0%)	1	(1%)
External data and safety monitoring board	0	(0%)	1	(1%)	0	(0%)	1	(1%)
External data and safety-monitoring board	0	(0%)	0	(0%)	1	(2%)	1	(1%)
External data-monitoring committee	0	(0%)	1	(1%)	0	(0%)	1	(1%)
External monitoring and safety committee	0	(0%)	0	(0%)	1	(2%)	1	(1%)
External safety and efficacy and monitoring committee	0	(0%)	0	(0%)	1	(2%)	1	(1%)
External safety monitoring board	0	(0%)	0	(0%)	1	(2%)	1	(1%)
Independent safety and data monitoring advisory committee	0	(0%)	0	(0%)	1	(2%)	1	(1%)
Independent safety committee	0	(0%)	1	(1%)	0	(0%)	1	(1%)
Internal monitoring board	0	(0%)	1	(1%)	0	(0%)	1	(1%)
International review advisory board	0	(0%)	0	(0%)	1	(2%)	1	(1%)
Medical monitoring committee	0	(0%)	1	(1%)	0	(0%)	1	(1%)
Performance and safety monitoring committee	1	(5%)	0	(0%)	0	(0%)	1	(1%)
Policy and data monitoring board	0	(0%)	0	(0%)	1	(2%)	1	(1%)
Protocol-monitoring committee	1	(5%)	0	(0%)	0	(0%)	1	(1%)
Response evaluation committee	0	(0%)	0	(0%)	1	(2%)	1	(1%)
Safety and efficacy data monitoring committee	0	(0%)	1	(1%)	0	(0%)	1	(1%)
Safety and monitoring board	0	(0%)	0	(0%)	1	(2%)	1	(1%)
Safety monitor ^d	1	(5%)	0	(0%)	0	(0%)	1	(1%)
Safety review board	0	(0%)	1	(1%)	0	(0%)	1	(1%)
Safety review committee	0	(0%)	0	(0%)	1	(2%)	1	(1%)
Safety-data monitoring committee	1	(5%)	0	(0%)	0	(0%)	1	(1%)
Safety-monitoring committee	1	(5%)	0	(0%)	0	(0%)	1	(1%)
Trial monitoring board	0	(0%)	1	(1%)	0	(0%)	1	(1%)
Total	21	(100%)	70	(100%)	50	(100%)	141	(100%)

Name are listed in descending order of overall frequency.

Percentage columns may not sum to 100% owing to rounding.

^d Blinded, non-participating observer who periodically reviewed coded clinical and laboratory.

TABLE 17 Most commonly used words in defining DMC name in all trials reporting DMC use

Naming elements	1990		2000		Total
	General medical journals		Specialist journals		
Monitoring	16 (76%)	67 (96%)	42 (84%)	125 (89%)	
Safety	11 (52%)	54 (77%)	43 (86%)	108 (77%)	
Data	12 (57%)	56 (80%)	36 (71%)	104 (74%)	
Committee	17 (81%)	30 (43%)	27 (55%)	74 (52%)	
Board	3 (14%)	40 (57%)	23 (46%)	66 (47%)	
External	0 (0%)	3 (4%)	5 (10%)	8 (6%)	
Efficacy	0 (0%)	2 (3%)	3 (6%)	5 (4%)	
Review	2 (10%)	1 (1%)	2 (4%)	5 (4%)	
Advisory	0 (0%)	0 (0%)	3 (6%)	3 (2%)	
Drug	0 (0%)	2 (3%)	0 (0%)	2 (1%)	
Independent	0 (0%)	1 (1%)	1 (2%)	2 (1%)	
Ethics	2 (10%)	0 (0%)	0 (0%)	2 (1%)	
Total	21 (100%)	70 (100%)	50 (100%)	141 (100%)	

Words are listed in descending order of overall frequency.

the lack of detail that could be extracted for this project; for example, it is unclear who was monitoring the trials that report planned interim analyses and whether there was an uncredited DMC. Certainly, from the authors' experience they know this to be the case for some of these trials.

Possible reasons for not reporting whether a DMC was used include not wishing to reveal the DMC membership, the publication policy of the chosen journal (e.g. inadequate space with word limits) and the authors not believing it to be important for their readers.

Discussion of strengths and weaknesses

This study had a mixed cross-sectional and longitudinal design; data were collected to cover 1990 and 2000, and general and specialist medical journals. Owing to resource constraints data from 1990 specialist medical journals were not collected. This limits the comparisons that can be made, for example regarding temporal change in specialist medical journals.

Journals with higher impact factors were chosen. If the impact factor is taken as a measure of trial quality, it is likely that the trials sampled will have DMCs more often than those in the wider published literature. However, the length of a report may be more limited in a high-impact journal and this could lead to more under-reporting of DMCs in these journals. However, while for these reasons the wider representativeness of the sample is uncertain for the reporting of DMC use, the factors identified as associated with the existence of a DMC for a given

trial should be relevant beyond this sample. The project was adequately sized to comment on the major issues associated with reporting DMC use and present plausible results.

A single researcher collected all of the data. There was no independent searching or double data entry. A 20% random sample of data was monitored by checking the source data against those recorded in the project database by the same researcher who collected the data originally. Some changes were made as a result of the sampling, but the number of changes required did not meet the specified criteria for checking all of the records. This method of monitoring checked only those trials that had already been found; therefore, the number of RCTs included could not be increased, but the number of trials with DMCs could be.

The main published reports of trials failed to present many of the data that were being collected for this project and this is likely to apply to the existence of DMCs. Thus, the estimated proportion of trials using a DMC is likely to be an underestimate. This issue was explored further in an in-depth survey of a subsample of the trials considered here. The authors of the subsample were contacted to find out more details. The findings are reported fully in Chapter 5. In brief, one of 24 trials for which there was no mention of a DMC was found to have had a DMC, whereas one of seven trials considered to have had a DMC based on the report, did not have one. These findings do not therefore suggest that any underestimate in the survey reported in this chapter is large.

Chapter 5

Surveys of policies and practice

Introduction

Background

This chapter describes three interlinked surveys of practices relating to DMCs in recently completed RCTs, practices relating to DMCs in ongoing RCTs, and policies about DMCs from major agencies involved with RCTs. The three surveys allowed the authors to consider the practice in trials conducted in the 1990s (and published in 2000), as well as current trials, and to relate these to current policies. The rationale for the surveys of practices was to identify a range of trials with information to address the 23 questions, while the policies survey examined relevant data monitoring policies of a range of organisations.

The main focus was to identify policies and practice that may be particularly relevant to trials with public funding in England. It was also felt that it was important to extend this to obtain information both from different funding sources and from different geographical bases. A further aim was to include single-centre as well as multicentre trials, and trials in major disease areas. It was for these reasons that plans for the survey of ongoing trials were changed from those outlined in the application for funding. In the original proposal, it was planned to limit the survey to trials funded by the NHS R&D HTA programme and the MRC. It was decided to broaden the range of trials considered to industry-funded trials and publicly funded trials other than those funded by the HTA programme and MRC. This did indeed provide a wider based survey, potentially enhancing its generalisability. This meant, however, that only a sample of HTA programme and MRC trials could be considered, rather than all of them, as originally planned.

Survey of DMC practices in recent trials

Aims

This part of the project aimed to determine the data monitoring practices in a sample of trials whose reports were published in 2000. It should be recognised that sampling trials by the year of their publication is likely to identify trials that ran

throughout the 1990s, and therefore the sample is more likely to give an indication of practice over that time than at a defined time-point.

Methods

The sampling frame was the primary reports of RCTs published in 2000, as identified and classified in Chapter 4.

Forty-five trials were selected from the database, stratified by whether the trial was single or multicentre, by disease area (cancer; cardiovascular, vascular or respiratory; and all others) and by whether or not a DMC was mentioned in the paper. The sampling strategy is shown in Appendix 11; it reflects the distribution of trials published in 2000 with respect to number of centres, disease area and mention of DMC in the published report. Trials were randomly sampled within each stratum. In addition, the sample was chosen such that for 15 of the trials the country of the first author was the UK, for 15 it was North America and for 15 another country. The sample did not take account of funding source (industry/public) as this information was not collected at the time of the trial identification.

In recognition of the possibility that trial reports might not mention a DMC unless the trial was stopped early at the DMC's recommendation, the PIs identified in the selected papers were contacted whether or not a DMC was mentioned (see Appendix 12). Copies of the trial protocol were requested. The information of relevance was extracted using a standard questionnaire (shown in Appendix 13). The content of this questionnaire was based on the global list of the 23 questions (*Box 1*). A telephone interview or e-mail followed where possible to complete data extraction. In some cases, it was not possible to make contact with the lead investigator named in the paper. For these trials, other investigators and/or sponsors were contacted for information about the trial. Personal contacts of the DAMOCLES team were used to make the first contact, whenever possible.

Results

Data monitoring information was gained from 28/45 potential respondents. A further three responded but did not agree to take part. Some

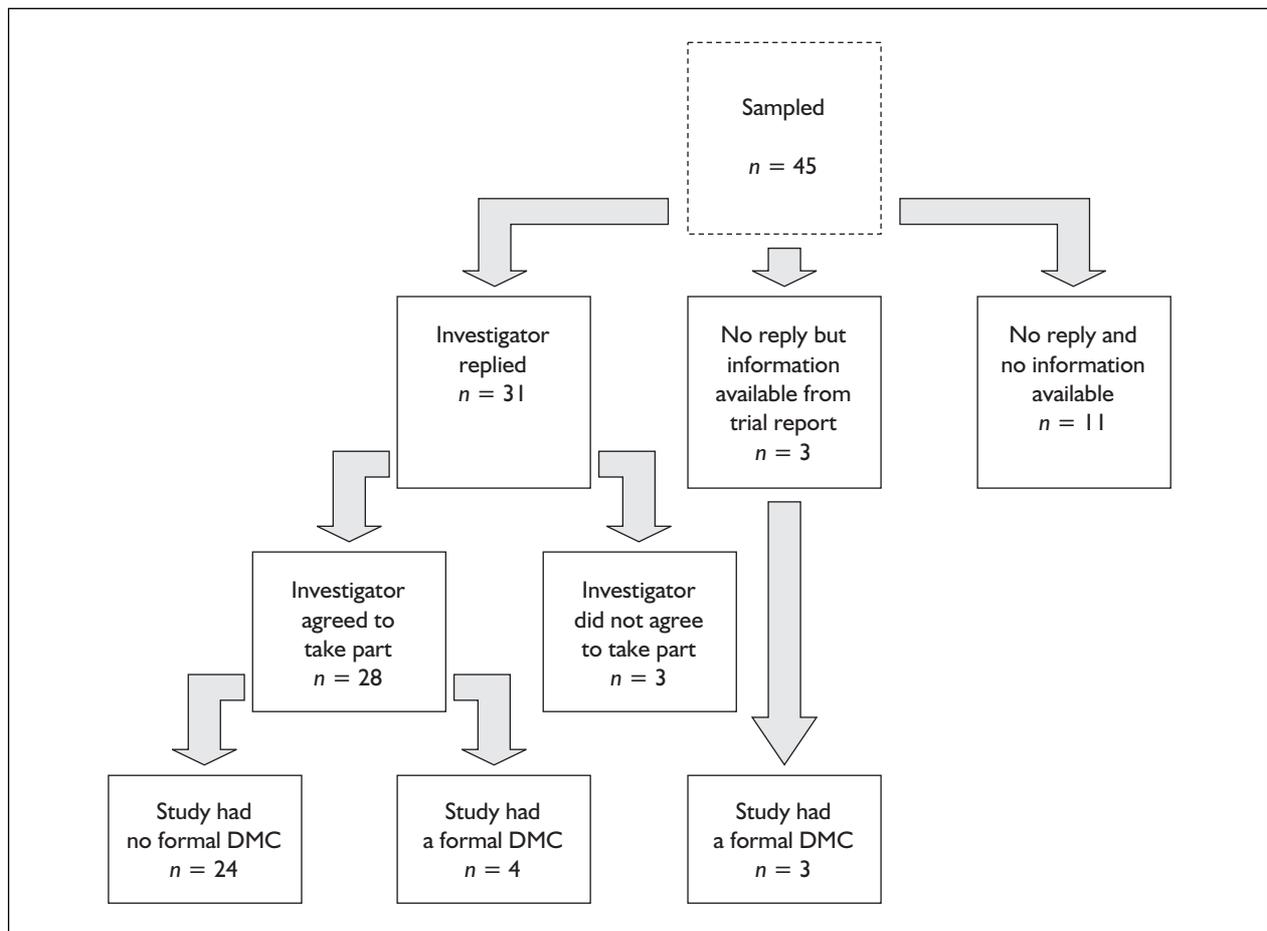


FIGURE 6 Responses received from trials sampled

information about the trial’s data monitoring procedures was available from the study report of another three trials, giving information on 31/45 trials (69%) in all (Figure 6).

The categories are not mutually exclusive in the following tables, as some of the respondents gave more than one answer to each question.

Higher response rates were obtained for multicentre trials and for trials dealing with cardiovascular or respiratory conditions (Table 18).

There was some data monitoring information available for all trials coded as having a DMC in the original database. However, in one of these trials, when contact was made with the trial’s PI, it transpired that the ‘external safety and efficacy monitoring committee’ was a monitoring body rather than a formal DMC operating to prespecified guidelines. This committee could have requested unblinding of the trial if it was thought that this was critical to patient

management; however, there were no guidelines describing circumstances in which it might do this. This committee is not included in the discussion of DMCs. Therefore, six of the seven trials with DMCs identified in the survey had formal DMCs.

One additional trial with a formal DMC was identified, although it had not mentioned a DMC in the trial report. This brought the total number of trials with a formal DMC to seven, including the three non-respondents for which data monitoring information was obtained from the trial report. Of the seven trials with DMCs, three were UK based, two were based in North America and the remaining two in other parts of Europe. Five were concerned with cardiovascular, vascular or respiratory pathology, one with cancer and one with other pathologies. One was a single-centre trial and the remaining six were multicentre trials.

Reasons for not having a DMC

Reasons given by respondents for not having a DMC are summarised in Table 19.

TABLE 18 Details of trials for which data monitoring information was available, either because the investigator agreed to take part or because mention was made of data monitoring provisions in the trial report

Details of trials	Responses/target
Mention of DMC in the article	
Yes	7/7
No	24/38
Centres	
Single-centre	8/15
Multicentre	23/30
Disease area	
Cancer	6/9
Cardiovascular/respiratory	13/15
Other	12/21
Country of first author	
UK	11/15
North America	11/15
Rest of world	9/15
Total	31/45

TABLE 19 Reasons given by respondents for not having a DMC

Reason for not having a DMC	Number of trials (n = 23)
Trial was not blinded, investigators were monitoring outcomes	6
Risk of adverse events judged to be low	6
Safety monitoring only by investigators	3
Small number of patients in trial	3
Healthcare professionals involved in the intervention were in a position to raise safety concerns	3
Short duration of trial	1
Trial did not use investigational drugs	1
No reason given	6

The most common reasons for not having a DMC were that the trial was not blinded (on the basis that informal monitoring of adverse events could be carried out during the course of the trial), or that the intervention was of a nature that made it seem unlikely to the investigators that there was a high risk of SAEs.

These reasons relate more to the safety aspect of data monitoring than efficacy. In addition, three trials performed ongoing safety monitoring, although not using interim analysis.

Of the seven trials with a DMC, three DMCs had recommended that all or part of the trial in question be stopped, one on grounds of safety, one on grounds of efficacy and one on grounds of

futility. A fourth DMC had recommended that the trial continue, but that the increased risk associated with the trial intervention be explained to patients before they entered the trial.

One of the respondents whose trial did not have a DMC added that if the trial were to be repeated now, updated good practice guidelines would require a formal DMC. This also applied, but was not stated explicitly, to another of the respondents, whose trial would now require the funder's standing DMC to oversee trial progress under its new data monitoring policy. None of the trials that did not have DMCs stopped early.

Timing and frequency of meetings

Of the four trials for which fuller DMC information was available, one DMC met seven times, one met six times, one met five times (which led to the trial stopping) and one met twice. The frequency of meetings ranged from every 4 months to annually.

Guidelines used to draft DMC procedures

Two trials used the MRC guidelines to draft their data monitoring procedures, and the other two did not use formal guidelines in setting up and defining the role of the DMC.

Time-point when the DMC was formed

One of the DMCs was a standing committee; two were formed before finalisation of the protocol (one of which suggested some changes to the protocol which were implemented), and the fourth was to have been formed before finalising the protocol, but in the event was formed after the trial had started.

Choosing the DMC membership

All four DMCs had clinicians experienced in the relevant fields; three had at least one statistician and two had epidemiologists (one of whom was a member of a DMC that did not have a statistician).

Position of the DMC with respect to the sponsor, trialists and participants

All DMC members were required to be independent of the trial, but in no case were there formal procedures to ensure this independence. For the trial with a standing DMC, the investigator commented that as the membership rotated, it sometimes became difficult to choose DMC members because clinicians could not become members while recruiting people into the trial. This was identified as a difficulty for large multicentre trials in clinical areas that have small numbers of specialist clinicians.

Conduct of meetings and means of communication used

For two of the trials, the PI or trial coordinator attended the first part of the meeting to answer questions. For the third, the investigator could attend but this was not routine and for the fourth the meetings were explicitly closed with no investigators participating. All of the trials had face-to-face DMC meetings, except for the trial with the standing DMC where it was stated that meetings would be face-to-face wherever possible, although occasionally they needed to be held by teleconference.

Training the DMC members for their role

One respondent did not discuss training the DMC members. For another, all the members had experience of DMCs so training was not felt to be an issue. Another investigator said that in the event the members had served on DMCs previously; however, they would still have been invited to serve on the DMC even if they had had no previous experience. One respondent said the DMC had inexperienced members but was not aware of any special requirements regarding training.

Who prepared the analysis, and what information was provided to the DMC?

In three cases the trial statistician performed the interim analysis; in the fourth, this was done by the epidemiologist member of the DMC. All DMCs considered recruitment rates to the trial. Two considered unblinded outcome data, with one specifying that anything of interest to the DMC would be included in the analysis. The last respondent, speaking of the standing DMC, said that recruitment rates and baseline data would be considered at each meeting until a prespecified number of events had occurred, and then an unblinded outcome analysis would be performed. One of the DMCs did not consider interim outcome data, but rather monitored recruitment rates and other relevant information.

Should information presented to the DMC be shared?

Views on sharing the interim information with other DMCs were consistent; the investigators were not enthusiastic about the DMC consulting others.

Scope of DMC recommendations and the decision-making process within the DMC

The four investigators gave an indication of the scope of the DMC's recommendations. For two, the DMC could advise stopping the trial if necessary, two said that it could suggest alterations

to the protocol, and two that it could suggest extension of patient recruitment. One investigator said that the DMC could make any recommendation regarding the conduct of the trial. Two investigators reported that DMC decisions were reached by consensus, whereas the other two gave no information on this point.

Advisory or executive role

The investigators all reported that the DMC's recommendations were advisory to the trial executive rather than being binding. In two cases, the DMC reported to the TSC, in one case to the trial funding body and in the last case to the trial PI.

Statistical stopping rules

Very little information was available on the use of statistical rules or guidelines. One investigator stated that a stopping rule was used to guide the DMC, but gave no further details. Two investigators added that in addition to using a stopping guideline, the DMC must take into account other information, which may include relevant information external to the trial. The fourth DMC did not use a stopping rule because there was no formal interim analysis.

Discussion of ethical issues

Three investigators felt that the DMC was free to discuss ethical issues specifically should it wish to do so; the other did not address this point.

The investigators all stated that they regarded the use of a DMC as valuable to ensure the appropriate running of the trial and independent oversight.

Discussion of survey of recent DMC practice

There was information available for 69% of the sample (31/45 trials). The missing data were due to refusal to take part in the study ($n = 3$) and inability to make contact with investigators ($n = 11$). Perhaps the most obvious explanation for this missing information may be that although the trials were published in 2000, in some cases they had been set up in the late 1980s. This lapse of time made investigators difficult to contact. It is possible that in some cases they were unwilling to revisit a former trial or viewed a survey of data monitoring practice as an implicit criticism of their trial (although assured that this was not the case).

There is also the possibility that amongst the researchers contacted there was a degree of self-

selection of the respondents, in that those more interested in data monitoring may be more likely to respond to the survey. Thus, the real proportion of trials with DMCs at this period might be even lower.

However, clearly, the main limitation of this survey is the small number of trials identified with a DMC. Some information about conduct and operation of DMCs was available for seven trials, with fuller details from only four.

Survey of current data monitoring practices

Aim

The aim of this part of the project was to describe current research practice in data monitoring in a sample of ongoing trials. The survey focused mainly on publicly funded trials being performed in the UK. However, some information was available from other trials.

Methods

As there was no formal register including all publicly and privately funded ongoing clinical trials in the UK, a random sample could not be selected.

The plan was to survey a total of 40 trials, of which 12 were to be funded by the NHS R&D HTA programme and 12 by the MRC to assess practice in trials funded by large government-supported research organisations. The remaining 16 were selected by contacting RECs; in the case of multicentre trials this was an MREC, and for trials with fewer than five centres this was an LREC. The aim of approaching RECs in this way was to broaden the range of trials considered to include projects conducted by individual researchers and industry-sponsored projects. The aim was to include ten industry-sponsored trials, six from the MREC and four from the LREC. The sampling strategy is shown in Appendix 14. Trials were randomly sampled from a list of 54 RCTs sponsored by the HTA programme and a list of 79 RCTs sponsored by the MRC. The HTA programme list was made available to use in January 2002 by staff at the National Coordinating Centre of that programme, and MRC trials (described as current in November 2001) were identified using the MetaRegister available at <http://www.controlled-trials.com/>. It was felt that this strategy, in the absence of a complete register of publicly funded ongoing trials, would provide a good range of trials in

terms of size, scope and funding. The RECs were identified and approached through personal contacts.

For each trial, the PI was identified and contacted directly for the HTA and MRC trials, requesting copies of the protocol and where necessary a follow-up interview to clarify data monitoring practices (see Appendix 15). For the REC-approved trials, initial contact was made by the RECs, and the DAMOCLES team completed the follow-up. The information requested from the investigators followed the questionnaire given in Appendix 16, which was based on the 23 questions shown in *Box 1*.

Results

Complete information was obtained for 32 of the 40 selected trials and partial information was available for another four trials. Information was obtained for all 12 MRC-funded trials and all 12 HTA programme-funded trials.

In practice, gaining access to information from the relevant PIs identified from REC applications proved problematic. This was partly due to delays. One source of delay was in identifying an LREC with sufficient number of trials (more than six) from appropriate specified disease areas with a mixture of industry and non-industry trials. In addition, once a suitable MREC and LREC had been identified and confirmed their support, the researchers needed to go through a two-stage process, with an initial letter being sent by the REC before they were able to make direct contact with the PIs. The most important source of delay was that several of the PIs referred the authors to the pharmaceutical company that supported the trial. Occasionally the company was then helpful, but more often they either refused outright, or agreed, but then did not provide the information. Where appropriate, the original request was followed up by e-mail, several telephone calls, repeat letters and using personal contacts. It is possible that with more time the response rate could have been improved.

Information was available for only two of the six LREC-approved trials, while there was some information available for all ten MREC-approved trials (and complete information for six of them).

Of the 36 trials for which at least some information was available, seven were conducted at a single centre and 29 were multicentre trials (involving more than one centre, and in the case of MREC-approved trials involving at least five

centres). Seven of the trials were funded by industry, while the remaining 29 were publicly funded; the four trials for which information was incomplete were all funded by industry. Eight of the trials investigated some aspect of cancer treatment, while another eight dealt with cardiovascular, other vascular or respiratory diseases. The other 20 considered other types of disease or pathology, including topics as diverse as back pain, prevention of HIV infection and treatment of head injuries.

Not all of the respondents answered all the questions, and some of the respondents gave more than one response to each question. The totals in the text and tables therefore do not necessarily sum to 36. The MREC and LREC trials are presented together.

Existence of a DMC

Twenty of the 36 trials had a DMC: 11 of the 12 MRC-funded trials, five of the 12 HTA programme-funded trials and four of the 12 REC-approved trials. Reasons for not having a DMC included:

- the TSC having discussed the issue and decided that there was no need for a DMC, for example owing to the nature of the intervention, which might be minor or involve minimal risk to patients
- the nature of the trial, which might compare the efficacy of two well-known and relatively safe interventions.

Of the 20 trials with a DMC, 14 had met at least once by the time of the survey. The guidelines on which the DMC procedures in these trials were based are summarised in *Table 20*.

The MRC Good Clinical Practice (GCP) guidelines were most commonly referred to, in relation not only to trials funded by the MRC, but also to those funded by the HTA programme (*Table 20*). This reflects the fact that the HTA programme now recommends that its investigators abide by the MRC guidelines.

Reasons for having a DMC

The reasons given by respondents for having a DMC are outlined in *Table 21*. It is noteworthy that

TABLE 20 Guidelines relevant to DMCs followed by investigators

Guideline	Source		
	MRC-funded (n = 11)	HTA-funded (n = 5)	REC-identified (n = 4)
MRC GCP guidelines	11	2	0
Advice from experienced DMC members	1	0	0
Modified MRC GCP	0	2	0
Past experience of investigators	0	1	0
Company-specific data monitoring rules	0	0	3
Old EORTC guidelines ^a	0	0	1

^a The current EORTC guidelines did not exist when the protocol for this trial was drafted.

TABLE 21 Summary of investigator reasons why a DMC was used (not mutually exclusive)

Reason	Source		
	MRC-funded (n = 11)	HTA-funded (n = 5)	REC-identified (n = 4)
To review interim analyses for efficacy	3	1	2
To perform safety monitoring (including assessing rates of adverse events)	6	1	4
To advise the TSC about possible protocol changes	1	0	0
Standard practice	3	1	0
To advise on stopping the trial	1	1	0
To give an overview of the protocol	0	1	0
To confirm recruitment targets and check the balance between groups	0	1	0

TABLE 22 Time-point at which the DMC was formed

Time point	Source		
	MRC-funded (<i>n</i> = 11)	HTA-funded (<i>n</i> = 5)	REC-identified (<i>n</i> = 4)
Before final protocol draft ^a	3	2	1
Before pilot phase of trial	1	0	0
Before trial commenced	4	1	0
After trial commenced	1	2	0
There was a standing DMC for all trials in this clinical area	2	0	1 ^b
Information not provided	0	0	2

^a In one case this referred to the DMC chair who alone had input into the trial protocol.

^b Data monitoring for this study was carried out by a group including investigators from other trials; protocol review was performed by a separate committee. Part of the way through the study the data monitoring arrangements were changed as the funder altered its DMC provisions.

the reasons given by REC-approved trials, of which three of the four trials were sponsored by industry, cover a much narrower spectrum.

Terms of reference for the DMC

The trials could be broadly classified into three groups in respect of terms of reference for DMCs. The first group (*n* = 11) had formal written terms of reference clearly identifying the DMC's mandate; for example: "To inform the steering committee if 1) there is proof beyond reasonable doubt that [treatment] is indicated or contraindicated to an extent that would influence patient management; 2) it is evident that no clear outcome will be obtained. The DMC may also suggest protocol changes." The second group (*n* = 4) had less formally defined terms of reference, for example stating that the DMCs were to monitor adverse events and advise the steering committee if there was a need to stop the trial. The third group (*n* = 5) had no information about terms of reference available. Some of the DMCs had input into their own terms of reference, and therefore it was not always possible for the protocol to define terms of reference if the DMC had not approved them.

Time-point when the DMC was formed and input into the trial protocol

Table 22 indicates the time when DMCs were formed; this information was not supplied for two trials.

Ten of the trials included in Table 22 specified that the DMC had had an opportunity to make an input to the protocol. This applied to seven of the ten funded by the MRC and two funded by the HTA programme; one was among the trials identified through RECs. Input to the protocol

included writing or contributing to the DMC's own terms of reference in all ten trials.

For the MRC-funded trials, some DMCs had input into the trial protocol, despite being formed after the final protocol had been drafted. In most cases this extended only to their own terms of reference and stopping guidelines. In one case a standing DMC had input into the draft trial protocol, which ensured that there was independent advice from a group that had good knowledge of clinical trials in the subject area.

Choosing the DMC membership

Of the 20 trials with DMCs, information on how the committee was chosen was available for 18. In 11, the PI or TSC nominated the members subject to funder approval; in three (of which two were pharmaceutical industry trials) the trial sponsor chose the DMC membership. In the remaining four trials the DMC was a standing entity and the investigators had no input into the members. Membership of DMCs is outlined in Table 23.

All of the nine MRC-funded trials that gave information on DMC membership included at least one relevant clinician and in many cases more than one, and seven included a statistician. In one of the two MRC trials whose DMC had neither a statistician nor an epidemiologist, the investigator explicitly stated that all the DMC members were well-versed in statistics. In the other, the membership was composed exclusively of clinicians and no mention was made of statistical abilities.

None of the trials in this sample had an ethicist as a DMC member. In addition, no trials included a

TABLE 23 Composition of the DMC

Expertise of member	Source		
	MRC-funded (n = 11)	HTA-funded (n = 5)	REC-identified (n = 4)
Statistician	7	4	2
≥ 1 Clinician(s) in relevant fields	9	4	2
Epidemiologist	2	1	0
Other profession	Biochemist	Nutritionist	0
	Nurse		
	Clinical trials expert		
Information not provided	2	1	1

TABLE 24 Position of DMC members and managing conflicts of interest

Independence of members	Source		
	MRC-funded (n = 11)	HTA-funded (n = 5)	REC-identified (n = 4)
Members are independent and there is a formal conflict of interest policy	0	1	0
Members are independent and there is no formal conflict of interest policy	11	4	2
Members are not independent	0	0	2

consumer representative, although one had a nurse to act as patient advocate.

Role of the chair

Two HTA-funded trials and eight MRC-funded trials gave some information about the role of the chair in DMC meetings, although this information was not very detailed. The role of the chair in the DMC was interpreted differently between the trials. In some cases, it was confined to chairing the DMC meetings. In other cases, the chair's responsibility was wider and could include deciding on the frequency and timing of the meetings, checking the data, passing queries to the PI, drafting the DMC report or circulating information to the other DMC members. The chair might also help with deciding the members of the DMC, especially if he or she had previously been on the DMC of a similar trial. In only one trial was it explicitly stated that the DMC had no fixed chair.

Position of the DMC with respect to the sponsor, trialists and participants

Members of the MRC-funded trial DMCs were all considered to be independent (see Table 24); however, none of the respondents described a formal policy for ensuring that conflicts of interest were addressed. (Where the respondents have not stated that there was a formal policy for dealing with conflicts of interest, it is assumed that there

was no policy.) One MRC-funded investigator described an informal situation where the TSC monitored the DMC for possible conflicts of interest, which were to be dealt with as they arose. In one case, one potential member of the DMC was omitted from the final committee because he worked at the same place as one of the trial investigators and it was thought that this might lead to difficulties in serving on the DMC. The consensus on a definition of independence among the MRC investigators seemed to be that the 'members should not be recruiting patients to the trial'; this definition was used by four of the 11 investigators who specified that the DMC members must be independent. No other interpretation of the requirement for independence was given by any of the MRC investigators.

For two of the five HTA programme trials it was explicitly stated that the DMC members were personal contacts of the PI who were not involved with, or recruiting to, the trial. This raises the issue of whether recruiting personal contacts of the PI to the DMC jeopardises independence and, if so, how members are to be recruited given that the pool of experts who are suitable potential DMC members is small.

One of the REC-identified trials' respondents whose DMC members were not independent of

TABLE 25 Non-DMC members present at some part of meeting

Present in addition to DMC	Source		
	MRC-funded (n = 11)	HTA-funded (n = 5)	REC-identified (n = 4)
PI	8	4	0
Trial statistician	5	2	0
Other	Data manager (1)	0	Pharmaceutical company representatives (1)
Closed to non-DMC members	0	0	1
No information	0	0	2

the trial was a pharmaceutical company where the DMC members were employees of the company, although not directly involved in the trial in question. They were not allowed to reveal the results of interim analysis to other employees.

Open, closed or mixed meetings?

The information about who should attend DMC meetings is summarised in *Table 25*.

The preference among the MRC and HTA programme trials seemed to be to have the PI present for the first part of the meeting to answer any questions that may have arisen about the conduct of the trial, and in some cases to review the recruitment or aggregated event data. Thereafter, the PI would leave the meeting. The interim results were often presented by the statistician responsible for carrying out the analysis; in the trials in this survey, this was always the trial statistician (see below).

Timing and frequency of the DMC meetings

All 20 trials with DMCs gave a response to the question of timing and frequency of meetings. Practical arrangements for DMC meetings varied and often depended on the nature of the trial. Some DMCs met regularly every 6 months or annually, whereas others planned analyses after a given number of events. For some DMCs the timing of the meetings was fixed in the protocol, whereas for others the members decided, or the chair suggested, how often meetings should take place. In some trials there was a nominal time interval, but this could be altered by the DMC according to the progress of the trial, for example if fewer events occurred than anticipated.

Means of communication used

Most respondents thought that it was desirable to meet face-to-face rather than having teleconferences. One investigator suggested that it

was beneficial to have the first meeting face-to-face even if the remainder were by teleconference, so that the members could get to know each other. However, the eight investigators who had had at least one meeting by teleconference agreed that sometimes they were necessary for the meeting to go ahead at all, especially when DMC members lived in different countries.

Experience of DMC members

All of the 20 respondents with DMCs had members with experience in data monitoring. Eight of the investigators commented that it was not necessary for all the members to be experienced, although the committee should contain some members who had served on previous DMCs. The consensus was that if a member had not been on a previous DMC, that member should at least understand the rationale for DMCs, and preferably have some background in clinical trials. One investigator recommended that a training programme be implemented for clinical experts in the field willing to serve on DMCs to increase the pool of possible DMC members.

Who prepared the data considered by the DMC?

For 17 of the 18 trials for which there were responses to this question, the trial statistician prepared the interim analysis, in two cases with input from the data manager. For the remaining trial, the analysis was prepared by the PI in blinded format, while the DMC held the randomisation codes to unblind the results if required.

Information provided to the DMC

Aspects of interim analysis that the investigators judged to be most important are described in *Table 26*.

Three of the five HTA-funded trials explicitly stated that any other trial information requested by the DMC would be provided.

TABLE 26 Information provided to the DMC

Information provided	Source		
	MRC-funded (n = 11)	HTA-funded (n = 5)	REC-identified (n = 4)
Baseline demographics	5	5	0
Recruitment rates	4	3	0
Outcome measures (for efficacy)	6	3	1
Proxy outcome measures (e.g. markers for the primary outcome)	1	0	0
Adverse event rates (for safety analysis)	5	1	3
Dropout data	3	0	0
Other	Compliance with treatment (1)	Differences between groups at baseline (1)	0
No response given	0	0	1

Among the four trials identified through RECs, the main observation is that the pharmaceutical companies placed emphasis on consideration of safety data. One company presented figures blinded by treatment group; the other company presented the information partially or completely unblinded.

Should information presented to the DMC be shared?

There was considerable variation in the investigators' opinions of whether a DMC should share information with other bodies, for example with the DMC of a similar trial, if the results of interim analysis were to give cause for concern.

Ten investigators would agree to the DMC sharing information with others if it thought this necessary; four felt that results should be kept confidential and six had no provision for this possibility. Among those who felt that the DMC could share information if required, many investigators specified that this should only be done if the DMC were concerned for the safety of trial subjects; one felt that it would be acceptable to share safety but not efficacy data. Another two suggested that any request for the DMC to share information should be passed on to the TSC, which would make a decision based on the individual case. Of those investigators who thought that the DMC should not share information, one investigator specified that the DMC should be at liberty to seek external advice, although not to divulge the results of interim analysis. The lead investigator on one of the trials, which had no clear provision for this possibility, said that any such situation would be dealt with by the TSC on an *ad hoc* basis.

Scope of DMC recommendations

For all 11 of the MRC-funded trials with DMCs

there was information on the scope of recommendations of the DMC. Five replied that the DMC would advise if stopping the trial were necessary, and two that the DMC would advise protocol changes if necessary. Seven investigators added that the DMC was free to make any recommendation. Of these seven, there was some difference in emphasis, with some investigators claiming that the DMC was free to make any recommendation it felt necessary, and others saying that although any recommendation could be made in principle, they would normally expect the DMC to confine itself to recommending that the trial be stopped if necessary.

Investigators in all five HTA-funded trials with DMCs gave information on this; three said that the DMC would advise if stopping the trial were necessary, two that the DMC would give advice on protocol changes, one that general advice about the running of the trial would be given, and one that advice about what information to release to the other investigators would be given by the DMC. A further two stated that in addition to these, the DMC could make any recommendation it felt necessary.

The four trials with DMCs identified through the RECs gave very little information on the type of decision open to DMCs, with one stating that the DMC would advise on stopping the trial, and the others giving no information on this point. One respondent in this category had their DMC provisions changed during the trial when the sponsoring body's new regulations came into force. Throughout the trial, however, the functions of protocol review and data monitoring were separate from each other, with a protocol review committee responsible for suggesting any changes to the trial design or conduct.

TABLE 27 Decision-making within the DMC

Process	Source		
	MRC-funded (n = 11)	HTA-funded (n = 5)	REC-identified (n = 1)
Consensus ^a	6	3	1
Vote ^a	2	0	0
Chair to define	2	0	0
Investigator unaware	1	1	0
Other	0	DMC to decide how decisions will be made (1)	0
No information provided	0	0	3

^a One investigator, for example, stated that a consensus would usually be reached; however, if there were great difficulty in doing so a vote would be taken.

The decision-making process within the DMC

Responses to the question of what form the decision-making process takes within each DMC are shown in *Table 27*. The most commonly reported approach was consensus, but two trials used a voting procedure. No information was provided for three of the four REC-identified trials.

Use of statistical stopping rules

Three of the 20 respondents whose trials had DMCs gave no information about whether or not the DMC used statistical stopping rules. In one trial no provision was made for this because there was no formal interim efficacy analysis. Fourteen had statistical guidelines. Respondents said that these were not to be used rigidly, but rather interpreted together with other information, such as new external information provided by the PI. A further trial used a more rigid statistical stopping rule; another, in contrast, had no formal stopping rule because the trial had multiple end-points and the PI considered that the decision to continue or stop the trial should be made by balancing the risks and benefits of the treatments.

Discussion of ethical issues

The consideration of ethical issues by the DMC was addressed in varying ways by the 16 investigators who answered this question. Two felt that in addressing the question of whether the trial should be allowed to continue, the DMC was examining a question that was primarily ethical in nature. Four investigators felt that the ethics of the trial did not really fall within the DMC's remit; one of this group felt that ethics were an issue for the REC to consider. Ten investigators felt that there was no reason why DMCs should not comment on ethical issues. The approach of this last group ranged from enthusiastic, where the

DMC had specified that it wanted to be able to consider ethical issues or where the investigator was quite happy for the DMC to discuss any aspect of the trial, to more cautious, where the investigators felt that ethical issues were not really entirely within the DMC's scope, but were willing for the DMC to identify any problems for the TSC. There was no information on this issue for four of the respondents.

Advisory or executive role of the DMC

The DMC was considered by 18 respondents to be advisory to the TSC of the trial; two respondents (both pharmaceutical companies) did not address the question of whether the DMC's output was advisory to, or binding upon, the trial executive.

Who received the report from the DMC?

The reporting system depended on the management of the trial. In 16 cases, the DMC submitted reports to the PI. In one case, the report was also submitted to a separate executive committee. In six cases the report was circulated to the PI or to a group of collaborators. No information was provided for one trial.

Discussion of survey of current DMC practice

Very little information was available on industry-sponsored trials as details of data monitoring were available for only seven; of these, four had provision for data monitoring although only two had formal DMCs.

Most of the investigators were satisfied with the data monitoring provisions of their trial. Two investigators suggested that it would have been helpful to have had a DMC meeting before the start of the trial for the members to familiarise themselves with the study and the form of the

interim analysis. One investigator commented that the statistician presenting the data did not appear to be entirely familiar with the data; it is not clear whether this was the trial statistician.

One investigator commented that the DMC was valuable, not only from an ethical and practical point of view (in ensuring that the trial was up to date with data entry and checking), but also to provide the statistician with a point of reference if he or she noticed any worrying trends while carrying out the analyses.

The formality with which the terms of reference were defined varied somewhat. A formal definition of the DMC's responsibilities may help a DMC, particularly if it has inexperienced members, to direct its discussions. In contrast, for DMCs with experienced members there may well be benefit in allowing the DMC to draft its own terms of reference and standard operating procedures, a course favoured by some of the investigators.

The choice of DMC members may be difficult if it were deemed necessary that members have previous experience and do not have a personal connection with investigators, particularly in clinical areas where there may be only a small potential pool of expertise to draw upon. Some respondents identified the need for some form of training programme or informal apprenticeship for novice DMC members. If there is a move towards including consumer representatives on DMCs, as some people have advocated, such a training programme would need to be flexible enough to cover the requirements of lay members who have had little or no previous experience of clinical trials, as well as experienced clinicians or statisticians who have not served on a DMC before.

There was also some disagreement about whether a DMC should share information. Many investigators were content to leave this to the DMC's discretion. However, some investigators seemed puzzled as to why or how this sort of situation may arise.

Finally, the question of whether a DMC should consider ethical issues elicited mixed responses. Although many of the respondents were willing for the DMC to make any recommendation it felt necessary, there was little common ground about whether ethical issues should be a subject for discussion in the DMC. The overlap of the RECs and DMCs in considering these issues seemed unclear to some investigators. None of the DMCs had a bioethicist, despite the fact that a bioethicist

is mandatory for some US trial DMCs (see next section). In addition, the investigators defined 'ethical issues' in different ways, adding further to the differences in approach.

Survey of DMC policies of key organisations involved with RCTs

Aims

The aim of this part of the project was to ascertain the current policies on DMCs of major funders of trials, regulatory agencies and other relevant organisations. It was felt that information about the policies of some influential organisations could usefully be compared and contrasted with the findings in the other two surveys described in this chapter.

Methods

A questionnaire was developed (Appendix 17) with a series of questions about data monitoring policy. The questions were drawn from the global list of 23 questions (*Box 1*). Questions of particular relevance to organisations funding, conducting or overseeing RCTs were chosen from the list by members of the DAMOCLES team to form the basis of the questionnaire. Organisations were also asked how long their policies had been in place, and whether any changes were to be made.

Given the source of funding for this project, it was decided to focus on UK-based organisations in the public sector, but also to investigate policies of some relevant overseas organisations and of the private sector. Collectively, the DAMOCLES group drew on its own experience to identify the most important funding organisations for trials within the UK, and supplemented this with information from key funders of trials in North America, South Africa and Australia. They also sought information from key organisations in industry and the regulatory agencies. A list of the organisations is given in Appendix 18.

Before contacting these organisations directly, as much of the survey proforma as possible was completed using information from their websites. The proforma was sent to each organisation, addressed to a named individual where possible. The request was either for checking or for additional information in the case of organisations that provided some information on their websites, or for completion by organisations that did not provide website information. The covering letter (Appendix 19) explaining the study and a short

summary (Appendix 20) were included. Copies of any relevant policy documents were requested.

Follow-up consisted of one postal reminder where necessary, and resolution of queries by telephone or e-mail.

Results

Work on the survey began in December 2001 and was completed by May 2002. Some information was available from the websites of 19 of 25 organisations identified; this varied from minimal to very detailed information. Some response to the letter and follow-up was received from all the organisations (25/25), although several e-mail or telephone reminders were needed for 19/25 (76%) of the organisations.

Responses for each of the 25 organisations surveyed are given in Appendix 18. These responses are summarised below for each of the questions asked. The categories are not mutually exclusive in the following tables, as some of the respondents gave more than one answer to each question.

As shown in *Table 28*, only one of the organisations had no policy about DMCs although it was considering developing a policy. A further six did not have formal policies, but provided information on their approaches to data monitoring (four of these six reported that the situation was under review). Five organisations had no formal policy but referred to ICH guidelines, and two had no formal policy but stated that they followed the MRC guidelines (which are based on the ICH 1996 guidelines). Eleven had formal policies (five referred also to NIH or ICH guidelines). Of the seven organisations without formal policies that did not refer to established guidelines, six stated that this was because they were small organisations and/or did not fund trials (although some of the organisations that did have policies did not fund trials either).

Plans to change data monitoring policies

Ten organisations were in the process of reviewing, or had plans to review, their policies on data monitoring. This included three of the organisations without formal data monitoring policies that expected to formulate policies in the future.

For the remainder of this section no distinction is made between formal and *de facto* policies. If a policy was described as under review and the new version not yet finalised, the authors referred to the version current at the time of response.

Which trials should have a DMC?

Nineteen of the organisations surveyed had a policy about which trials should have a DMC; details of their policies are given in *Table 29*.

Ten of the 19 organisations addressing this question viewed the institution of a DMC as a default position for all trials.

Terms of reference for the DMC

Twenty of the organisations had terms of reference for DMCs (*Table 30*). As the categories in the table were not prespecified but simply summarise the responses, the answers may underestimate the number of organisations that considered any of the categories to fall within the terms of reference. The most frequently described objective or purpose of the DMC was to consider data from interim analyses. The form and content of the analysis were trial dependent, but were usually unblinded. As a general rule, this information was used as the basis of a report recommending continuing or stopping the trial, or amendment of the trial protocol. In most cases (18/20 respondents) this report was in the form of recommendations (i.e. advisory), but for two organisations it was considered binding.

TABLE 28 Existence of DMC policies

DMC policy	Number (n = 25)
No policy	0
No policy but policy under consideration	1
No formal policy but <i>de facto</i> policy	2
No formal policy but <i>de facto</i> policy and formal policy under consideration	4
No formal policy but refer to ICH guidelines	5
No formal policy but follow MRC guidelines	2
Formal policies (including five referring to NIH/ICH guidelines)	11
No information	0

TABLE 29 *Trials that should have a DMC*

Type of trial	Number (n = 19) ^a
All trials as default	10
Large/multicentre/long-running	8
With public health impact	5
High risk/more than minimal risk/potentially toxic regimens/vulnerable populations	5
Phase III	4
Phase II, especially if going on to Phase III	2
For registration	1
Blinded/masked	1
Decisions made on a case-by-case basis	1
No policy	6

^a The number in parentheses in this table and in Tables 30–32 refers to the total number of respondents. Some respondents gave more than one category of response and therefore the totals may sum to more than the total number of respondents.

Terms of reference	Number (n = 20)
To protect patients in the trial	3
To consider trial protocol	3
To consider which data should be provided/request additional data	4
To consider outcome data from interim analyses	16
To consider data about safety/adverse events from interim analyses	18
To consider data about recruitment (including that from individual centres)	8
To consider 'performance' (e.g. compliance, data quality) in trial (including that from individual centres)	3
To establish/agree stopping rules	2
To apply stopping rules	7
To consider extension/progression from Phase II to Phase III	2
To consider implications of external information	7
To report on continuation/stopping/amendment	11
Resources/funding issues	4
To consider requests for interim information	4
To comment on any part of the trial	1
No policy	5

When the DMC should be initiated

All the organisations that had a policy about when a DMC should be initiated stated that the DMC should be set up at an early stage, in most cases adding that this should be early enough to comment on the trial protocol before recruitment began (Table 31).

Size and composition of the DMC

Eighteen organisations had policies about the size and composition of the DMC. The membership of those based in the UK tended to be around three or four people, whereas those based in the USA were usually larger (six or more).

Most of the respondents ($n = 14$) specified the need for appropriate clinical and statistical expertise; three USA-based organisations supplemented this with bioethicists and one with a patient advocate. Eight referred to the model of a

standing committee covering a portfolio of trials, adding appropriate experts where necessary. In nine organisations the policy was that DMC members were nominated by the trial sponsor, and in six nomination was by the investigators and their research institution, with or subject to the approval of the sponsor. In the remaining three organisations with policies, the sponsor nominated the chair, who then chose the rest of the members.

Position of the DMC with respect to the sponsor, trialists and participants

All 19 organisations with DMC policies said that the DMCs should be independent. It was not always clear what 'independence' meant in practice. Two referred to independence from the trial, and 11 specified that this meant independence from the clinical investigators and trial participants. Four also specified independence from the host institution, three

TABLE 31 When should a DMC be initiated?

Initiation of DMC	Number (n = 17)
Before the trial begins	10
As soon as the trial begins	2
At the first meeting of TSC	3
Standing committee for a group of trials already established	2
No policy	8

TABLE 32 Who receives the report from the DMC?

Recipient of the DMC report	Number (n = 25)
Sponsor	10
TSC	5
PIs	4
IRB	5
Others involved in the coordination and running of the trial ^a	3
No policy	7

^a Comprising personnel at the data centre, the study coordinator and the chair of the clinical group of the sponsor organisation responsible for general oversight of the trial.

from the TSC and one from the sponsor. Note that there is some overlap in these responses, which were not predefined in the proforma sent to the respondents.

Payment for DMC members

Fifteen of the respondents had no policy about payment for DMC members. Of the remainder, one paid an honorarium for face-to-face meetings (not teleconferences). A further nine paid expenses (usually travel and accommodation if necessary). One of these nine organisations also paid compensation for members' time and another for members' services.

Dealing with conflicts of interest

Only 11 of the organisations had policies for addressing conflicts of interest, all involving a declaration of potential conflicts. In addition, one of the 11 specified that this documentation should be regularly updated, and another that a person with a conflict of interest should leave the room during relevant discussions, if this was acceptable to the rest of the DMC.

Open, closed or mixed meetings (are non-members of the DMC allowed to attend)?

Thirteen of the organisations did not have a policy. Of the 12 that did, one respondent reported that DMC meetings were completely closed. The other 11 had a policy of mixed meetings in which unblinded data were seen in closed session, but others (e.g. investigators and/or

sponsor) could be invited to attend an open session. In five of these 11, there was a provision to invite the trial statistician to the closed session if deemed appropriate.

Who has access to accumulating data during the trial (in addition to DMC members)?

For three of the 17 respondents with a policy, only the trial statistician and the DMC had access to the accumulating data. One allowed data centre personnel access to the interim data; seven respondents stated only that participants in the trial should not have access. The six NIH organisations had a provision for access by key institute staff involved in the trial. One of these organisations said that there was also provision for the data to be seen occasionally on a confidential basis by others, usually the DMC of another trial.

Who receives the report from the DMC?

The policy for ten of the organisations was that the report should be given to the sponsor. In addition, nine organisations specified that the TSC and/or investigators also receive a copy of the report (Table 32).

Disposal of the DMC's meeting papers after the meeting

Seventeen of the organisations did not have a policy about the disposal of the DMC's meeting papers after the meeting. For three, the DMC kept the papers. The question did not specify which papers (i.e. with or without unblinded information),

so this information was unavailable. Two respondents stated that papers were destroyed at the end of the meeting. One respondent stated that the papers would be collected, but was not specific about arrangements for archiving them. Two did not have a policy about disposing of the DMC's papers, but stated that DMC minutes would be forwarded to the trial sponsor. They did not discuss whether and to what extent the minutes would contain discussion of confidential interim data.

Timing and frequency of the DMC meetings

Seventeen organisations had a policy about the timing and frequency of meetings. Eleven stated that this depended on each individual trial and would be specified in the trial protocol, although one stated that meetings should take place at least once a year. A further four organisations reported that meetings should be at least annual, and two that meetings should be at least 6-monthly.

Means of communication used (personal contact, teleconference, e-mail, etc.)

Twenty organisations had no policy on the way in which meetings should be held. Two had policies that face-to-face meetings were preferable, but teleconferences would be acceptable if necessary. Another two stated that either medium was equally acceptable. One organisation replied that meetings were usually conducted by e-mail, but could be supplemented by teleconferences as required; no mention was made of holding face-to-face meetings. This organisation had a standing DMC to review all of its trials.

Training the DMC members for their role

Twenty-three organisations had no policy about training members of the DMC. One respondent said that the organisation had no formal policy about training members, but that the first meeting of each DMC was used to orientate the members to their task and the trial. Another recommended that potentially interested participants attend DMC meetings as observers to encourage capacity building in data monitoring. This would depend on the observers maintaining independence of the trial in question.

Who produces the data considered by the DMC?

Seventeen organisations had no policy about who produces the data. Six expected the trial statistician to perform the interim analysis and prepare the DMC reports. For a further two organisations, this function was to be carried out by the DCC without an explicit statement that the report would be prepared by a statistician.

Information provided to the DMC (including whether relevant information external to the trial is included in DMC meeting discussions)

Sixteen organisations had no policy on what information would be included; nine organisations had some policy in this respect. Four stated that this would depend on the type of trial. Another three stated that the information would be unblinded, but gave no further details. Examples given of the type of information to be included in the DMC report were adverse events ($n = 1$), efficacy data ($n = 2$), information on data quality ($n = 1$), information on protocol violations ($n = 1$) and toxicity data ($n = 1$). One organisation had guidelines as to the information to be included in the report, but these were not made available to the research team. Five of the nine expected that external information (such as new data from other trials) would be considered, while another stated that consideration of external data would be unusual.

The decision-making process within the DMC

Only two organisations had a policy about how a DMC should arrive at its recommendations. Both expected decisions to be made by voting; one of these added that *ex officio* members of the DMC and observers were not permitted to vote.

Policy about addressing issues of safety and efficacy differently (e.g. giving separate guidelines for stopping)

Sixteen respondents did not address the issue of whether safety and efficacy data should be treated differently. The policy of eight organisations, all of whom referred to the ICH guidelines, was that stopping rules for efficacy should be more conservative than for safety, and that the rules for both should be specified in the trial protocol. The remaining organisation stated that these rules should be drafted on a case-by-case basis for each trial.

Are issues of patient recruitment discussed by the DMC as a matter of policy?

Fifteen organisations had no policy about whether or not patient recruitment should be considered by a DMC. The policies of the other ten varied from an unwillingness for this to be part of the discussions ($n = 1$) to an important part of the discussions ($n = 3$).

Discussion of ethical issues

Seventeen organisations did not respond to a question about policies for the discussion of ethical issues. Of the eight that did, six said that the safety and well-being of patients in the trial

was paramount ($n = 4$), important ($n = 1$) or addressed by the DMC ($n = 1$). Four respondents, all from the USA, referred to bioethicists as members of the DMC, and one of these also mentioned the need for feedback to be given to the IRB.

How long have the policies been in place?

Of the nine organisations reporting how long policies had been in place, one said it had had its DMC policies for 7 years. The other respondents' policies were more recent, with three implemented in 1998, two in 1999, two in 2001 and one currently under development.

Discussion of survey of DMC policies of key organisations involved with RCTs

In the context of this survey, some organisations reported no formal policy, but proposed ways in which they might meet the needs of investigators or trials requiring input about data monitoring procedures – these were referred to as *de facto* or informal policies. Other organisations have written procedures to provide guidance on data monitoring, which are referred to as formal policies. In many cases the demarcation between formal and informal policies was not clear from the responses received; therefore, no distinction was made between the different types of policy when reporting the findings of the survey. In many cases, even the formal policies were not very detailed, some referring to guidelines from other bodies, and some to little more than a requirement that provision for data monitoring should exist. Some of the guidelines produced by the organisations seemed to be intended for investigators' information, rather than for enforcement by the organisation.

Whereas many issues were common across organisations, some showed differences especially between North America and the UK. The NIH and its constituent organisations had some of the most detailed policies, with differences between the policies reflecting the different nature of the trials they fund. In the UK, the MRC guidelines were the most detailed, explicitly addressing most of the issues raised. Two other UK organisations referred to these guidelines. Recently established or smaller organisations, such as charities or governmental coordination bodies, often either did not have fixed policies or referred to guidelines such as the ICH GCP guidelines. For those organisations adopting ICH or MRC guidelines, however, it was not always clear to what extent the full details of these guidelines were observed. In addition, the ICH guidelines were not detailed in several areas.

The sample for the survey does not represent a comprehensive or representative sample of all organisations involved with RCTs, and as such the results should be seen as indicative only of the state of policies among these organisations at the time of the survey. In addition, the survey covered different types of organisation, including those that conducted trials, those that funded trials and those that had responsibility for overseeing the conduct of trials (see Appendix 18). Many respondents indicated that the issue was under discussion, pointing to changes such as the EU Directive and Research Governance in the UK. It is also possible that for some organisations the survey acted as a stimulus for the organisations to rethink or revisit their policies.

Chapter 6

General interviews with experienced data monitoring committee members and case studies of trials with difficult data monitoring decisions

Introduction

Background

The constitution and working practices of DMCs can vary considerably between trials, and the impact of these factors on the quality of their decision-making is currently unclear. For example, the size and balance of groups vary, the procedures for choosing the chair and membership are rarely specified and there is varying participation of the trialists in DMC meetings. There is also debate about the frequency and timing of meetings, the optimum communication medium, the role of the chair, what data should be presented, how decisions are made, and how decisions are communicated to collaborators and participants. These issues may have a significant influence on DMC decision-making.

It is against this background that qualitative methods were used to explore decision-making processes in DMCs that made 'difficult' decisions. These components of the project are described in this chapter. Data were derived from a combination of general interviews with experienced DMC members regarding their experience across a range of trials and in-depth case studies of trials where the decision-making had been 'difficult'. For the purpose of this study, a 'difficult' decision included trials that stopped early for a number of reasons (futility, efficacy, safety, toxicity) and trials that had continued despite circumstances where early stopping might have been considered. To maintain confidentiality, names and specific details relating to trials have been removed.

Part I: General interviews with experienced DMC members

Methods

For the general interviews, a purposive sample of DMC members was identified from the knowledge

and experience of the DAMOCLES project team. Potential interviewees were selected because of their extensive experience across a range of trials, and included statisticians and clinicians, in addition to some consumer representatives. In total, 15 potential interviewees were contacted by letter or e-mail (Appendix 21), of whom 14 agreed to be interviewed.

A semistructured interview schedule (Appendix 22) was used to interview DMC participants; questions focused on the interviewee's experiences of DMC decision-making and general conduct across a range of trials. Interviews were conducted face-to-face ($n = 13$) or by telephone ($n = 1$), and lasted for between 25 minutes and 1 hour and 15 minutes. All interviews were audio-recorded and transcribed verbatim, with the interviewer verifying the accuracy of the transcript.

Nvivo software (version 1.3) was used to code the data, organise similar topics into categories and continually compare these topics with earlier data. The interviewer carried out the analysis; another member of the research team separately analysed a selection of transcripts to compare coding and emerging themes.

Findings

Structure and organisation of DMCs

Size of DMC

For more complex trials, interviewees felt that a broader range of perspectives was needed to ensure that the right level of expertise and experience is provided. Although experiences of DMC size varied, it was generally felt that ideally committees should be limited to five or six members, and should be no fewer than three. However, most importantly, it was felt a DMC should be large enough to provide a diversity of perspectives and full representation at the level of expertise required. For trials that are particularly complex, it was agreed that consideration should be given to a larger DMC:

“I would say specifically from three to five people for a DMC. I find that with more than five you begin to get too many people who are not really concentrating on what the study is about. If you go to less than three I don't think you are getting a big enough range of experience and balance.”

“My feeling is that the more important the trial is, there is a case for having a bigger group of people with a wider range of backgrounds, but maybe that is wrong ...”

Selection of DMC members

The importance of selecting the right people to serve on DMCs was seen as crucial, particularly in small DMCs:

“Certainly we found three to work reasonably well, although it is not so great if you have chosen wrongly on your DMC and you have a bit of a maverick and you get into a bit of trouble because they have quite a lot of influence. One of three has more influence than one of five.”

“... People have been appointed as being the great and the good, and have not a clue about data analysis and even the function of DMCs. So, if I am formulating a DMC, I would certainly want to be extremely careful to select wisely.”

“In my experience, it is more important who you have got on the DMC rather than any rules or guidelines you might like to put down.”

Although all interviewees generally felt that DMC members should be relatively experienced and well-respected in their field, one interviewee felt strongly that the selection criteria should be exclusively for senior individuals:

“... only very senior people should be on DMCs, who have cut their teeth on clinical trials, because it is an awesome responsibility and I really think there is no place for tokenism. I think you really need very, very experienced, very senior people who carry authority and who are respected through their scholarship in the subject.”

The selection of DMC members appears to happen largely by word of mouth through the relevant networks, and it was suggested that the demand for DMC members is exceeding current supply:

“There are not enough people that are either asked or have acquired the interest or are interested in participating. A lot of the same people are involved on many DMCs.”

“You need to have people who are well-respected in the general area. That actually narrows down the field

quite a lot. Increasingly we find, as we did with [trial name removed], going across to the continent of Europe to get members on to the DMC.”

In terms of who does the selecting, interviewees reported that (in the UK) it is typically the trial organisers and PIs who make suggestions to the TSC, which approves and ensures that the suggested candidates are appropriate choices. This practice was perceived to work quite well, ensuring confidence among the PIs, TSC and trial organisers. However, as it would seem that many of the same people are selected to serve on DMCs, greater consideration may need to be given to the selection process and how best to increase the pool of potential members.

Selection of DMC statistician

Specific expertise in the clinical field is an obvious prerequisite for any DMC, in addition to an experienced statistician. Although it was collectively felt that all members have an important role to play in a DMC, it was suggested that the statistician has a particularly important role:

“... the statistician is probably the most important person at the end of the day; this is not because I myself am a statistician, but I think by virtue of their training they can grasp the data, grasp the issues much faster, and can be extremely influential.”

“I would expect the statistician to have the most leverage in any decision to stop the trial because stopping the trial would simply be based on numbers, as well as clinical aspects of the depth of adversity as it were, but as a statistician I would expect to be among the most important inputters if not the most.”

Such views appear to be based on the assumption that the statistician is closest to understanding and interpreting the data. Often the presentation of data by the trial statistician will be quite complex, requiring them to interpret and explain it, especially to the less statistically minded committee members.

In terms of the role of the statistician, it was summarised as advising on stopping rules, weighing up external evidence where appropriate, and assisting with decisions about whether a trial should continue or not.

Selection of DMC chair

The selection of the DMC chair was also considered very important to the conduct of the committee, yet the chair was commonly described as being the most difficult post to fill. Specifically,

the chair was viewed as playing a pivotal role in directing discussions and framing the decision-making:

“From the trials I have been involved in, it is a pretty critical role. If they are a good chair, they can usually direct the discussion in the direction that they feel appropriate and have a major influence on the recommendations; it’s pretty critical actually, the chair.”

As to who should select the chair, it was widely agreed that responsibility should lie with the TSC or trial organisers. From the collective experience of the interviewees, the chair was typically a clinician. However, concern was expressed as to whether this should always be the case, and whether the chair needs to be an expert on the clinical area under discussion:

“I think it is very important for the chair to be somebody who is really an expert in clinical trial methodology and also very familiar with how perverse the play of chance can be ... I think for the chair it is less important that they should have expertise in the clinical area under discussion. It’s more important they should have a really good understanding of clinical trials and also of stopping rules of clinical trials, methodology and dangers being brought about by easily suggested unconvincing evidence.”

More generally, it was felt that the selection criteria for the chair should focus on their experience of chairing meetings, preferably DMCs, their ability to understand the complexity of issues, to facilitate effective group interaction, and overall to protect the validity and credibility of the trial:

“They have to embody and always keep in mind the primary responsibility of a DMC, to protect and serve the study patient and to assist and advise the principal investigators with the ultimate objective of protecting the validity of the trial, but also very importantly its credibility ... you would like them to have a track record of doing it before, you would want them to be articulate and pretty even tempered. I would always want them to have a sense of humour.”

“I think probably the most important thing is to make certain that everybody on the committee has the chance to express themselves, and is not dominated by one of the members.”

In this collective experience, these interviewees felt that the role and responsibility of the DMC chair is based on the assumption that everyone knows what the job entails:

“Nothing was explained to me ... I had no direct contact with the funders but it would seem to me, this

is a good question as to who should specify the role of the chair. I don’t remember discussing it within the committee. I think it was assumed that everyone knew what the role was.”

None of the interviewees who had served as a DMC chair reported having any kind of remit explained to or discussed with them. Nevertheless, it was widely agreed that the role and responsibilities of the chair fall broadly into two categories. First, it is their responsibility to chair meetings and provide everyone with the opportunity to express their points of view. Second, they are expected to communicate and accurately reflect the decisions and opinions of the group to the TSC.

Although the chair is recognised as being very important in the conduct of DMCs, it was emphasised that the chair should not be totally in charge of proceedings, but rather encourage open discussion, without forcing their own opinions or views upon the committee.

Consumer representatives and ethicists

In terms of other areas of expertise to be included on a DMC, consideration may be given to the potential input of consumer representatives and ethicists. However, when interviewees were asked their thoughts on this, there were very mixed feelings not only about their possible presence on a DMC, but also what is meant by the terms ‘consumer’ and ‘ethicist’.

The perceived benefit of having a consumer representative on a DMC is the added patient perspective that they are able to bring to proceedings, which may otherwise be overlooked. However, opinions were mixed and, in general, tended not to be very supportive of consumer input on a DMC. In contrast, the contribution of consumers at the trial design stage was considered more favourably.

“Consumers don’t represent anybody any more than I do, they are just another person who maybe has the diseases of interest. Certainly on TSCs and when you design a trial I am very in favour of consumers, if for no other reason than to protect you against the maniac consumers who criticise.”

“My view is that the person who is the consumer is the person who is offered entry into a clinical trial and not some do-gooder standing in as a surrogate ...”

“It doesn’t make sense to me. If you are saying you are bringing in people who are there because they understand the biology and they understand the

science of determining efficacy and safety, consumers don't have any of those."

The most frequently described reason for not having a consumer representative on a DMC was because of the perceived difficulties faced by consumers in understanding complex data:

"Most people are only content to sit and look at the data, and just believe it. In the event I think you have to be able to look at it extremely carefully in detail. It is a very highly specialised task, and I think the chances of any consumer representative having those very skills are quite small."

Further concern was raised in relation to the potential emotional involvement of a consumer representative, and the potential stress it would place them under, particularly if there were a decision about whether to release a result that had an impact on patient care:

"If you are trying to make quite a difficult decision about whether to release a result which will then have an impact on people's care, I think it must be quite hard to disassociate yourself from that emotional type of involvement."

Related to this issue, it was felt by some interviewees that consumer representatives would have a tendency possibly to over-interpret interim data; this could potentially lead to some trials stopping prematurely.

Other interviewees opposed to consumer input on DMCs stated:

"You'll find that the efficiency of the DMC would go down and therefore it just gets dragged out."

"It's not quite as easy as people might think. Whereas I can get up to speed very rapidly ... I think it is asking an awful lot of a lay person to achieve that level of sophistication and although it is not politically correct, I would oppose it. I think it would be just out of political correctness and it would be absurd to expect a lay person can just be taken off the street to do that."

Such views were opposed by those who felt consumer representatives have a potentially positive and important role to play on DMCs:

"It is almost to be expected that professionals will dismiss the probability that uneducated people, in their terms, have a contribution to make. That may be excusably paternalistic, but it is also a bit arrogant."

"I think the idea is good. If nothing else, it makes people who sit on the committee feel more

accountable, I would have thought. I think it would be great to have a consumer on a DMC, but again you have to have the right consumer. Someone who is knowledgeable in the area and is thoughtful."

In contrast to the ambiguity regarding consumer representatives on DMCs, the same could not be said for ethicists, as their potential input on a DMC was viewed very negatively:

"I have a personal prejudice against the word ethicist, simply because I think it implies as if somehow their views on ethics are more valid than others, and I do not accept that. That doesn't necessarily mean they couldn't contribute to the DMC, but I would not be in favour."

"I have sat on data monitoring committees with an ethicist, which has not been a good experience ... I think ethicists mix up everything. The only rationale I can find is trying to create an issue of medical ethics by making things more complicated than they need to be."

Practical arrangements and procedures for DMC meetings

Role and responsibilities of the DMC

On the whole, it was felt that DMCs perform a variety of tasks in meeting their prime responsibility of safeguarding trial participants. Descriptions of their role and responsibilities were very broad in terms of monitoring incoming data, identifying adverse events and acting in an advisory capacity to the TSC on whether the trial should continue or not. It was also felt that the DMC should generally assist and advise the PI and TSC, in protecting the validity and credibility of the trial.

In terms of specific tasks for the DMC, it was widely felt that they should not be involved in writing trial protocols, but they should have a role before and after trial recruitment. Specifically, it was felt that the DMC should review and agree protocol contents, particularly if there are concerns with any of the primary goals of the trial or proposed monitoring boundaries.

In a broader sense, it was suggested that the DMC has a responsibility in ensuring that the trial stays on track and possibly should even be involved in the deliberations for the final published report. Indeed, it was suggested by one interviewee that in some situations, the DMC should arbitrate between the TSC and journal editors where there may be some controversy.

In respect of to whom the DMC reports, there was no ambiguity that this should be the TSC.

Interviewees were clear on DMCs' advisory capacity, accepting that, ultimately, it is the study investigators who retain the final responsibility for trial progress and conduct.

Although interviewees were able to provide a good, broad overview of the role and responsibilities of a DMC, it was suggested that new or inexperienced DMC members were not always clear on such issues. This was particularly well highlighted by an interviewee who described how they struggled to obtain much material or background information before their first meeting:

“When I was invited, I enquired of [name removed] as to what a statistician does on a DMC, but they had nothing to give me to read, and despite them wanting to help, I was a little bemused as to what it was I was going to be doing. I felt I was very lucky that [name removed] was the trial statistician and they attended all the meetings and prepared all the analysis for the meeting. They were telling me what I ought to be deciding.”

Terms of reference documents

Most of the interviewees were able to recall a terms of reference document at some stage during the life of a DMC, and although there were variations, they were generally described as useful documents outlining the broad role and responsibilities of the DMC. However, when asked about how and to what extent the document was used in practice, it became evident that it was commonly sidelined:

“We tend not to spend a great amount of time [on the terms of reference] or go into a great amount of detail. I don't know whether that is because people are experienced ... they don't worry too much and it is rare that we have to turn to it, but every now and again we do when things get a bit difficult. When things get difficult, process is really quite important, and this is what it is, process, but typically it's not a big issue.”

For new or inexperienced committee members, some concern was raised that they did not always fully understand the terms of reference document. Therefore, it was considered vital that more time should be given to discussing the document and its implications, especially at initial DMC meetings.

Meeting format

Although there is a variety of approaches to DMC meeting formats, there was strong agreement among interviewees that the initial meeting of a DMC is very important for discussing not only the terms of reference, but also the protocol and

general procedures for the conduct of future DMC meetings. As the DMC constitutes a very important component of a trial, it was considered essential that more emphasis be given to ensuring that all DMC members, particularly new members, fully understand the role and responsibilities of the DMC and agree on what guidelines and procedures to adopt. Many interviewees even felt that where possible, DMCs should be appointed before the trial has started recruiting, so that members have an opportunity to meet before any data are available to learn about the trial and become familiar with the protocol.

After any initial meetings have taken place, the format described by most interviewees for subsequent meetings was open sessions attended by the DMC members, study investigators, trial statisticians and perhaps representatives of the sponsor, funder or regulator with a closed session to discuss trial efficacy and safety data. Interviewees felt that an open session was a very useful forum for reviewing trial progress and exchanging information, with all members benefiting from such participation and involvement. Subsequent closed meetings are usually limited to the DMC members and possibly the trial statistician responsible for conducting the analyses.

Timing of DMC meetings

It would seem that the timing of DMC meetings varies. The collective experience of interviewees was usually an annual meeting, but often more frequently, subject to the nature and requirements of the specific trial. However, it was suggested that perhaps more consideration should be given to the timing of future meetings.

Communication media for DMC meetings

There was near unanimity among interviewees that for DMC meetings, face-to-face communication is preferable to telephone conference calls, as this is perceived to facilitate more effective group interaction. However, it was accepted that the use of telephone conference calls is inevitable, mainly because of the heavy demand on those who serve on DMCs, which makes it logistically unreasonable to expect members to attend all meetings in person:

“All meetings in the perfect world would be best using face-to-face communications, but you just can't do it, flying everyone around the world ... so I think providing you do have some meetings face-to-face, then some teleconferencing is acceptable. But I think if any major concern arises, then a meeting is pretty important.”

“I prefer a face-to-face meeting anytime. I think most people don’t like phone conferences, they just put up with them.”

Nevertheless, it was strongly felt that at least the initial DMC meeting should take place face-to-face, particularly when members do not know each other. It was also suggested that a face-to-face meeting should be arranged if possible where a DMC reaches a key decision-making stage:

“I think it would be very important not to have a key decision-making DMC by teleconference. So if you could predict that you might have to make a really difficult decision about a trial, I think it is quite difficult to have to do it by teleconference.”

Although conference calls are easier to arrange, and appear to be more efficient, interviewees did raise serious concerns about using this medium for DMC meetings. In particular, where members do not know each other it was felt conference calls do not facilitate effective communication at the same level as a face-to-face meeting. Further, some members also acknowledged that they probably participate less in a conference call and are more easily distracted, and less focused than they would be in a face-to-face situation:

“In my office I am distracted by other things, watching e-mails coming in and all that kind of stuff. Once people get together they can focus better ... I suspect that you get a more thorough discussion in a face-to-face meeting and you would be less likely to feel uncomfortable at the end of it. I really don’t know. What matters, of course, is what is decided and how comfortable people are about it.”

“If everyone is having a meeting by teleconference, you just happen to be talking to a machine in the middle of the table, which makes it very hard to pick up all the conversations and comments. It sounds like a good idea because it saves people flying across the place, but I think it’s got problems.”

Concern was also raised with regard to using conference calls when not all DMC members speak the same first language. While on the whole it was not reported as a serious problem, some interviewees were able to recall occasions when it had led to misunderstandings and difficulties in the group, which might have been avoidable in a face-to-face meeting.

Information presented to DMCs

The general experience of interviewees on the level and quality of data provided to DMCs had been satisfactory, with no reported cases of a DMC being unable to make a decision owing to

inaccurate or incomplete data. Nevertheless, a couple of interviewees did express their concern that this is an area that has been neglected, and requires greater attention:

“It seems to me that there should be dialogue between the trial statistician and the DMC prior to the first interim analysis relating to what proposed information is provided. In my experience what happens is the trial statistician writes the report and they decide what’s in it ... and sometimes they attach their own interpretation of what it is saying ... I think there is a debate to be had about what information does the DMC want, as its very common that the committee find there are things it wants that aren’t there, very common especially at the first one.”

“The quality of statistical reports for DMCs is a subject that requires greater attention than it has received; although some reports lack essential details, others often contain an excess of unnecessarily detailed tables of minor issues not pertinent to the focused ethical and scientific monitoring functions of a DMC.”

“Some of the poorer reports are vast because no-one is focused on what a DMC really needs to know and they waste a lot of paper and time, and they don’t necessarily focus on the issues of inference and ethics that a DMC needs to keep an eye on. A good report can be much shorter and written nearer to the style that you would put in a publication.”

Interviewees who had experience of DMCs liaising at the outset of a trial directly with the trial statistician on the contents of the data to be presented, felt that it was extremely helpful in ensuring the provision of an acceptable level of data for the DMC to work with. The practice of sending out information to the DMC in advance of meetings was also considered very helpful by providing committee members with an opportunity to digest the data fully, and to identify issues for discussion at the forthcoming meeting.

Decision-making procedures

The interviews suggested that one of the most commonly neglected issues with regard to DMCs is the decision-making process. Apart from stopping rules/guidelines that may be incorporated in some trials, no formal procedures or methods of decision-making are traditionally used. This was demonstrated by the fact that on only one occasion was an interviewee able to recall a DMC using a voting technique to facilitate its decision-making.

Although the use of formal statistical stopping rules is incorporated into many trial designs, they serve only as guidelines to the DMC’s decision about continued accrual to the trial, and even

then, are not necessarily hard and fast rules. In addition to considering *p*-values, DMCs consider many other aspects of trials, such as toxicity/safety, number of patients and events observed, external information and ethical concerns. No general guidelines or procedures are commonly used to assist with such issues. Instead, the collective experience of interviewees was for a general consensus to be reached by way of open-ended discussion. Usually, the chair will engage the committee in discussion of the most pertinent findings to develop opinions, and then seek to formulate a consensus that is acceptable to the group.

In terms of ways to assist and improve the decision-making process in DMCs, interviewees did not appear convinced that any procedures other than what they already used could be successfully adopted. Instead, interviewees emphasised the importance of retaining flexibility in the DMC decision-making process owing to the unique features of individual trials and scenarios faced by committees:

“A DMC would be destroying itself if you made it absolutely perfect. The essence of it is you fully respect each other and work together. That is why I like to keep it small so that you can have this feeling of unity you don’t get in a much larger group.”

“If you have to have a vote to stop or not, I think you should probably not, because if on a DMC you are not certain about whether to stop or not then the world is not going to be certain and you had better keep going. I would say you would be better to keep going until you have got a unanimous agreement.”

Reporting of DMC recommendations

Once a DMC has reached a decision, the standard practice common to all interviewees was for the DMC chair to formulate a written summary, reflecting the opinion and recommendation of the committee, to be addressed to the chair of the TSC and or study coordinators.

Minutes of meetings

Although the majority of interviewees felt that it was beneficial to record minutes from closed DMC meetings, there were some variations:

“Absolutely not for closed sessions. Real minutes tell you who says what on all the major issues and this is a confidential meeting and I don’t think that should be documented as it leaves the DMC open to exposure.”

“I’m not sure what I think about minutes. I suppose it’s how likely you think it is that the DMC may have to justify decisions they have made, and remember

why they reached that decision at that time. ... most of the DMCs I’ve been involved with have always left it to the DMC to decide if they want minutes.”

Although all interviewees were concerned to a certain degree on issues of confidentiality, it was accepted that it is not necessary to provide a verbatim account of meetings, so long as there is sufficient detail of the key issues discussed and, most importantly, the rationale for the DMC’s recommendations. There was, however, unanimous agreement that when minutes are recorded, individual DMC member names should not be attributed to any specific details in the minutes. Typically, the DMC chair is responsible for drafting the minutes of meetings, although there were some examples of other members of the DMC or the trial statistician recording minutes.

Although there were mixed feelings on the level of detail that should be recorded, it was widely agreed that it is important to record some record of meetings, particularly where meetings may only be annual, and members needed prompting of previous discussions and the rationale for decisions reached. Another but less frequently mentioned reason for recording and keeping minutes was to provide protection against potential future litigation claims that may arise. To a lesser degree, some interviewees felt it useful to record minutes or at least to summarise discussions from open sessions with the study investigators.

Training for prospective members

As it is becoming more commonplace for trials to incorporate DMCs, there is an increasing demand for members to serve on these committees. However, concern has been raised that this demand has led to members being appointed to DMCs without sufficient experience or training:

“There is a total absence of any training or enlightenment for people who are going on DMCs, what their role is and indeed what the role of the committee is.”

“There are people coming on to DMCs who seem to me to know very little about trials. Ideally you need people on DMCs who know about trials, who know about the content, what the treatment is, what the disease is, and some knowledge of statistics.”

However, there were mixed feelings on how best to prepare prospective DMC members:

“Well I wouldn’t want to set up a DMC where everybody sort of knew the game. I think new

members on DMCs can learn from the folks who have more experience than them. I am not sure I see any value in setting up formal training, as you might go on one of these courses and never be asked to be on a DMC ...”

“I think first of all there actually needs to be a wider discussion as much in public as possible, as to what the role of the DMC is. If there [are no] agreed objectives, then knowing what training to offer the role of a consumer doesn’t make a great deal of sense.”

Essentially, two approaches have been broadly advocated: first, formal training, by way of seminars and/or training packs, and second, adopting an observational approach. Although it was widely agreed that it is not possible formally to train up prospective DMC members, there was a strong feeling that there needs to be at least an improvement in the provision of background information on DMCs, combined with the use of short training seminars:

“I think apprenticeship is good, but I think we need to think more seriously about training, because it is not widespread enough. For those people who come into it, it is often very different from what they would otherwise be doing in the normal part of their research life. So I think there is a need for much clearer training than takes place at the moment.”

“I would love to have had more insight into what was expected of me. It was a steep learning curve for me ... I think that it would have been good to have attended a short course or something which told me exactly what these committees can and can’t do, and how we should weigh things up. I think I would have been more confident. As it was, I felt daunted by the seniority of the people around me, so I think more training is an excellent idea.”

Those interviewees who suggested more information combined with training seminars acknowledged that the provision of such training should be limited to either a couple of half-days or one full day. In terms of who is best placed to offer such training, it was suggested that experienced DMC members would be preferable, but perhaps consideration could also be given to incorporating professional societies involved with clinical trials. It was also suggested that any such training should aim to include case-study examples of difficult DMC decisions to provide prospective members with a feeling for what they might be faced with:

“I suppose those who have got the T-shirts could do a seminar sort of thing using worked examples ... I think people can handle this type of training much more effectively if it is populated by worked examples with the sorts of issues that might come up.”

The other main training approach advocated was based on the premise that the optimal way to provide any type of training for prospective new members is by engaging them as an observer in a real DMC. For example, the candidate would be invited to shadow a senior member of the committee for a couple of meetings, so they could be exposed to the workings of a DMC, and gain an insight into their expected role and responsibilities on the DMC:

“My own view is to have someone sit in as an observer. Maybe not for the whole series of meetings, but at least one or two to see how they function and see what people’s roles are. I think that sort of practical experience would be particularly helpful. I am sure [that] to have some more structured guidance for members would also be helpful. The trouble is, no matter how thorough that information was, you would still leave gaps because you can’t foresee every situation in every study, so laying down general principles would be fine, but actually having members who are sufficiently confident in their area and have experience of seeing how DMCs work would be very helpful.”

Although it was generally accepted that some form of training should be provided for prospective DMC members, there was a contrary minority view that no form of training was appropriate. This was largely based on the view that such a position is essentially an ‘apprenticeship-type’ role, and therefore members can only learn from their actual experience of serving as a member of a committee.

Part II: Case studies of trials with difficult data monitoring decisions

Methods

A purposive sample of trials was identified from the knowledge and experience of the DAMOCLES project team and experienced DMC members interviewed about their general experiences of DMCs. A sampling frame of 15 potential case-study trials was drawn up and five trials were selected for inclusion. However, owing to difficulties contacting DMC members from one of the trials, only four case studies have been actually described.

The trials selected were chosen to reflect a range of difficult DMC decision-making situations, across different clinical areas. For the purposes of recruitment, the PIs were considered the gatekeepers and so they were contacted initially by letter or e-mail (Appendix 23) to seek their

consent for including their trial in the study, and for permission to contact the trial DMC members.

Once consent has been received from the PI(s), DMC members were contacted by a letter or e-mail (Appendix 24) outlining the project and inviting them to participate. For each individual trial the aim was to interview as many of the DMC members as possible in addition to the PI(s). Across the five trials, a total of 26 DMC members were identified and contacted. Of the 26 contacted, 23 agreed to be interviewed. The remaining three were not interviewed owing to non-response or unavailability.

A semistructured interview schedule (Appendix 22) was developed to interview informants about the general conduct of DMC meetings and explore what made the decision-making difficult. Because of time restrictions, the majority of interviews were conducted by telephone. All interviews were audiotape-recorded and transcribed verbatim for analysis; the interviewer verified accuracy. Any relevant documents such as reports, letters and journal articles were included to supplement analysis of interviews.

Nvivo software (version 1.3) was used to assist with coding the data, organising topics into categories and facilitating comparison of topics with earlier data. The interviewer carried out analysis; another member of the project team separately analysed a selection of transcripts to compare coding and emerging themes.

Case study A

Issues under consideration by the DMC

The trial was evaluating an expensive and invasive treatment for critically ill patients. It was set up to assess whether a new treatment had a beneficial effect on survival to 1 year without severe disability in comparison with conventional management. The main difficulty for the DMC was the two-part outcome variable: effects on mortality emerged before effects on long-term disability could be assessed.

DMC membership

All five people serving on the DMC were interviewed:

- chairperson (clinician)
- two clinicians
- one epidemiologist
- one statistician.

One of the PIs was also interviewed as they were in attendance at closed meetings.

Background and experience of DMC members

Most of the DMC members knew one another fairly well and perceived it to be a well-chosen committee with a good range of experience and expertise. However, one member occasionally raised some doubts about their ability to serve on the committee, as they were not a clinician involved in the clinical trial area:

“The only one I felt slightly worried about was myself, otherwise it was absolutely the right mix I think ... I don’t remember being dissatisfied with anything except myself ... my particular weakness was that I am not a clinician and I don’t do this [disease treatment] area.. I think that put me in slight difficulty, but then this was also true of two of the others.”

With the exception of one DMC member, the committee had a considerable amount of previous experience serving on DMCs. In particular, the chair was an extremely well-respected and experienced DMC chair, although without any clinical expertise in this particular field.

Rather unusually, both the PIs were invited by the chair to attend DMC meetings as they were not directly involved in entering participants into the trial. Although it is not common practice to have the PIs in attendance at DMC meetings, no DMC members expressed unease with this arrangement.

Structure and organisation of meetings

There was a total of four DMC meetings, which took place over a 2-year period. All the meetings took place face-to-face, with the first meeting used to discuss the terms of reference, protocol and dummy table structures for future reports and tables of results. At each meeting, a report was prepared by the trial statistician that was used to guide DMC meetings. At the end of each meeting, agreement was sought regarding the DMC report to be communicated to the steering committee.

DMC members recalled being presented with good-quality trial information, which provided sufficient trial background information for the committee:

“I do think the documentation was exceptionally good. We had an enormous folder of stuff, which described what the trial was about, and what it was trying to do in great detail and how it had been put together. And we had all the documentation that the trial participants would have had and so on. So that was put together extremely well, I wasn’t wanting for any of that.”

However, as the trial progressed and data were presented to the DMC, one interviewee expressed

concern that the data processing and checking procedures were not always of a high standard:

“I did have slight trouble where the data didn’t come in as rapidly as it should have done, and when it came in, it wasn’t always checked as carefully as it should have been done. But that is a technical problem and certainly we put it right in the end, but especially if they are very big trials, it is absolutely essential that the administration in the data processing and checking is impeccable.”

DMC deliberations and decision to recommend termination of trial

It would seem that, from the first meeting, there was quite a strong suggestion that there were differences in mortality rates. However, there were few data available early on, and they were difficult to interpret at this stage. Indeed, the use of such long-term outcome variables for future trials was questioned by one of the DMC members:

“I would think very carefully in designing a future study using a complex long-term variable like that, when the stopping time is so crucial.”

As the trial progressed, statistical issues became less important because the difference in mortality was apparent without the need for statistical testing. Instead, the focus of deliberations was with regard to ethical questions:

“... almost all we ever discussed was who are we disadvantaging by continuing the study?”

Indeed, interviewees described how issues were tossed backwards and forwards between the statistician and clinicians:

“... the thing divided really into the statisticians and clinicians. The clinicians turned up for meetings thinking the statisticians would have the answers. The statisticians said it was not really a statistical question at all, it is a clinical question, so it’s over to you guys; it batted backwards and forwards.”

“I don’t think you can make formal rules for DMC where you are trying to balance information about different end-points with different importance. How on earth can you balance one death against another death?”

All the interviewees considered the role of the chair as crucial during DMC deliberations. Although to a certain extent the chair was described as taking the lead, their experience and guidance was considered very important in guiding and framing the decision-making:

“... [name of chair removed] is a very pleasant person to work with, and is a brilliant mind, and very carefully brought everybody together; and got us to understand very quickly what we really had to look at.”

“I think the chairperson took a lead role but it was definitely a group decision, but the chair certainly did take the lead in respect of conduct of the meetings and in framing the decision-making.”

In terms of the time taken to discuss issues, all of the interviewees felt their meetings were very thorough, and issues were explored comprehensively:

“People were generally asking lots of questions and trying to work out what an extra 6, or 12 months would produce. And in the end, we all realised it wasn’t going to produce anything. I think we got our views logically. There were no terribly strong contra feelings being expressed. It was just that people were trying to turn over every stone we hadn’t considered.”

Despite the fact that the interviewees were comfortable that they had discussed the issues as thoroughly as possible, one DMC member felt that the input of a lay person may have been useful:

“I think even though we weren’t directly involved in it, we were too close to the study to be really able to balance that as a member of the general public would. And I would like to have known, I wouldn’t want to have been overrun, but I really would have liked to have had a feel from somebody who wasn’t involved in the study, as to what the value of that balance was, or where that balance should lie.”

As the trial progressed and more data became available, it became clearer that the intervention was saving lives; however, it was less certain for how long the trial should continue:

“... we knew it was saving lives, and the question is how far do we keep going before we are convinced that there is a net benefit ... one had to take a longer term view of the importance of getting the right information.”

However, this member felt comfortable that the committee made the right decision to recommend continuing the trial for as long as it did:

“I think in that situation my feeling is, in terms of overall balance of benefits to the greatest good to the greatest number of people, yes some people will have missed out, but I still think it was right to carry on.”

Undoubtedly the decision-making was complex and difficult, particularly owing to the nature of

the long-term outcome variables at which the DMC was looking. Although no formal methods of consensus were adopted, interviewees felt that the chair played an important role in terms of helping them to focus on the most important issues. Although towards the end the clinicians were reported as being very keen to continue the trial, the statistician convinced them that they wouldn't be gaining what they expected by continuing:

“Although the clinicians were keener to carry on than the statistician, I think they were able to demonstrate to us that really we wouldn't be gaining what we thought we might be gaining and I think that was useful. In the end there was a lot of discussion, but we certainly all agreed without any difficulty in the end, we talked ourselves to a consensus.”

By the end of the final meeting, the DMC judged that there were enough data to conclude there was an absolute clear effect on the combined end-point. It was 2 months before recruitment was due to end formally:

“The DMC recommended to the steering committee that they look at the data with a view to stopping the trial. And the trial stopped early, 2 months before formal recruitment was due to stop.”

With regard to satisfaction with the decision reached, interviewees felt they did the best they could under the circumstances. However, it had been a difficult process, which is perhaps best summarised by one of the interviewees:

“I guess this is a trial where the difficulty lies with the data to be monitored rather than the difficulties within the committee. This is a situation where another committee could have come against a very stormy time whereas that didn't happen ... that is what we were worried about and that is why we chose this group so carefully, unusually highly respected and experienced.”

Case study B

Issues under consideration by the DMC

The key concerns of this DMC centred on their early misgivings about numbers recruited to one of the treatment options and the adverse effects resulting from dosage levels. It was intended that patients would opt for either option A or option B. Option A would randomise them between a placebo and two treatments, and option B would randomise between the two treatments with no placebo arm. The DMC anticipated that, in such a situation, few patients would opt for A, when B assured them of at least some treatment. These concerns came to fruition as the trial progressed.

DMC membership

Owing to the international nature of the trial, the DMC was comprised of three members from two countries: two joint chairpersons, two medical specialist and two statisticians. Of the six DMC members, four agreed to be interviewed, in addition to one of the PIs. The remaining two DMC members were unable to be interviewed.

Background and experience of DMC members

In terms of previous experience, all of the members had served on an earlier DMC and had experience of the trial area. Prior to that, only two members had previous knowledge or experience of serving on a DMC.

Interviewees felt comfortable with the group's mix of experience; it was also felt that an equal balance in the international composition, including the chairs, worked well, and provided a well-balanced model for the DMC:

“They were a mix of quite different skills and I think they had a particularly effective way of working as a result of monitoring [trial name removed], which they navigated very successfully. It was felt this was a very good model for a DMC.”

“They were balanced by a person with the same expertise from the other country, and I think that was an added benefit.”

In particular, interviewees felt that the background and experience of the joint chairs was valuable to the group, and provided a balanced perspective to meetings. The fact that one of the chairs did not have a clinical or statistical background did not appear to be problematic to the committee:

“These were people who had substantial experience in committee work and in ethics and law. The way I saw their role was they provided a lay and ethical oversight, and the opportunity to represent a common-sense view that stood aside from the professional input from the clinical side and the detailed analysis of numbers from the statisticians ... maintaining a proper balance between the risks that the trial participants are undergoing against the benefit for the greater good of patients to come, and people of the future.”

Structure and organisation of DMC meetings

The DMC had preliminary sessions with senior investigators before the trial started, which interviewees felt had been very valuable in allowing them to discuss how they were going to proceed in future meetings. In addition, senior investigators met with the DMC before meetings on an informal basis to provide an up-to-date summary of progress and problems.

All the DMC meetings were held face-to-face in English (not the first language of three members), and meeting venues alternated between the two countries represented. It was apparent from the interviewees, however, that difficulties with language made some discussions problematic.

All the relevant documentation was produced in English, but not circulated to members in advance of meetings. With the exception of one interviewee, it was felt that the interim analysis should have been sent out in advance of meetings to allow members more time to study the data:

“The arrangements for presentation of data at the routine meetings of the DSMC were satisfactory and ensured confidentiality. At the meetings for the interim analysis, where much more extensive data were provided, there would have been some advantage if the data sheets to DSMC members had been securely mailed a few days in advance of the meeting.”

However, as mentioned previously, owing to the particular circumstances of this trial running parallel to another major trial, some interviewees felt that sending out the interim analysis in advance of meetings would have imposed too much of a logistical burden on the coordinating centre.

The trial protocol planned for an interim analysis after 15 months, and the DMC in the early stages saw no reason to recommend any change to this. The DMC met to review the data on four separate occasions. For various reasons interviewees recalled how the provision of accurate and timely data was difficult:

“... the only problems were the ones of availability and accuracy and their presentation ... I think that really gives the dilemma about the timing which would be appropriate to make decisions and the timing in which you got the maximum material, and I think really, that is a judgement call.”

Members were provided with a terms of reference that clearly laid out the role and responsibilities of the DMC; however, interviewees did not recall this as being a particularly important or prominent document at meetings.

The general format for meetings constituted an open session between the DMC and senior investigators, followed by a confidential closed session for committee members. These open sessions with the investigators were described as being very informative especially in learning about

other relevant studies. Despite this, a couple of interviewees described feeling quite anxious about similar ongoing trials, and their possible impact on the decision-making of this DMC:

“I do think there is one thing which I think was missing which worried me from time to time. I was worried about whether at each meeting we knew about what else was going on in the world ... which could be relevant to the decision-making of that DMC meeting. ... I think that would be the thing I remember worrying about all the time, I kept thinking there is a lot going on the world out there ... is there something which would change our decision?”

This was supported further by one of the interviewees, who stated:

“The impact of other trials on this trial concerned us greatly. We were very interested in what was going on in the outside world.”

It was suggested that it might have been useful if the DMC and coordinating committee had discussed in more detail at the outset the types of problems and complexities that might arise and how they should be handled. However, it was acknowledged that in reality this might not have made any difference:

“... I think it would be very hard at the beginning of a very complicated process when other stuff is coming through all the time to have made any predictions. It might be right, but I don't feel that it would necessarily solve it.”

DMC discussions and recommendation to stop the trial

From the outset, members had expressed concerns about the trial, particularly in relation to the treatment options:

“We had misgivings about the trial. We were going to be dealing with people in an advanced stage [of disease], and the one thing we were constantly being reminded of was that we never really knew at what point these people developed the disease.. For all we knew, we could be looking at 3-year-old cases or 3-month-old cases ... It came as no surprise to us when we found we were seriously beginning to question whether the trial was really worth continuing. We did, of course, eventually reach the stage where we thought the trial should stop, and we knew this was going to cause some discussion.”

During deliberations, it would seem that statistical issues were paramount as things progressed, with one of the statisticians reported as taking a prominent role. There were no formal rules for the early termination of the trial, but the DMC

members were able to have a preliminary discussion with some of the PIs before their formal meeting to discuss possible scenarios under which the trial might be terminated.

The DMC came to their final meeting with the realisation that it was unlikely to recommend termination of the trial on grounds of a clear advantage to either group; the results presented at earlier meetings had shown only moderate differences in crucial end-points, which were not consistent in direction. However, the absence of marked differences in efficacy might justify an early termination of the trial, on the grounds that continuation was unlikely to affect the picture to any important extent.

Interviewees recollected how discussions had been relaxed, and after much discussion (at the closed DMC meeting) committee members became satisfied that there was no suggestion of consistent trends becoming clearly established with longer follow-up:

“We took the view that although consideration of the sequential nature of the analysis is important, the whole set-up in this trial was so complicated that you couldn’t easily define the conditions under which you would want to stop ... I think we took the view that a purely significant difference by itself isn’t enough. You really need to be fairly clear that the difference is big enough to make people change their practice.”

The DMC took the view that the expectations of further clarification were not high, and the case for continuing the trial had to be measured against the disadvantages of doing so. A clear consensus was reached with no members reporting feelings of unease about their recommendation to the coordinating committee, that the trial should be terminated; however, the coordinating committee did not accept this recommendation. Although the DMC members accepted that their role was advisory, there were feelings of surprise among them when the steering committee did not accept their recommendation:

“The co-ordinating committee, of course, was entitled to reject the advice of the DMC and future deliberations by the two bodies led to a general if, on the part of the DMC, reluctant agreement to continue the trial ...”

“I don’t think there was any particular row about it. I suppose we might have been a bit surprised and a bit disappointed. I don’t think we felt they were wrong to do that, because there was no particular ethical argument against continuing to randomise. After all, if there wasn’t much of a difference in these

treatments you didn’t do anyone any harm by continuing to give one half of them one, and the other half the other. It was a different sort of problem to one that would arise if there was a big difference and you felt there was a real ethical problem in continuing at that stage.”

The coordinating committee asked the DMC to accept that the trial should continue for a further short period, and that the DMC should then review whatever information emerged. Although the DMC accepted that the coordinating committee was entitled to reject the advice of the DMC, future deliberations between the two bodies led to a general if, on the part of the DMC, reluctant agreement to continue the trial for a short period.

In the end, the trial continued for another 7 months, at the end of which the coordinating committee reported that:

“The suggestion of a longer survival with the [removed] at our previous analysis had disappeared.”

Although it was suggested that it might have been more useful if some issues had been considered more fully before discussion, it was acknowledged that, in practice, this would probably have been very difficult:

“In hindsight it might have been useful if the DSMC and coordinating committee had discussed more fully, at the outset of the trial, the types of circumstances that might lead to crucial recommendations about termination. It is likely, though, that the relevant circumstances would not have been clearly envisaged at that stage and in any case the views of members of both committees might well have changed with the passage of time.”

Case study C

Issues under consideration by the DMC

A crucial feature of this DMC was the fact the committee had access to an earlier similar dose-ranging trial looking at the effects of different dosage regimens. Results from this previous trial had not been available before this trial was initiated; therefore, the DMC was very concerned at the lack of evidence relating to dosage levels being used in this trial.

DMC membership

Of the four people serving on the DMC, three were interviewed:

- chair (clinician)
- clinician
- statistician.

The fourth DMC member (statistician) was unable to be contacted for an interview. Two of the PIs were interviewed, although they were not in attendance at any DMC closed meetings.

Background and experience of members

All committee members had a good knowledge and understanding of clinical trials, and were experienced DMC members; the chair had previously served on a DMC as an ordinary member; however, this was only their second experience as a DMC chair.

Although it was generally felt that the DMC composition was satisfactory, one interviewee felt quite strongly from the outset that the committee would have been better placed with additional clinical expertise:

“I felt the composition was incorrect. [Removed] was a clinician, but I was the only hands-on clinician who understood this drug. [Removed] and the [removed] were statisticians and knew nothing about it ... I realised I was the only one from the DMC who knew anything about the drug or anything really about the active clinical area at this time ... the composition was wrong.”

Structure and organisation of DMC meetings

There does not appear to have been any preliminary briefing session before trial recruitment began to discuss stopping rules or how they were going to proceed generally in meetings. However, a document similar to a terms of reference was prepared by the DMC that outlined some guidance for managing the trial. It would seem that this document was not shared with the TSC and never formally approved. This was a source of frustration and concern for one interviewee:

“... that document had never been shared with the steering committee and was never formally approved. That was a clear gap in the management of the study that the document was not even viewed by the steering committee and therefore they were not aware what rules the DMC were following. ... they were making a judgement that was not supported by any kind of document that was available to everyone.”

In general, most of the DMC meetings were conducted face-to-face, except when an urgent meeting was called and a teleconference was arranged. Meetings were a mixture of open and closed sessions, usually with the sponsors in attendance at the open sessions. These meetings were described as ‘interactive sessions’ in which the DMC reported to the sponsor, thus providing an opportunity to discuss issues of concern.

Meetings followed the structure of the statistician’s report to the committee, and members liaised directly with the contract research organisation (CRO), which was responsible for presenting the data. This arrangement appeared to work very well, and ensured that the quality and style of reports were acceptable to the DMC.

DMC deliberations and decision to recommend termination of trial

Before any major deliberations were underway, one of the DMC members indicated that they were very unhappy with the DMC composition, and felt strongly from the initial meeting they were the only member who fully understood the complexities of the treatment being assessed.

As discussions progressed and more data became available, this DMC member continued to feel that they were the only one who understood how serious the implications of this new treatment could be. In particular, concern centred on its withdrawal effects:

“... I don’t think they understood how serious the issues were. My problem was that the other DMC members didn’t understand the importance of the dose and the dose interval here.”

Approximately 4 months after the first patient was randomised, weekly updates were being produced that led to growing concerns in the pattern of excess mortality. At this point a DMC teleconference was convened, followed by a face-to-face meeting. Although interviewees were unable to recall exact details from those meetings, it was clear that members were very concerned by the emerging data and for the safety of trial participants. At this stage, some criticism was directed at the chair:

“[name removed] was afraid to be courageous and the whole time they were trying to explore what would people think if they did this, or did that. [Name removed] was very concerned with that.”

In comparison, one of the statisticians was described as being braver, yet perhaps too focused on the numbers:

“They were extremely courageous, but totally focused on the numbers and he didn’t have a feel for what were the consequences of what we were about to do. ... we were picking up that this drug was killing people like flies and I think they were very wary about this, and this is what DMCs are all about, they are about protecting patients and this trial was not doing that.”

Following a number of teleconference and face-to-face meetings the crucial DMC meeting took place, which was to lead to its recommendation of stopping the trial. From the clinical perspective, there was concern that terminating the trial would have serious implications for this promising type of treatment in the future. For the others, concern rested on the numbers and the rate of excess mortality.

From one member's perspective, it was clearly felt unethical to continue, as patients were being exposed to a drug where there had been little prior evidence of its effects. Also, in the earlier Phase II trial there had been a slight indication that the mortality rate was going the wrong way:

"I felt the phase II trial that had been done earlier, also had a hint of mortality trending the wrong way, but it was obviously far too small to carry a lot of weight on its own I felt that based on this early mortality ... the chances of the drug actually seeing benefit for the primary outcome were extremely low ... there was no prior evidence of this drug from other sources ... I felt it was unethical to continue."

So, after much discussion, the DMC chair concluded that the trial should be stopped, based on the apparent significant adverse effects of the drug compared with the placebo. This had also been suggested in the small amount of data in the earlier study. However, even though the chair described the final decision as "clear-cut", others felt that there were differences in the strengths of agreement, with one DMC member expressing their dissatisfaction with the decision reached:

"Basically it was not my view, basically I thought I was a single dissenter to this and I thought we should make every effort to modify the protocol based on what we knew about the drug and not try to stop something because I knew what the consequences of this would be."

However, when asked to describe how strongly the recommendation being made to the steering committee was resisted, the interviewee was unable to recall. In addition, none of the other interviewed DMC members recalled any disagreement in the decision reached. However, one committee member acknowledged that there were different strengths in the decision reached:

"... there were graduations of strength of stopping ... and some were more strongly for stopping than others. But there was no-one really against the recommendation, so it was a unanimous recommendation."

Once the written recommendation had been made to the TSC, a joint meeting was held with the DMC to reveal the data behind the decision. With suggested differences in the opinions within the DMC, there were feelings among the senior investigators that the most outspoken individual on the committee drove the DMC decision:

"... there was one of the members who was particularly outspoken on the DMC, and felt very definitely that the trial should be terminated. So they were not necessarily all of the same mind, but I believe that viewpoint determined the committee's final decision."

After the TSC had studied the data, one DMC member described how at least one of the steering committee members remained unconvinced:

"The representatives of the trial steering committee, or at least one of them, didn't get convinced by the results we had, and wanted to continue the trial. We were convinced that we should not do that, so we tried to reach some type of consensus here, but it was not possible to do that because the steering committee member didn't want to stop the trial ..."

"... there was a considerable discussion about whether or not [name removed] was willing to continue as a member of the DMC ... I felt very strongly that once a DMC member dropped out, especially someone of [name removed] stature, it had to be the end. I would not have participated if they had dropped out. I would not have continued, I would have felt I was doing something wrong and so we had to convince [name removed] that these modifications actually were solving the problem and it was the design that was wrong"

During this crucial meeting, the DMC and TSC were joined by representatives from the sponsoring company, who announced that they were no longer going to fund the trial. Members of the steering committee and DMC members were surprised at this announcement; however, for those members who had advocated for the trial to stop, it was considered to be the right decision.

Undoubtedly, it had been a difficult decision-making process, and some interviewees made suggestions for future trials, especially with regard to safety reviews for future new drugs. For example, although the safety stopping guidelines taken from a data monitoring wallchart stated that there would be a safety review every 6 months, they tended to be held more frequently:

"I think for a new drug in hindsight there should have been safety reviews more often than that, although in practice we did it more often."

However, perhaps the most controversial part of this data monitoring experience was the fact that the DMC oversaw and had access to data from a previous unpublished dose-ranging trial:

“When I look back at it in retrospective, I should have refused to participate in the DMC if they were going to do these two trials in parallel, ... you can't do two trials simultaneously trying to find out what the appropriate dose is in a mortality trial.”

“The problem was, the dose levels were not well known at the time ... the best way would have been if they had closed the first dose-finding study to see what doses they should recommend, and then started the other one, but that was not done.”

Case study D

Issues under consideration by the DMC

The key issue under consideration by the DMC was to do with new external evidence that came to light from a number of sources. Details of the external evidence were provided to the DMC by the PIs along with analysis of the first couple of hundred patients recruited to the trial; an urgent DMC meeting was then convened to discuss the data. As there were so few data from this particular trial, almost the same information was available to the DMC, PIs and TSC members.

DMC membership

All four DMC people who served on the DMC agreed to be interviewed:

- chair
- statistician
- two clinicians.

In addition, one of the PIs was interviewed, as he serviced the committee and attended all DMC meetings.

Background and experience of DMC members

In terms of previous experience, only one interviewee had not served on a DMC before. However, all the committee members appeared to have a good knowledge and understanding of, and practical experience with, clinical trials. Although none of the committee members had worked together before or was familiar with each other's expertise, this was generally not regarded as being very significant:

“... the calibre of the DMC member is far more important than whether you know them or not. I am on quite a few DMCs and have no problem at all working with people I don't know.”

All the interviewees collectively agreed that the role of the chair was extremely important for the quality of group functioning. In this case, the chair was a well-respected clinician with extensive experience and knowledge of multicentre clinical trials. However, they had no knowledge of this particular field and little previous experience of serving on a DMC. This was also their first experience as chair of a DMC.

Despite this lack of clinical expertise and DMC experience, the chair felt very clear and confident about their role and responsibilities:

“I was to work closely with the chairman of the trial steering committee to monitor the data on an interim basis so that the trial would not continue longer than was necessary ... and to be kept apprised of the science of the subject and any data that existed prior to the trial, or that appeared during the trial, bearing in mind that I knew nothing about the subject itself.”

When asked whether they felt it was a disadvantage in not having the specialist clinical knowledge under discussion, they described feeling:

“Entirely comfortable because the principles of clinical trials and the statistics of clinical trials can be generalised across all subject areas.”

With limited knowledge of the workings of DMCs and no previous experience of chairing such committees, there was no discussion of their role and responsibilities as chair:

“It wasn't explicitly described, but the assumption was a fair assumption that I know about the workings of a DMC.”

Structure and organisation of meetings

The DMC had had no preliminary briefing session or introductory meeting before trial recruitment had begun, and so their first meeting was called (by teleconference) with the specific remit to discuss the emerging external evidence. All the relevant information had been circulated to committee members at least a week in advance of the meeting. Members were also provided with terms of reference which broadly outlined the role and responsibilities of the committee.

It was strongly felt by almost all the committee members that it would have been beneficial if there had been an opportunity to meet before the trial began, to discuss how they were going to proceed and handle issues for future meetings. Added to this, concern was raised about the use of teleconferencing for their first meeting:

“... if we had met as a group almost as soon as the trial had been funded and agreed, if we had met then we would have been better prepared for what followed, because our first contact wouldn't have been in relation to some crisis ... having a chance to meet and decide how as a group we were going to deal with the terms of reference I think would have been very helpful.”

“ I think looking back it would have been easier if there had been some communication, at least from the chair of the committee. The only communication I had had was with the trial group. Face-to-face meetings in advance, or at the time would have been good, but I recognised that it is awkward when people are long distance. But having never even spoken with the chair before that meeting made it a bit difficult to know what the plan was for the meeting to proceed.”

In terms of how the teleconference was handled, there was general dissatisfaction regarding its conduct and how the final decision was reached. In particular, criticism has focused on the role of the chair, with descriptions of it being a rushed meeting with no initial discussion about how best to proceed:

“The chairperson was certainly the most dominant figure, there is no doubt about it. I seem to remember we all assembled and the chairperson's secretary was there and they came on the phone to sort this out and it was all a very brisk affair. That was my only lasting memory of the individuals involved.”

“As I recall ... the chair took a fairly strong view and very much took the lead, probably more so than they would have done in a face-to-face meeting because I think there has to be a fairly disciplined approach to a teleconference. There was a perception that this had to be done very quickly. I am not sure why that was, but it was done by teleconference and it did move very quickly, but I think the chair was certainly very much in the lead.”

“The shortest DMC meeting I have ever had is that one about the [removed] ... half an hour, I would have thought.”

DMC deliberations and decision-making

It would appear that the main tensions in the DMC deliberations and decision-making process were between the clinical interpretation and the methodology:

“There was a methodologist who knew nothing about the topic area arguing that the trial must continue. Yet the two people who were involved in the topic area were much more uncertain about it.”

The general feeling from the interviewees was recollections of shared confusion about whether it

was even relevant for the DMC to be considering external evidence, and what weighting to give it. None of the committee members had been in a similar situation before and they felt very unsure on how best to make a decision and recommendation to the TSC:

“There was confusion about what they should or should not recommend and to what extent they should or should not take note of external evidence. They felt they should take note of external evidence, but they didn't know how much weight to give it, whether it was of relevance to them, and if so, how it was relevant to them and what they should do with that information. There was quite widespread confusion and I shared that confusion because I had no idea. It was all new to all of us.”

During the discussion the chair was described as taking a dominant role, yet as they did not have any expert knowledge in this clinical area it was felt that they had to rely quite heavily on the PI in attendance:

“... Suddenly faced with this very difficult decision about the trial, they had no idea at all about the topic area, and it made it extremely difficult for them to be an effective chair. There was one other person on the committee who had no experience of this field, so there was a lack of knowledge about the topic area which made it quite difficult for them to make judgements.”

“The chairperson didn't say they were vulnerable in any way, but they did keep asking for input into the clinical relevance of this.”

In terms of discussing the issues and engaging in the decision-making process, it seems that, in addition to the chair, there was one other individual who played quite a dominant role which resulted in other members participating less:

“I think a lot of the committee felt very under-empowered to contribute very much. The two people who contributed the most were the chair ... who needed to because it was a teleconference ... and [name withheld], who again is extremely experienced. Those were the two most vocal members and those were the two who knew nothing about the area.”

“When you are talking against two trialists, its very difficult to argue with them ... [Name withheld] was extremely strong in saying the trial must continue, which was extremely reassuring for the other DMC members, even though they couldn't quite necessarily understand the logic behind it ... I think it was a very good demonstration of group dynamics where one person can almost force everybody else into agreeing with them when that isn't their instinct and wasn't their instinct when they first went into the

meeting. If you are terribly forceful, that can happen.”

This was further supported by another interviewee, who felt that it was difficult to contribute and fully participate in the meeting owing to the telephone conference situation:

“I believe that I made my views known on that conference call, but I didn’t find it easy to do so. I would have found it easier face-to-face, but whether there would have been more interest in my perspective if I had been face-to-face and a difference in the end result, I don’t know.”

In reaching a consensus for the recommendation to the TSC, there appear to have been mixed feelings about the strength of decision reached:

“I don’t recall there being a good consensus reached ... I recall a more middle of the road kind of result at the meeting ... I don’t recall it being a strong recommendation.”

In the end, the chair concluded that, based on what had been discussed, the DMC should

recommend that the trial continue, subject to the trial protocol being amended. Although no one was reported as disagreeing with the chair’s conclusion, some members clearly had been very dissatisfied with the decision reached:

“I don’t think people were happy with that decision necessarily, and the inability to express their unhappiness was because of the situation, the telephone conference. If it had been face-to-face, it would certainly have been easier to pick up that they were unhappy because it would have shown. The whole thing could have been explored more.”

After lengthy discussions, the TSC decided that continuing with the trial could not be justified, and recruitment was stopped. The decision of the TSC led to mixed feelings from DMC members:

“I actually was supportive of stopping the trial. I was relieved to hear they had stopped it.”

“... It was a pragmatic decision that they thought they would not get the recruitment they had projected because people would be unwilling to take part in it. I think scientifically that was a poor decision.”

Chapter 7

Discussion

Introduction

The DAMOCLES project used a range of approaches to consider behavioural, procedural and organisational aspects of data monitoring in RCTs, and these have been described in earlier chapters of this report. The project aimed to develop guidance for future practice. Structured around the 23 prespecified questions (*Box 1*), this chapter compares and contrasts the findings of the different approaches and discusses their implications for future DMCs. Where clear views have emerged and are endorsed by members of the DAMOCLES group, these have been highlighted as recommendations in Chapter 8.

Which trials need an independent DMC? (Question 1)

The sample survey of published reports of RCTs showed that the proportion with DMCs mentioned among those reported in general medical journals more than doubled between 1990 and 2000. DMCs were more likely if trials had larger sample sizes, were multicentre and/or multicountry, had survival as a primary outcome measure, or were likely to take a relatively long time to complete.

Nevertheless, in only 26% of trial reports in the general journals was it stated that there was a DMC, the percentage ranging from 3 to 35% across the six journals sampled. The overall rate in the general journals was higher than that found in specialist journals, among which there was also wide variation in reported usage. DMCs were relatively commonly described in trials reported in cardiology and infection journals, but none of the 76 trial reports identified in psychiatry journals mentioned a DMC.

The survey of policies about DMCs of major organisations involved in trials (such as funders and regulatory agencies) is likely to provide a pointer to the role of DMCs in future trials. This showed that funders are increasingly prescriptive about the need for DMCs in trials that they support. Nineteen of the 25 organisations had a policy about which trials need a DMC. For ten, the policy was for trials to have a DMC 'as default',

whereas for the others the policy was more selective (see *Table 29*).

The review of the literature on DMCs found broad agreement that nearly all trials need some form of formal data monitoring. Common models for DMCs vary in their degree of independence (see *Table 2*). However, independent DMCs are increasingly accepted components of RCTs. Suggested characteristics of trials that need a DMC (see *Box 2*) include definitive trials likely to have a profound effect on practice, trials with vital status or irreversible serious morbidity as primary outcome, trials of long duration, blinded (masked) as opposed to open trials, trials that require complex monitoring (e.g. to assess the balance of risks and benefits) and trials in vulnerable groups of patients.

A further suggested category was trials where there is a strong reason for independent evaluation because of concerns about likely vested interests. In principle, there are potential vested interests in any trial that may jeopardise the trial's integrity. For this reason, it may be more appropriate to assume that in general a DMC is required, and rather to reverse the question and to ask which trials do **not** need a DMC. There appear to be three broad scenarios where this may apply. The first is where it is not possible for a DMC to make a contribution to a trial. For example, a trial may be of such short duration as to make a DMC infeasible. This is also likely to apply to many cross-over trials. The second scenario is where any observed differences between trial groups, however extreme, would not prompt any change in the trial's protocol (such as early stopping). It has been suggested that this could, for example, apply to small trials with outcomes that are 'minor'. The third scenario is where there is no reason for thinking that an independent DMC would reach any conclusions that significantly differed from decisions that would be reached after internal monitoring. This latter criterion appears to be behind the suggestions that open trials, and specifically trials testing a behavioural or an administrative intervention, do not require a DMC (see *Box 3*). This does not, however, seem appropriate as a general rule. Participants in these sorts of trials need protection from the vested

interests of investigators and sponsors in just the same way as participants in other trials, and open trials can, and arguably should, have blinded interim analyses.

A plethora of different names has been used to describe groups responsible for data monitoring in trials (see Chapter 4, *Table 16*), and this is potentially confusing. A standard term would be desirable and the DAMOCLES study group favours 'data monitoring committee' (DMC).

Who should decide the details of how a DMC operates? (Question 2)

The DAMOCLES project has explored in detail many aspects of DMC operation and showed wide variation between trials in many of these. Differences among DMC members (and others involved in the trial) in their understanding of these could lead to difficulties within the committee (or between the committee and those to whom it is responsible). For this reason there is a general view that all parties (DMC, investigators and sponsors/funders) can beneficially agree many of the details of how a DMC operates in advance. This could be in the form of standard operating procedures, or a charter. It is, however, implicit in the independent nature of a DMC that it has some flexibility (such as in requesting extra analyses or meetings as it sees fit, or in choosing to modify the criteria upon which it makes recommendations).

A template for a DMC charter was developed within this project and is presented as *Table 33*. It aims to cover the range of operational issues that are relevant to DMCs in a systematic way, adaptable for individual trials.

What should the DMC's terms of reference cover? (Question 3)

One aspect that would be covered in such a charter is often called the terms of reference: a description of what the DMC should do. Terms of reference have varied between trials, although there has been little direct disagreement. The surveys of recently completed trials showed that terms of reference tend to be of two types: specific guidance about monitoring interim data, or a description of the purposes of DMCs in more general terms. The terms of reference identified in

the review of funders tend to be of the latter type, outlining the core tasks that funders expected to be covered by a DMC (see Chapter 5, *Table 30*); the three most commonly mentioned were 'consider outcome data from interim analyses', 'consider data about safety and adverse events', and 'report on continuation/stopping/amendment'. When the experienced DMC members were interviewed, they mentioned how important terms of reference can be when there are difficult decisions to be made. They thought that it was very important that time was put aside to agree these at the beginning of a trial. However, their experience of DMCs had been that often little attention had been given to this at the times when DMCs were being established.

In the review of the literature on DMCs, terms of reference were explored in more detail. The DMCs' roles (what DMCs do) were distinguished from their responsibilities (to whom DMCs are responsible). Roles have been divided between major and ancillary (see Chapter 2, *Table 3*). The major roles could all be relevant to an individual trial, although not all are essential and the emphasis may vary. This table therefore provides a useful checklist when a DMC is established as a basis for agreeing in advance what it will or will not do (and indeed these are all covered in the template for a DMC charter; see *Table 33*).

In its deliberations, a DMC should take into account the interests and concerns of a number of groups (see Chapter 2, *Box 4*): trial participants, future patients to be enrolled in the trial, patients with the target condition who will be treated after the trial, society in general, the investigators, the TSC and the sponsor. Explicit recognition of this in a DMC's terms of reference should clarify later deliberations, particularly at times when the interests of the various groups seem to conflict.

Does the DMC have a role before the trial recruitment phase? (Question 4)

The main roles suggested for DMCs before trial recruitment starts are: to agree how the DMC will operate (e.g. through a charter), to agree what it will do (terms of reference), and to review the trial protocol and procedures, including guidelines for stopping early and the analysis plan. There was wide agreement among the experienced DMC members who were interviewed of the value of an early meeting to address these issues.

The likely benefits of a charter and of agreed terms of reference have been outlined above. Consideration of interim data by a DMC without such structures in place risks less effective functioning by the DMC and hence poor decision-making. In addition, if it postpones such decisions until later on, knowledge of interim analyses could adversely affect a DMC's ability to agree its working arrangements.

People invited to become members of a DMC should only do so on the basis that the trial's protocol is acceptable to them. Some aspects of a trial's protocol have a major bearing on the DMC. These include the choice of primary outcome, the analysis plan, the size of difference between trial groups that is thought to be clinically important, and what statistical approach will be used to monitor data. It is difficult to see how a DMC could function if it was unhappy about any of these; the deliberations of a DMC before the start of the trial may therefore reasonably lead to changes in any of these aspects of a protocol, although these are likely to be in detail only. A wider role for the DMC in protocol development is questionable as this is primarily the responsibility of the investigators.

An early meeting before any trial data are available may also provide an easier atmosphere for members to get to know each other. One suggestion has been that an early meeting may also be used to discuss hypothetical scenarios and how the committee may respond if these situations actually occurred in the trial. It is not clear, however, whether this has ever been tried.

How should regulatory issues impact on the DMC? (Question 5)

The commercial sensitivity of a trial performed for drug licensing purposes may make a company reluctant to establish an independent DMC. Both the ICH⁵⁷ and FDA³⁶ encourage independent DMCs. They argue that this benefits the sponsor as well as the participants and enhances the credibility of the trial. In particular, the sponsor is protected from pressure to disclose results prematurely for commercial reasons.

The survey of recent reports of trials showed that around 25% of those with pharmaceutical company involvement explicitly mentioned a DMC and there was some evidence that this rate was higher than for other trials. It was not possible to distinguish trials mounted for regulatory purposes from other trials supported by pharmaceutical

companies. It proved particularly difficult to obtain information about pharmaceutical company trials in the survey of ongoing trials; the four trials for which information was incomplete were all in this category. Of the three pharmaceutical trials with DMCs for which there is information, one DMC was independent, one had independent 'voting' members but with additional non-voting company members, and the third had a DMC drawn from within the company.

There are aspects of trials performed for regulatory purposes that have important implications for independent DMCs. The need to report to the regulatory authorities brings extra responsibilities. Some authorities expect to see in advance a copy of the protocol, which would include details of how a DMC will function. ICH E9 and draft FDA guidance state that all DMC meeting records should be submitted to the regulatory body, although they do not expect to see interim analyses and do not want to be an "observer ... or member ..." of a DMC. Significant protocol changes recommended by a DMC have to be notified to the FDA.

Any decision by the DMC in a pharmaceutical trial could have major regulatory consequences. Early stopping of a trial before there is sufficient information to meet regulatory requirements could mean that a useful drug is not licensed or its licence is delayed, and the company would be penalised commercially. Where a DMC is thinking of recommending that a pivotal trial (on which regulatory approval will depend) closes recruitment early, consultation with the FDA may clarify the implications, although the FDA would "rarely, if ever", advise a sponsor on whether or not to stop a trial.³⁶

The commercial sensitivity of a regulatory trial enhances the need for confidentiality in all dealings of the DMC. There may be pressure from the sponsor to allow access to interim analyses. The FDA expects to be notified if this occurs, and ICH E9 says that the role of any sponsor representative on the DMC must be clearly defined. In these circumstances, it is not unusual for analyses to be performed by a statistician who is independent of the company to ensure complete confidentiality and objectivity of interpretation.

What should the membership of a DMC be? (Question 6)

The size of DMCs varies considerably: the median size identified in the survey of published reports

of trials was four, ranging from one to eight, and the review of the literature found suggestions ranging from three to more than 20, although these could include people attending who were not members. There was evidence from the review of organisations' policies that DMCs in the USA tend to be larger than those in the UK. The conclusion of the review of the literature on small group processes was that size is likely to have little impact on the decision made, but may affect the quality of the decision-making. Very small groups (e.g. three or four members) are less likely to represent the full range of opinion and individuals are more likely to dominate, hence poorer quality decisions are more likely. In larger groups (e.g. 12 or more members) there may be reluctance to express views, conflicts may appear and there may be a bias towards riskier decisions. On the basis of this literature a size of six to 12 members appears optimum. There are practical difficulties associated with larger committees, such as finding people who are qualified and willing (given the small pool available), arranging meeting dates, ensuring confidentiality and covering the costs (especially if international). The experienced DMC members in their interviews thought that the size should be limited to six or fewer, while recognising that DMCs should be large enough to provide appropriate diversity of perspectives with the right level of expertise and experience. Choosing an odd number has been suggested if voting is to be used (see below).

The review of the literature identified three models for DMCs. In the first model, all members (defined in this report as those who are fully involved in the decision-making process) are completely independent of the trial and an independent statistician conducts the analyses. This model is less commonly used than the others, principally because of concerns about the ability of independent statisticians to do appropriate analyses when they are not intimately involved in a trial; there are also practical difficulties finding an independent statistician prepared to undertake what are often complex analyses. In the second model, people involved in the trial attend the meeting but decision-making is limited to members, who are all independent. A common approach is for the trial's statistician to prepare and present interim analyses to the DMC. The trial's statistician may sit in on the DMC's discussions or be asked to leave once the report has been presented. If others associated with the trial attend, such as representatives of the investigators or the sponsor, the meeting is often split into open and closed sessions, with

confidential information only discussed in closed sessions after these people have left the meeting. In the third model, people involved in the trial, particularly the study investigators, are involved in decision-making and hence, by definition, are members of the DMC. Often the majority of the DMC members are independent, although sometimes independents are in the minority. The potential advantage of involving study investigators in the decision-making is that the deeper knowledge of the trial that an investigator brings to the meetings should increase its competence, while the involvement of independent members should protect against biased decision-making. Knowledge of interim analyses may, however, jeopardise the impartiality of the investigator, affecting his or her ability to lead the trial. The view of the DAMOCLES group is that a member of the trial group who is not involved in patient recruitment, such as the trial statistician or another non-clinician, should attend the DMC, but the formal members should all be independent. Others involved in the trial, such as investigators recruiting to the trial and the sponsor, may usefully be involved in open sessions (see below) where confidential information is not discussed, but then leave the meeting when trial analyses are considered.

As discussed above, an appropriate range of membership is needed while keeping the size of the group manageable. Statistical and clinical input is clearly essential. More than one clinician may be needed to give the range of input required and to avoid over-dependence (or perceived over-dependence) on a single individual, as illustrated in Case Study C (see Chapter 6). The review of the literature on small groups suggested that diversity is likely to improve decision-making, provided that any conflict is handled appropriately. Involvement of a consumer representative may improve the quality of decision-making, provided that they are able to participate fully. Some of the experienced DMC members when interviewed were sceptical about whether such a person could participate fully given the technical nature and complexity of the process, and questioned whether they could be fully independent. There was no support from experienced DMC members for an ethicist to be a member of DMCs. The policies of three of the US organisations surveyed were to supplement membership of their DMCs with an ethicist, although none of the current trials surveyed included an ethicist. Experienced DMC members when interviewed expressed strongly held views about the importance of selecting 'the right people' to serve on DMCs, arguing that they

should be 'senior and experienced'. They were concerned about the effect that a 'maverick' member could have on the functioning of a DMC. These uncertainties suggest that extension of DMC membership beyond clinicians, trialists and statisticians should be formally evaluated.

The ways in which DMCs are chosen also vary. A common approach is for the investigators or TSC to suggest members, subject to approval by the sponsor. In two of the three ongoing pharmaceutical company trials surveyed, the DMC was chosen by the company. In four of the other ongoing trials the DMC was a standing entity responsible for a number of trials and the investigators had no influence on this. The important requirement is that the DMC is truly independent, with the necessary range of expertise. It is also important, however, that both the sponsor and investigators have confidence in the DMC; it therefore seems reasonable for them both to agree membership before it is finalised.

Experienced DMC members who were interviewed saw the appointment of the chair of the DMC as crucial. They thought that the chair should have an understanding of both clinical and statistical issues, and should have had experience of chairing meetings, with the ability to facilitate effective interaction in the group. The findings in the small group processes review were that chairs have a big impact on decision outcome and the quality of decision-making. The review suggested that sound decision-making was more likely if the chair was facilitating (rather than directive) and impartial (in the sense of being open to others' opinions and not expressing their own views until after a full discussion).

How is independence to be maintained? (Question 7)

Table 4 (Chapter 2) lists characteristics of independence and lays out the arguments for and against inclusion of potential types of DMC members. As discussed earlier, a common approach is to limit the DMC to people who have no link with, or apparent vested interest in, the trial and its results. It therefore seems reasonable for there to be a formal check for potential conflicts of interests before or when the DMC first meets. Arguably, these characteristics should be monitored to ensure that independence is maintained. The review of decision fiascos underlined the importance of small groups being clearly accountable for their decisions. The

process by which DMC decisions are made should be explicit and transparent. In respect of payments, it appears to be generally accepted that reimbursement of travel, accommodation and communication expenses is appropriate, and that any other payments should be so modest as to have no likely effect on decision-making. Nevertheless, consideration should be given to providing some recompense for the time involved.

Should the DMC deliberations be open or closed? (Question 8)

As a general rule interim trial data are kept confidential and restricted to the DMC and selected people such as the statistician who performs the interim analyses. The basis for this is that trends in the data, which may well be due to chance, could lead to false conclusions. Current or potential trial participants, or the clinicians involved in recruitment, would then leave the trial, and the trial would fail to provide a clear and reliable answer to the question being addressed. In addition, others with a vested interest in the results, such as a sponsoring company, may withdraw support, leading to (inappropriate) early termination. Deliberations of a DMC are therefore usually closed, although it is not uncommon to have an open session with the trial investigators and/or sponsors to discuss general issues such as recruitment rates. This widely held view has been challenged, as outlined in Chapter 2 (Question 8). The argument for totally open data monitoring reflects a different view of what is in the best interests of trial participants, future participants and society. More experience is needed of this approach to clarify its effects.

One of the three common models for DMCs is for people involved in the trial, such as the trial's statistician, to attend the DMC meetings, but not as formal members. The reviews of small group processes concluded that the implications of having non-members at a meeting were unclear: it may be inhibitory such that members would be more inclined to vote with the majority, or it may increase the DMC's sense of accountability.

What are the optimal practical arrangements for interim analysis and data monitoring? (Question 9)

The view of the experienced DMC members was that the optimal timing for meetings varies from

trial to trial and so the frequency should be flexible and at the discretion of the DMC or its chair. Most DMCs build in a minimum frequency. In the survey of ongoing trials, this was generally 6-monthly or annually, or after a given number of outcome 'events'. The effects of such practical arrangements on other types of small decision-making groups do not appear to have been studied.

The review of small group processes did, however, suggest that face-to-face meetings are likely to be a more effective way of facilitating communication between DMC members. This was the preferred option of both the experienced DMC members and the respondents to the survey of ongoing trials, particularly for the first meeting, for any meeting where a major decision is made, or for multinational DMCs who do not share the same first language. Respondents considered that teleconference was a less satisfactory medium, because it can inhibit communication and hence decision-making. However, they thought that it had a place because of the practical difficulties in bringing some DMCs together. To the authors' knowledge, anonymous electronic discussions have not been tried. These can allow anonymity, which can enhance quality of decision-making in small groups. Future DMCs should consider using these and building in an evaluation of their usefulness.

What sort of training or preparation should DMC members have? (Question 10)

In their interviews, experienced DMC members expressed concerns that increasing demand for DMCs may have led to the appointment of members who have insufficient experience or expertise. Some thought that formal training would help, although others were sceptical about its value. The findings in this project show that training and preparation of DMC members have hitherto received little attention. In none of the recently completed trials had members received any formal training (partly because many had previous experience) and 24 of the 25 organisations surveyed had no policy about training. Most commonly, new members learn from more experienced members 'on the job', with the first meeting providing orientation. It is widely accepted that all DMCs should include members with DMC experience, although what represents the minimum is not clear. The introduction of inexperienced members is easier in larger

committees and this is one attraction of the approach used by North American cooperative groups, which is to have a large DMC covering a number of trials. Other models are for inexperienced people to attend DMC meetings as observers, or to be mentored by more experienced members of the DMC that they join. Other suggested approaches to training are through informal study of published case studies and by formal training courses. The review of decision-making in small groups suggested that chairs of DMCs may benefit from training to develop facilitation, conflict management and impartial chairing skills. All members would need training if formal decision-making approaches (such as devil's advocacy) were used. The DAMOCLES group discussed the value of training in ethics to provide a framework for DMC discussions. No examples of this were found, and the experienced DMC members held strong views that involvement of ethicists in DMC deliberations had not been helpful in their experience. Nevertheless, opportunities to participate in discussions about ethical dilemmas in advance of DMC meetings may help some inexperienced DMC members. The view of the DAMOCLES group is that development of training for DMC membership should be pursued further, but initiatives should include evaluation so that their value can be assessed.

What material should be available to a DMC? (Question 11)

Table 5 (Chapter 2) lists the areas of a trial that a DMC may consider and the specific aspects where they may wish to have information. This could provide a useful checklist when a DMC is considering what materials it wishes to receive. It is likely to be useful for the DMC to agree the template of the report in advance, including the detailed structure and content of the tables. This should ensure that the committee receives what it requires, but not more detail than it needs. If the meeting is to have both open and closed sessions, two reports (or two formats) will be necessary. The analysis plan should be outlined in the protocol, but should be agreed with the DMC. In their interviews, the experienced DMC members emphasised the value of early discussions with whoever will write the reports to the DMC (describing the interim analyses) and the importance of being given the right amount of information; their experience was that too much detail can be overwhelming. The review of small group decision-making suggested that too much detail could increase the likelihood of making a

wrong decision, since the amount of the evidence may cloud the quality of the evidence. The surveys suggested that the information provided to DMCs varies (see *Table 26* in Chapter 5 for examples), although this may be in emphasis rather than content. The survey of ongoing trials suggested that there is more emphasis on safety data in trials funded by pharmaceutical companies than in other trials. The small group processes review, however, suggested that DMCs should be given all the information about benefits and risks in a balanced way, on the basis that partial disclosure may affect decision-making. This review also suggested that excessive publicity related to the trial should be avoided if possible, as this can cause significant bias in small group decision-making. This could happen, for example, because of the commercial importance of a major pharmaceutical trial.

One area of controversy is whether the treatment groups should be masked in DMC reports. Although some respondents argued in favour of this on the basis that it may prevent inappropriate premature decisions, most commentators felt that masking hampers the DMC from doing its job properly because aspects of data monitoring require knowledge of the allocation. Either way, the format should be agreed with the DMC in advance.

The general feeling from the review of the literature on DMCs was that receiving the report in advance of each DMC meeting is of value because it allows members to have a chance to read it thoroughly; the experienced DMC members endorsed this. There is also wide agreement that DMCs should routinely consider evidence from other similar studies that have been reported. Marshalling this information can involve a large amount of work and so it is unrealistic to expect the DMC to do this; commonly, the investigators provide a systematic review, which is updated for each report. Again, the DAMOCLES group recommend that arrangements are agreed in advance of the DMC seeing any interim trial analyses. As described in Chapter 2 (Question 11; Should there be interaction with other DMCs?), the issues around sharing information with another DMC of a similar trial being mounted by other investigators are more complex because of the confidential nature of the committees' deliberations and the fact that both DMCs are considering accumulating data. It is not clear what is best in these circumstances. There are merits in the committee chairs making contact and agreeing to consult each other if their committee is faced

by, or has decided to make, a decision that would change that trial's protocol (including an early end to recruitment).

It is widely agreed that DMCs should see analyses that are as up to date as possible. It has been argued that this should include unchecked data, but that efforts should be made to assess the extent to which these data may change after they have been cleaned.

Who should own the interim data and analyses? (Question 12)

Little information about the ownership of interim data and analyses was found in any of the components of this project. While it seems fair to assume that the owners of the overall dataset also own the interim data, the ownership of interim analyses is more problematical (see Chapter 2, Question 12). It may be more appropriate to see the DMC as guardians (rather than owners) of the interim analyses and in that role the DMC would decide who, if anyone, outside the DMC could see them. Once the trial has been completed and the full dataset analysed the DMC's guardianship role of interim analyses would have been discharged.

Should non-comparative analyses (which are administrative and not separated by treatment arm) be carried out? (Question 13)

Administrative analyses are usually considered to be those that assess factors important to the integrity of a trial without the need to reveal comparative outcome data. They cover aspects of the trial such as recruitment, treatment compliance, randomisation, data quality and data completeness that affect data monitoring but are the prime responsibility of the trial organisers and TSC. It is these aspects that are commonly discussed at open sessions with those involved in running the trial. Non-comparative analyses of outcome data are sometimes considered or requested, for example for reassessing the assumptions behind the original sample size calculations, or for presenting to participating clinicians to encourage their continued participation. These can be based on control data only, experimental arm data only or pooled overall data. As discussed in Chapter 2 (Question 13), there are potential dangers in these analyses. The choice of analysis, the people to whom the analysis

will be made available and likely implications should all be thought through carefully in advance.

Is the DMC advisory (to make recommendations) or executive (to make decisions)? (Question 14)

An advisory rather than executive function for DMCs was favoured in all parts of the project. A common approach described in the surveys and the interviews with the experienced DMC members was for the chair to report the recommendations of a DMC to the PI or TSC, on the basis that it is the trial organisers who are ultimately responsible for the conduct of the trial. The survey of organisations involved in trials, however, showed that the majority with a policy expected the DMC's report to go to the sponsor. Although it is usual for the trial organisers to accept a DMC's recommendations, they can still choose not to, as for example happened in Case Study B (see Chapter 6). The two organisations whose policies were that DMC decisions were binding (i.e. executive) were both North American.

What decisions and recommendations should be open to the DMC? (Question 15)

Although the surveys of DMCs in current and completed trials (described in Chapter 5) suggested variation in the types of recommendation that a DMC could make, this probably reflects differences in emphasis rather than true disagreement. The range of options open to a DMC is described in detail in Chapter 2 (Question 15).

Recommendations can be made about changes to the trial's protocol before a trial starts. Once the trial has started, the most common recommendation is that a trial should continue without modification. Other options are stopping the trial completely or partially, or continuing the trial with modifications. The implications of any decision depend on the stage that the trial has reached. If recruitment is continuing, recruitment can stop early, usually with early reporting; if recruitment is complete but trial treatment continuing, the less effective treatment can be stopped early, again usually with early reporting; if the trial is in the follow-up stage, just early reporting can be recommended. At the outset, a DMC should understand the range of options open to it and the implications that these would have for the trial.

However, it is reasonable for a DMC to make any suggestions (which may or may not be acted on) that it thinks will enhance the conduct of the trial.

How should the decisions or recommendations be reached within the DMC? (Question 16)

Only two of the 25 organisations surveyed had a policy about the way in which DMCs should reach their decisions and recommendations. The experienced DMC members who were interviewed saw this as a neglected area. In their experience there had been no pre-agreed procedure, apart from stopping guidelines, and the use of voting had been rare, as had other formal procedures for decision-making. Discussion within the DMC had led to the development of opinions and then unanimous agreement had been reached. The experienced DMC members generally favoured this approach. Where information was available in the trials surveyed, unanimous agreement had been the approach most commonly used. In other trials the decision-making approach had been left to the DMC or its chair to decide the method to be used, while others used voting. An odd number of members has been recommended if voting is to be used. The review of small group processes suggested that standards of proof should be explicit in DMCs. Decisions should be unanimous where possible, with voting encouraged, but only after a full discussion. This review also suggested that formal decision-making tools (e.g. devil's advocacy, electronic discussions which avoid one person dominating) may be useful for DMCs, especially where the information is complex. These warrant further exploration.

What should be the role of formal statistical methods in DMCs? (Question 17)

Monitoring of clinical trials always involves some form of statistical analysis. It is widely accepted, however, that statistics are only one of a number of considerations that a DMC needs to take into account when monitoring accumulating data. Others include the balance of risk and benefit, the internal consistency of results, the consistency with any external evidence and the likelihood that the results would influence clinical practice. Statistical criteria should therefore be considered guidelines rather than rules. The various approaches to statistical monitoring of accumulating trial data

are summarised in Appendix 1. It is important for the DMC to understand the statistical approach chosen and the meaning of any statistical guidelines derived from this. It is essential that both the DMC statistician and the trial statistician are competent to apply them to the interim analyses.

Should specific trial designs influence the proceedings? (Question 18)

The review of the literature on DMCs identified situations where the design of a trial would affect its data monitoring. For example, standard data-dependent stopping guidelines generally assume individual randomisation and these would not be appropriate for cluster randomised trials. Difficulties are presented to DMCs by trials with composite outcomes, particularly if the outcomes become known at different times, as in Case Study A (see Chapter 6), and by trials where the relative effect on an outcome may change over time, such that there is a disproportionate difference early in the trial. Data monitoring in equivalence trials must take into account compliance levels if a misleading claim of equivalence is to be avoided. Some commentators have suggested that asymmetric statistical boundaries should be used in circumstances where the interest is only in establishing superiority (or greater toxicity) of one arm of a trial. However, data monitoring usually involves weighing benefits and risks with no assumption of direction of effect, in which case symmetrical boundaries would be more appropriate.

How should ethical issues be handled in DMCs? (Question 19)

The primary purpose of a DMC may be seen as ensuring that continuing a trial according to its protocol is ethical. RECs will have agreed the ethical basis for that protocol, and the DMC should approach their role from that starting point rather than their own personal perspectives. Ethical dilemmas for a DMC are often characterised as balancing the interests of participants against the interests of future patients. The authors are inclined to agree with Armitage⁵⁵ that this is too simplistic; rather, it is a question of when the evidence is sufficiently persuasive that it is clear what is in the best interests of both current participants and future patients. The degree of

conservatism or radicalism in the decision-making of a DMC is reflected in its terms of reference and monitoring plans, which include the statistical guidelines. Evidence from the small group processes review suggests that DMC members, especially the chair, should have some experience of discussing this type of issue. Whether the DMC has a broader remit in respect of ethical issues is more controversial, and this was reflected in responses in the survey of recently completed trials. While some felt that the DMC should restrict itself to ethical issues related to whether or not the trial should continue, others saw no reason why the DMC should not comment on other ethical issues. Some of these respondents felt that wider ethical issues were the responsibility of the TSC or RECs. The different views of what ethical issues are the responsibility of a DMC are reflected in the fact that some US organisations recommend that a bioethicist should be a member of DMCs, whereas some hostility to this was identified in the interviews with experienced DMC members.

What should DMCs do with their decisions or recommendations? (Question 20)

As discussed above and described in Chapter 2 (Question 20), DMCs usually report to the sponsor or the investigators (in the form of a representative executive committee). To avoid any conflict between the two it may be better if the DMC reports to both at the same time and involves both in subsequent discussions. Sometimes the sponsor makes the final decision and sometimes it is a joint decision between the sponsor and investigators. Appropriate regulatory authorities and RECs should also be kept informed, and this is the responsibility of the organisers rather than the DMC.

If there are no concerns about the trial, it is likely that only a brief, but carefully worded, statement from the DMC chair is needed, encouraging progress in the trial while avoiding any mention of the content of any confidential interim analyses. If a change to the protocol is being recommended by a DMC a much fuller report is likely to be needed. Alternatively, a meeting may be arranged with the investigators where the interim analyses are shared. In contrast, it has been argued that no data should be released if the DMC is executive, on the basis that the final analyses will then be conducted without knowledge of what the interim analyses showed; the rationale and feasibility of this are questionable, however.

Both ICH E9 and the draft FDA guidance document indicate that minuting of DMC meetings is expected, and state that in regulatory trials all minutes should be submitted, possibly in a blinded form, to the regulatory authorities. The review of the literature on DMCs suggested almost unanimous agreement that a formal record should be made for both closed and open meetings, and some funders (including the UK HTA programme) now require this. The record should document the major points of discussion, any decisions and actions and their reasons, and any additional information required for future meetings. It was suggested that attribution of names should be limited to members with a specific expertise or a particular view. A useful checklist of the areas that may be covered was given in Chapter 2 (Question 20; Are minutes of the meetings or notes of decisions made?). The experienced DMC members who were interviewed favoured keeping a record of each meeting that described the key issues discussed and the rationale for any decisions taken. They thought that a summary of open sessions would also be useful; such a record acts as a reminder and aids future decision-making when meetings are some time apart. Some also thought that the record could be important if there was any future litigation about the trial, albeit that this is an unlikely event. The experienced DMC members when interviewed thought that minutes would be too detailed and they were not comfortable about naming individuals in any report of a meeting. Commentators recognised that keeping a record can involve a significant amount of work. If a representative of the data management centre attends the DMC, this person is often asked to keep a record (for later approval by the chair). Otherwise, a member of the DMC will have to do this. This should be agreed in advance.

What should be done in ‘difficult’ situations? (Question 21)

In their interviews, the experienced DMC members emphasised that having terms of reference and standard procedures in place is particularly valuable when data monitoring becomes difficult. The proposed charter (*Table 33*) provides a template for defining these. While the agreed procedures may include a set of prearranged meetings, the DMC should build in flexibility to call meetings at short notice if a difficult issue arises. A problem may be due to a development within the trial or to pressure coming from outside the trial, such as from the

sponsor or mass media. Closed sessions restricted to DMC members provide the best forum for formulating a response. The review of small group processes suggested that increasing conflict caused by difficult situations may actually improve decision quality and outcome, provided that all members express their views. This review identified the importance of making sufficient time available. Factors that make it more difficult for members to participate (e.g. short notice, telephone conference call) could reduce the quality of decision-making and this appears to have occurred in Case Study D (see Chapter 6). Formal decision support techniques may be helpful, particularly where unforeseen circumstances increase the complexity of the information to be considered.

Should some DMC decisions be considered to be ‘errors’? (Question 22)

It is difficult to judge whether a DMC has made a good or poor decision. At the time of the decision, it incorporates a subjective element and later judgement has the benefit of hindsight. In other settings, errors are identified by post hoc assessment by public opinion, or where the consequences of a decision were not those intended (see section ‘Error and bias in small group decision-making’, p. 52). Scenarios where an erroneous DMC decision is likely or possible are listed in Chapter 2 (Question 22). There are examples of trials that have stopped early for a benefit that has disappeared or is no longer clinically significant in the final analysis (e.g. Case Study 1 in Chapter 2⁷⁹). A decision to continue a trial in the hope that a benefit will emerge, despite evidence of harm, can be criticised if no benefit emerges, but the decision may still have been correct at the time.

Where a DMC has an advisory rather than an executive role, it is not the DMC that has the final decision and so arguably the DMC is not responsible for the decision. It is rare, however, for a DMC recommendation not to be accepted. Nevertheless, the group that receives the recommendation may not be independent: an investigator may wish the trial to continue to provide an even clearer result, while the sponsor, such as a pharmaceutical company, may wish to stop the trial for other reasons, such as commercial considerations. Where the decision-making body, such as a TSC, does not agree with a

DMC's recommendation, it has been suggested that a third committee (based on an 'escalation' clause in the terms of reference) be established. This group may include representatives of both the DMC and TSC, as well as independents.

One of the principal arguments for including a representative of the trial within the DMC deliberations, irrespective of whether or not as a member who can vote, is that the investigators' perspectives can be incorporated in the decision-making. Building a consensus that includes the investigators is likely to reduce the chances of later disagreement when a DMC makes a recommendation.

Concerns have been expressed about who would be deemed liable in a legal challenge about decisions made during the conduct of a trial. Although hitherto this does not appear to have been an issue, it would be reasonable for DMCs to seek clarification of this when they are first established.

The review of small group processes suggested ways to reduce the chances of a decision error: thorough review of evidence, accurate comprehension of instructions, active participation by all group members, resolution of differences through discussion, and systematic matching of case facts to the criteria for various

decision options. The review suggested that absence of these increases the likelihood of an error.

What should the DMC's role be concerning publications? (Question 23)

The possible involvement of the DMC in publication of the trial results has received little attention. There are good reasons for the DMC at least being able to comment on a draft of the trial report. Members of the DMC may have a useful contribution to make in the interpretation of the results because of their knowledge of the trial data. (They should not be authors of the report as this would be contrary to their independent status.) Members can also voice any difference of opinion, so that disagreement after publication is avoided if possible. The report should also describe the DMC and the data monitoring process, and it is reasonable for the DMC to have the chance to check this.

Failure to report a trial is a form of scientific misconduct. Some commentators have suggested that it is the DMC's responsibility to ensure that reporting occurs, even by writing the report themselves if the investigators fail to do so. It is, however, questionable how feasible this would be.

TABLE 33 Charter for DMCs. (Also reported in the Lancet: DAMOCLES Study Group. A proposed charter for clinical trial data monitoring committees: helping them to do their job well. Lancet 2005;365:711–22.)

Content	Comments from DAMOCLES and illustrative examples
<p>1. Introduction</p> <p>Name (and sponsor's ID) of trial plus ISRCTN and/or EUDRACT number</p> <p>Objectives of trial, including interventions being investigated</p> <p>Outline of scope of charter</p>	<p>Insert name (and sponsor's ID) of trial and registration number (e.g. ISRCTN and/or EUDRACT number)</p> <p>Insert objectives of trial, including interventions being investigated from protocol. Suggest including a flowchart of the trial design (insert as Figure 1)</p> <p>Summary of the purpose and content of this document</p> <p><i>Illustrative example:</i> <i>The purpose of this document is to describe the roles and responsibilities of the independent DMC for the [– give name –] trial, including the timing of meetings, methods of providing information to and from the DMC, frequency and format of meetings, statistical issues and relationships with other committees</i></p>
<p>2. Roles and responsibilities</p> <p>A broad statement of the aims of the committee</p>	<p><i>Illustrative example:^a</i> <i>“To protect and serve [trial] patients (especially re: safety) and to assist and advise principal investigators so as to protect the validity and credibility of the trial.”</i> <i>“To safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, and monitor the overall conduct of the clinical trial.”</i></p>
<p>Terms of reference</p>	<p><i>Illustrative example:^a</i> <i>“The DMC should receive and review the progress and accruing data of this trial and provide advice on the conduct of the trial to the TSC.</i> <i>The DMC should inform the chair of the TSC if, in their view:</i> <i>(i) the results are likely to convince a broad range of clinicians, including those supporting the trial and the general clinical community, that on balance one trial arm is clearly indicated or contraindicated for all participants or a particular category of participants, and there was a reasonable expectation that this new evidence would materially influence patient management; or</i> <i>(ii) it becomes evident that no clear outcome would be obtained.”</i></p>
<p>Specific roles of DMC</p>	<p>Interim review of the trial's progress including updated figures on recruitment, data quality, and main outcomes and safety data.</p> <p>A selection of specific aspects could be compiled from the following list:</p> <ul style="list-style-type: none"> • assess data quality, including completeness (and by so doing encourage collection of high-quality data) • monitor recruitment figures and losses to follow-up • monitor compliance with the protocol by participants and investigators • monitor organisation and implementation of trial protocol (the DMC should only perform this role in the absence of other trial oversight committees) • monitor evidence for treatment differences in the main efficacy outcome measures • monitor evidence for treatment harm (e.g. toxicity data, SAEs, deaths) • decide whether to recommend that the trial continues to recruit participants or whether recruitment should be terminated, either for everyone or for some treatment groups and/or some participant subgroups • suggest additional data analyses • advise on protocol modifications suggested by investigators or sponsors (e.g. to inclusion criteria, trial end-points or sample size) • monitor planned sample size assumptions • monitor continuing appropriateness of patient information • monitor compliance with previous DMC recommendations • consider the ethical implications of any recommendations made by the DMC • assess the impact and relevance of external evidence

continued

TABLE 33 Charter for DMCs (cont'd)

Content	Comments from DAMOCLES and illustrative examples
3. Before or early in the trial Whether the DMC will have input into the protocol	All potential DMC members should have sight of the protocol/outline before agreeing to join the committee. Before recruitment begins the trial will have undergone review by the funder/sponsor (e.g. peer review for public sector trials), scrutiny by other trial committees and a research ethics committee. Therefore, if a potential DMC member has major reservations about the trial (e.g. the protocol or the logistics) they should report these to the trial office and may decide not to accept the invitation to join. DMC members should be independent and constructively critical of the ongoing trial, but also supportive of aims and methods of the trial.
Whether the DMC will meet before the start of the trial	It is recommended that, if possible, the DMC meets before the trial starts or early in the course of the trial, to discuss the protocol, the trial, any analysis plan, future meetings, and to have the opportunity to clarify any aspects with the PIs. The DMC should meet within one year of recruitment commencing. Consideration should be given to an initial 'dummy' report, including the use of shell (empty) tables, to familiarise the DMC members with the format that will be used in the reports.
Any issues specific to the disease under study	Issues specific to the disease under study should be described.
Any specific regulatory issues	The DMC should be aware of any regulatory implications of their recommendations.
Any other issues specific to the treatment under study	Issues specific to the treatment under study should be described.
Whether members of the DMC will have a contract	Members of a DMC, particularly for a commercially sponsored trial, may be advised to have a contract making clear the need for confidentiality and the liability status of the DMC members. When there is no such contract, DMC members could formally register their assent by confirming (1) that they agree to be on the DMC and (2) that they agree with the contents of this charter.
4. Composition Membership and size of the DMC	Membership should consist of a small number of members (perhaps four to five), who include at least one clinician experienced in the clinical area and at least one statistician. Additional members experienced in clinical trials should reflect the other specialities involved in the trial. Consideration may be given to consumer representation. In the case of intergroup trials or trials with international collaboration consideration should be given to broad representation. The members should be independent of the trial (e.g. should not be involved with the trial in any other way or have some competing interest that could impact on the trial). Any competing interests, both real and potential, should be declared. A short competing interest form should be completed and returned by the DMC members to the trial coordinating centre (Annex 1). The members of the DMC for this trial are: (1) [give name] (2) [give name] (3) [give name] It may be helpful to provide the trial coordinating centre with brief personal details (say, one paragraph) of all DMC members, especially relating to experience relevant to the trial and to the operation of DMCs (such information need not be contained within the charter).
The chair, how they are chosen and the chair's role (likewise, if relevant, the vice-chair)	The chair should have previous experience of serving on DMCs and experience of chairing meetings, and should be able to facilitate and summarise discussions. The chair is sometimes chosen by the sponsor or the investigators running the trial and sometimes by the DMC members themselves. The chair is expected to facilitate and summarise discussions.
The responsibilities of the DMC statistician	The DMC membership will include a statistician to provide independent statistical expertise.

continued

TABLE 33 Charter for DMCs (cont'd)

Content	Comments from DAMOCLES and illustrative examples
The responsibilities of the trial statistician	The trial statistician, [give name], will produce (or oversee the production of) the report to the DMC and will participate in DMC meetings, guiding the DMC through the report, participating in DMC discussions and, on some occasions, taking notes.
The responsibilities of the trial office team	The trial office team (e.g. trial manager, etc.) usually only inputs to the production of the non-confidential sections of the DMC report.
The responsibilities of the PI and other members of the trial management group	The PI may be asked, and should be available, to attend open sessions of the DMC meeting. The other members of the trial management group will not usually be expected to attend but can attend open sessions when necessary (see Organisation of DMC meetings).
5. Relationships	
Relationships with PIs, other trial committees (e.g. TSC or executive committee), sponsor and regulatory bodies	A diagram can help to clarify relationships when there are several interrelated committees. A short statement of the responsibilities of the other committees should be given if these are not provided in the protocol.
Clarification of whether the DMC is advisory (make recommendations) or executive (make decisions)	It is customary that the DMC does not make decisions about the trial, but rather makes recommendations to an appropriate executive committee or its chair.
Payments to DMC members	Members should be reimbursed for travel and accommodation. Any other payments or rewards should be specified.
The need for DMC members to disclose information about any competing interests	Competing interests should be disclosed. These are not restricted to financial matters involvement in other trials or intellectual investment could be relevant. Although members may well be able to act objectively despite such connections, complete disclosure enhances credibility (see Annex 1). DMC members should not use interim results to inform trading in pharmaceutical shares, and careful consideration should be given to trading in stock of companies with competing products.
6. Organisation of DMC meetings	
Expected frequency of DMC meetings	The exact frequency of meetings will depend on any statistical plans specified, and otherwise on trial events. The wishes of the DMC and needs of the trial office will be considered when planning each meeting. It is recommended that the DMC meet at least yearly.
Whether meetings will be face-to-face or by teleconference	The first meeting should ideally be face-to-face to facilitate full discussion and allow members to get to know each other. It is recommended that all subsequent meetings should be face-to-face if possible, with teleconference as a second option.
How DMC meetings will be organised, especially regarding open and closed sessions, including who will be present in each session	A mixture of open and closed sessions is recommended. Closed and open sessions should be defined. Commonly, only DMC members and others whom they specifically invite, e.g. the trial statistician, are present in closed sessions. In open sessions, all those attending the closed session are joined by the PI(s) and/or the head of the trials office, and sometimes also representatives of the sponsor, funder or regulator, as relevant. The format of the meetings should be described.
	<p><i>Illustrative example:</i></p> <ol style="list-style-type: none"> 1. Open session: introduction and any 'open' parts of the report 2. Closed session: DMC discussion of 'closed' parts of the report and, if necessary, 3. Open session: discussion with other attendees on any matters arising from the previous session(s) 4. Closed session: extra closed session

continued

TABLE 33 Charter for DMCs (cont'd)

Content	Comments from DAMOCLES and illustrative examples
7. Trial documentation and procedures to ensure confidentiality and proper communication	
Intended content of material to be available in open sessions	<p><i>Illustrative example:</i> Open sessions: accumulating information relating to recruitment and data quality (e.g. data return rates, treatment compliance) will be presented. Toxicity details based on pooled data will be presented and total numbers of events for the primary outcome measure and other outcome measures may be presented, at the discretion of the DMC.</p>
Intended content of material to be available in closed sessions	<p><i>Illustrative example:</i> Closed sessions: in addition to all the material available in the open session, the closed session material will include efficacy and safety data by treatment group.</p>
Whether or not the DMC be blinded to the treatment allocation	Blinding is generally not recommended for DMC members, although opinions vary.
The people who will see the accumulating data and interim analysis	<p>These should be specified</p> <p>DMC members do not have the right to share confidential information with anyone outside the DMC, including the PI.</p>
Responsibility for identifying and circulating external evidence (e.g. from other trials/systematic reviews)	Identification and circulation of external evidence (e.g. from other trials and systematic reviews) is not the responsibility of the DMC members. The PI or the trials office team will usually collate any such information.
To whom the DMC will communicate the decisions/recommendations that are reached	<p>The DMC usually reports its recommendations in writing to the TSC or sponsor's representative. This should be copied to the trial statistician (or trial manager) and if possible should be sent via the trials office in time for consideration at a TSC meeting. If the trial is to continue largely unchanged then it is often useful for the report from the DMC to include a summary paragraph suitable for trial promotion purposes (see Annex 2).</p>
Whether reports to the DMC be available before the meeting or only at/during the meeting	It is usually helpful for the DMC to receive the report at least 2 weeks before any meetings. Depending on the trial, it may sometimes be preferable for all papers to be brought to face-to-face meetings by the trial statistician; time would then be needed for DMC members to assimilate the report.
What will happen to the confidential papers after the meeting	<p><i>Illustrative examples:</i></p> <ol style="list-style-type: none"> 1. The DMC members should destroy their reports after each meeting. Fresh copies of previous reports will be circulated with the newest report before each meeting. 2. The DMC members should store the papers safely after each meeting so they may check the next report against them. After the trial is reported, the DMC members should destroy all interim reports.
8. Decision-making	
What decisions/recommendations will be open to the DMC	<p>Possible recommendations could include:</p> <ul style="list-style-type: none"> • no action needed, trial continues as planned • early stopping due, for example, to clear benefit or harm of a treatment, futility, or external evidence • stopping recruitment within a subgroup • extending recruitment (based on actual control arm response rates being different to predicted, rather than on emerging differences) or extending follow-up • stopping a single arm of a multiarm trial • sanctioning and/or proposing protocol changes
The role of formal statistical methods, specifically which methods will be used and whether they will be used as guidelines or rules	<p>This charter should include or provide reference to the planned interim analyses and statistical guidelines, i.e. the DMC should review and agree any interim analysis plan.</p> <p>Formal statistical methods are more generally used as guidelines rather than absolute rules. This is because they generally only consider one dimension of the trial. Reasons should be recorded for disregarding a stopping guideline.</p>

continued

TABLE 33 Charter for DMCs (cont'd)

Content	Comments from DAMOCLES and illustrative examples
How decisions or recommendations will be reached within the DMC	<p>Issues to be specified can include:</p> <ul style="list-style-type: none"> • The decision-making methods and criteria that will be adopted for guiding deliberations. • The process of decision-making, including whether there will be voting or other formal methods of achieving consensus. The method of deliberation should not be revealed to the overseeing committee as this may reveal information about the status of the trial's data. • The role of the chair: to summarise discussions and encourage consensus; it may be best for the chair to give their own opinion last. <p>It is recommended that every effort should be made for the DMC to reach a unanimous decision. If the DMC cannot achieve this, a vote may be taken, although details of the vote should not be routinely included in the report to the TSC as these may inappropriately convey information about the state of the trial data.</p> <p>It is important that the implications (e.g. ethical, statistical, practical, financial) for the trial be considered before any recommendation is made.</p>
When the DMC is quorate for decision-making	<p>There should be a minimum number of attendees before the DMC is quorate for decision-making; this should be specified.</p> <p><i>Illustrative example:^a</i> <i>"Effort should be made for all members to attend. The trials office team will try to ensure that a date is chosen to enable this. Members who cannot attend in person should be encouraged to attend by teleconference. If, at short notice, any DMC members cannot attend at all then the DMC may still meet if at least one statistician and one clinician, including the chair (unless otherwise agreed), will be present. If the DMC is considering recommending major action after such a meeting the DMC chair should talk with the absent members as soon after the meeting as possible to check they agree. If they do not, a further teleconference should be arranged with the full DMC."</i></p>
Can DMC members who cannot attend the meeting make an input	<p>If the report is circulated before the meeting, DMC members who will not be able to attend the meeting may pass comments to the DMC chair for consideration during the discussions.</p>
What happens to members who do not attend meetings	<p><i>Illustrative example:</i> <i>If a member does not attend a meeting, it should be ensured that the member is available for the next meeting. If a member does not attend a second meeting, they should be asked if they wish to remain part of the DMC. If a member does not attend a third meeting, they should be replaced.</i></p>
Whether different weight will be given to different end-points (e.g. safety/efficacy)	<p>This should be specified and will depend on the trial.</p>
Any specific issues relating to the trial design that might influence the proceedings (e.g. cluster trials, equivalence trials, multiarm trials)	<p>This should be specified and will depend on the trial.</p>
9. Reporting	
To whom will the DMC report their recommendations/decisions, and in what form	<p>Usually, this will be a letter to the TSC or sponsor's representative. A timescale should be specified, e.g. usually within 3 weeks. It is helpful if a copy of this is lodged with the trial office.</p>
Whether minutes of the meeting be made and, if so, by whom and where they will be kept	<p>These details should be specified (separate records may be required for open and closed sessions). The DMC chair should sign off any minutes or notes.</p>
What will be done if there is disagreement between the DMC and the body to which it reports	<p>Specify which committee has primacy or how disagreement will be resolved, e.g. a further committee may be convened to adjudicate.</p>
	<p><i>Illustrative example:</i> <i>"If the DMC has serious problems or concerns with the TSC decision a meeting of these groups should be held. The information to be shown would depend upon the action proposed and the DMC's concerns. Depending on the reason for the disagreement confidential data will often have to be revealed to all those attending such a meeting. The meeting should be chaired by a senior member of the trials office staff or an external expert who is not directly involved with the trial."</i></p>

continued

TABLE 33 Charter for DMCs (cont'd)

Content	Comments from DAMOCLES and illustrative examples
10. After the trial Publication of results	At the end of the trial there may be a meeting to allow the DMC to discuss the final data with principal trial investigators/sponsors and give advice about data interpretation. The DMC may wish to see a statement that the trial results will be published in a correct and timely manner.
The information about the DMC that will be included in published trial reports	DMC members should be named and their affiliations listed in the main report, unless they explicitly request otherwise. A brief summary of the timings and conclusions of DMC meetings should be included in the body of this paper.
Whether the DMC will have the opportunity to approve publications, especially with respect to reporting of any DMC recommendation regarding termination of a trial	The DMC may wish to be given the opportunity to read and comment on any publications before submission.
Any constraints on DMC members divulging information about their deliberations after the trial has been published	It should be specified when the DMC may discuss issues from their involvement in the trial, e.g. 12 months after the primary trial results have been published, or when permission is agreed with the overseeing committee.
Illustrative examples are shown in italic text. ^a Based on real trial protocols. <ul style="list-style-type: none"> – Insert figures and appendices: – Figure summarising trial – Figure showing relationship of trial committees, including DMC – List of abbreviations and glossary – Annex 1: Competing interest form – Annex 2: Illustrative letter from DMC to TSC – Annex 3: Details of interim analysis plan (if not in protocol) 	

Annex 1 Suggested competing interests form

Potential competing interests of Data Monitoring Committee members for [Insert trial name (and sponsor's ID)]

The avoidance of any perception that members of a DMC may be biased in some fashion is important for the credibility of the decisions made by the DMC and for the integrity of the trial.

Possible competing interest should be disclosed via the trials office. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) DMC member should remove the conflict or stop participating in the DMC. Table 1 lists potential competing interests.

TABLE 1 *Potential competing interests*

- | |
|---|
| <ul style="list-style-type: none"> • Stock ownership in any commercial companies involved • Stock transaction in any commercial company involved (if previously holding stock) • Consulting arrangements with the sponsor • Frequent speaking engagements on behalf of the intervention • Career tied up in a product or technique assessed by trial • Hands-on participation in the trial • Involvement in the running of the trial • Emotional involvement in the trial • Intellectual conflict, e.g. strong prior belief in the trial's experimental arm • Involvement in regulatory issues relevant to the trial procedures • Investment (financial or intellectual) in competing products • Involvement in the publication |
|---|

Please complete the following section and return to the trials office.

No, I have no competing interests to declare

Yes, I have competing interests to declare (please detail below)

Please provide details of any competing interests: _____

Name: _____

Signed: _____

Date: _____

Annex 2 Illustrative report from DMC to TSC where recommendation is to continue the trial according to the protocol

[Insert date]

To: Chair of Trial Steering Committee

Dear [Chair of Trial Steering Committee]

The Data Monitoring Committee (DMC) for the [insert trial name] trial met on [meeting date] to review its progress and interim accumulating data. [List members] attended the meeting and reviewed the report.

The trial question remains important and, on the basis of the data reviewed at this stage, we recommend continuation of the trial according to the current version of the protocol [specify protocol version number and date] with no changes.

We shall next review the progress and data [provide approximate timing].

Yours sincerely,

[Name of meeting chair]

Chair of Data Monitoring Committee

On behalf of the DMC (all members listed below)

DMC members:

- (1) [Insert name and role]
- (2) [Insert name and role]
- (3) [Insert name and role]

Chapter 8

Conclusions and recommendations

For the conduct of data monitoring in RCTs

Which trials need an independent DMC? (Question 1)

Criteria derived from this project for those RCTs that do not need an independent DMC are: where it is not possible for a DMC to make a contribution to a trial, where any observed differences between trial groups, however extreme, would not prompt a change in the trial's protocol (such as early stopping), and where there is no reason for thinking that an independent DMC would reach a conclusion that differed significantly from decisions that would be reached after internal monitoring.

Recommendation

Some form of data monitoring should be considered for all RCTs, with an explicit reason given where there is a decision either to have no DMC or to include members in a DMC who are not independent.

Who should decide the details of how a DMC operates? (Question 2)

The evidence reviewed suggested that clarifying and agreeing in advance a DMC's roles and responsibilities decreases the chances of later difficulties. This may be considered most easily within a structured charter, and a template for this with potential issues listed as a checklist was developed within this project for this purpose (see *Table 33*).

Recommendation

At the start of a trial, DMCs, investigators and sponsors/funders draw up a charter describing a DMC's planned operations.

What should the DMC's terms of reference cover? (Question 3)

A range of roles has been suggested for DMCs. Central is monitoring accumulating evidence related to treatment benefit and toxicity, but other aspects of trial conduct will usually be considered. Variation in the emphasis of a DMC's roles has been reflected in a plethora of names and this can be confusing. A DMC is responsible to a number

of groups or parties (including current participants, future participants, future patients, investigators and sponsors) and needs to take account of these potentially conflicting perspectives.

Recommendation

A DMC pre-agrees its roles and responsibilities (and the proposed charter in *Table 33* provides a template for this). The DAMOCLES group recommend that groups responsible for data monitoring be given the standard name 'data monitoring committee' (DMC).

Does the DMC have a role before the trial recruitment phase? (Question 4)

It has been argued that, if as recommended above, a DMC pre-agrees how it will operate, it is best if this is done before the DMC sees any trial data. A meeting before recruitment starts also allows a DMC to review and agree relevant aspects of the trial protocol and procedures, including guidelines for stopping early and the analysis plan; in addition, it allows members to get to know each other in advance of any decision-making about the trial.

Recommendation

A DMC meets early before any outcome data have accrued, ideally before recruitment starts.

How should regulatory issues impact on the DMC? (Question 5)

Both the ICH and FDA encourage independent DMCs. This study found no reason why DMCs of trials performed for regulatory purposes should differ significantly from other DMCs, although they should be aware of any special requirements that this entails and should take into account the regulatory consequences of any decisions that they take.

Recommendation

Similar principles are used for DMCs of regulatory trials as for other trials, although committees should take the regulatory consequences into account when making decisions.

What should the membership of a DMC be? (Question 6)

Advantages were identified for both larger sized DMCs (full range of specialist skills without over-dependence on individuals, low risk of dominance and a wider range of opinion) and smaller sized committees (fewer practical difficulties finding appropriately qualified people and of arranging meetings, less reluctance of members to express views, less risk of conflict and less potential for a bias towards riskier decisions). The optimal size will reflect a balance of these considerations and is likely to be between three and eight. There is general agreement that a DMC should be independent and multidisciplinary, with at least one member being a statistician and another a clinician with appropriate specialist knowledge. The involvement of consumer representatives in DMCs is controversial and should be explored. While there was recognition that DMC members would be likely to benefit from introduction to the ethical considerations in data monitoring, little support was found for ethicists being members of DMCs and their involvement should also be researched. The chair is recognised as being particularly influential, and likely to be most effective if experienced in both data monitoring and chairing small groups, having an understanding of both statistical and clinical issues, being facilitating in style and impartial. It is common practice for the investigators to agree the DMC membership with the trial sponsors.

Recommendation

The size of a DMC is chosen to optimise performance, members are independent and from an appropriate range of backgrounds, and the chair is experienced and facilitating. Although they would not be members of the DMC, it is appropriate if selected trial personnel conduct the confidential analyses and attend DMC meetings. (The model in which all members are completely independent of the trial and an independent statistician conducts the analyses has considerable drawbacks, whereas the model in which people involved in the trial are DMC members runs the risk of biased decision-making.)

How is independence to be maintained? (Question 7)

Characteristics of independence have been described (see Chapter 2, *Box 5*), and include no commercial, clinical or intellectual conflict of interest. It is generally accepted that potential competing interests should be formally identified, with active consideration of whether they jeopardise independence and credibility such as to

make a person ineligible for membership. The review suggested that rewards must be so minimal as to have no effect on decision-making. Nevertheless, costs such as travel and communication should be covered and consideration should be given to providing some recompense for time involved.

Recommendation

DMC members are screened for potential conflicts of interest at the start of a trial, with later checks to ensure that independence is maintained.

Should the DMC deliberations be open or closed? (Question 8)

It is common practice to have open and closed sessions at DMC meetings. At open sessions, general trial issues, such as recruitment, are discussed with investigators; at closed sessions, there is discussion of confidential information, such as interim analyses.

Recommendation

DMC meetings have both open and closed sessions, but with the closed sessions limited to those for whom access to confidential interim analyses has been pre-agreed by the DMC.

What are the optimal practical arrangements for interim analysis and data monitoring? (Question 9)

Optimal timing of DMC meetings depends on the particular trial. It is usual to have a minimum frequency, with the committee able to meet at shorter notice if a reason arises. There is evidence that face-to-face meetings should be the preferred method of communication, especially for the first meeting or when difficult decisions are predictable, although a chair may elect to use teleconferencing when the discussion appears straightforward or when there are practical difficulties in bringing the committee together.

Recommendation

A minimum frequency of meetings is agreed, with flexibility for more frequent meetings if a reason arises. Meetings should be held face-to-face, if possible and practicable.

What sort of training or preparation should DMC members have? (Question 10)

It is widely accepted that some members at least, including the chair, should have previous experience of trials and serving on DMCs. There

is no evidence on which to judge the value of suggested approaches to training and preparation. These include apprenticeship training, possibly enhanced by more formal mentoring by an experienced member of the DMC, attendance at other DMCs as observers and formal courses. The value of basic instruction in relevant ethical principles and experiential training in discussing ethical dilemmas is also unclear. The special training requirements of chairs of DMCs should also be addressed.

Recommendation

Some members of a DMC should have prior experience. Approaches to training members of DMCs should be developed and evaluated.

What material should be available to a DMC? (Question 11)

The materials required by a DMC depend on the areas of the trial that will be monitored.

(Potential areas are summarised in Chapter 2, *Table 5*.) The general view is that information to be included in a report to a DMC and its format should be agreed in advance with the DMC. Information about benefits and risks should be given in a balanced way, summarised so as to be accessible, avoiding too much detail, and as up to date as possible. While there is a theoretical argument that DMCs should consider blinded analyses, this may not be possible in practice, and anyway many DMCs need to know the group allocation to perform their monitoring functions fully. The report should also include information about comparable studies and be available in advance of the meeting. Interaction with DMCs of other similar trials is controversial. The issues and potential implications are complex and some commentators have recommended caution.

Recommendation

The information to be included in a report to a DMC and its format are agreed in advance with the DMC.

Who should own the interim data and analyses? (Question 12)

Little was found in this project about the issue of ownership of interim data and analyses.

Recommendation

A DMC should be seen as having a guardianship role in respect of deciding who outside the DMC, if anyone, could be allowed to see confidential interim analyses. This role would be discharged once final analyses have been completed.

Should non-comparative analyses (which are administrative and not separated by treatment arm) be carried out? (Question 13)

Information about 'administrative' factors, such as recruitment, compliance and data quality, which are important to the integrity of a trial, are commonly considered by DMCs and shared with the trial's investigators. Non-comparative analyses of outcome data may occasionally be indicated, but should only be conducted with caution, and in a way that ensures the confidentiality of the interim trial analyses.

Recommendation

Administrative analyses are usefully discussed at open sessions of a DMC. Non-comparative outcome analyses should only be performed for a specific purpose and in a way that does not jeopardise the integrity of the trial.

Is the function of the DMC advisory (to make recommendations) or executive (to make decisions)? (Question 14)

The general, but not unanimous, view is that DMCs should have an advisory rather than executive role on the basis that it is the trial organisers who are ultimately responsible for the conduct of the trial. The organisers then choose whether or not to accept the DMC's recommendations (although it is unusual for them not to do so).

Recommendation

DMCs are given an advisory role, with the trial organisers taking ultimate responsibility for any decisions.

What decisions and recommendations should be open to the DMC? (Question 15)

Variation between trials in the decision options open to DMCs seems to reflect differences in emphasis rather than disagreement. The implications of potential decisions depend on the stage that the trial has reached. Before a trial starts recommendations can be made about changes to the trial's protocol. Once the trial has started, the DMC can recommend that a trial should continue without modification, or stop completely or partially, or continue with modifications.

Recommendation

Members of a DMC should understand the range of recommendations or decisions that is open to them and the implications that these could have for the trial.

How should the decisions or recommendations be reached within the DMC? (Question 16)

The ways in which DMCs reach decisions vary. Usually, this is by consensus, but other approaches are sometimes used, including voting, in which case an odd number of members has been recommended. The evidence suggests that decisions should be unanimous where possible, with voting encouraged only after a full discussion. There is general agreement that the process by which the DMC makes decisions should be explicit and transparent.

Recommendation

A DMC agrees in advance how it will reach a decision. A record should be kept of each DMC meeting that describes the key issues discussed and the rationale for any decisions taken.

What should be the role of formal statistical methods in DMCs? (Question 17)

A range of formal statistical approaches can be used in interim analyses of trials (the principles behind these are outlined in Appendix 1 of this report). However, this is only one of a number of considerations that a DMC would take into account and statistical criteria should be considered guidelines for stopping rather than rules.

Recommendation

A DMC should understand and agree the statistical approach (and guidelines) chosen for a trial. Both the DMC statistician and the trial statistician should be competent to apply this method to the trial's interim analyses.

Should specific trial designs influence the proceedings? (Question 18)

Unusual trial designs have implications for data monitoring. These designs include cluster trials, equivalence trials, and trials with a composite outcome or where the difference in outcome is disproportionately larger soon after entry. These circumstances are unusual, but should be identified and taken into account in advance of any data monitoring.

Recommendation

DMCs should recognise in advance the implications of any unusual aspects of a trial's design and take these into account in their deliberations.

How should ethical issues be handled in DMCs? (Question 19)

The aim of a DMC should be to decide when the

evidence is sufficiently persuasive that it is clear what is in the best interests of both current participants and future patients. The degree of conservatism or radicalism to be adopted in making this decision should be reflected in the DMC's terms of reference and the trial's monitoring plans, which include the statistical criteria chosen as guidelines. RECs will have agreed the ethical basis for the trial's protocol, and the DMC should approach its role from that starting point.

Recommendation

The primary purpose of a DMC is to ensure that continuing a trial according to its protocol is ethical, taking account of both individual and collective ethics. Whether the DMC has a broader remit in respect of wider ethical issues is controversial; the view of the DAMOCLES group is that these are primarily the responsibility of RECs, TSCs and investigators.

What should DMCs do with their decisions or recommendations? (Question 20)

DMCs usually report to the sponsor or the investigators (in the form of a representative committee) and there can be advantages in reporting to both at the same time. If there are no concerns about the trial, it is likely that only a brief, but carefully worded, statement from the DMC chair is required. A much fuller report is needed if a change to the protocol is being recommended by a DMC.

Recommendation

It should be agreed in advance to whom a DMC reports, how it does this and what record-keeping is required.

What should be done in 'difficult' situations? (Question 21)

There is wide agreement that a DMC must have the flexibility to call meetings at short notice if a difficult issue arises. The importance of these meetings having sufficient time available is also recognised. Closed sessions restricted to DMC members provide the best forum for formulating a response. Factors that could make it more difficult for members to participate (such as calling a meeting at short notice or using a telephone conference call rather than an in-person meeting) should be avoided if possible.

Recommendation

A DMC should agree in advance how it would respond to difficult circumstances. This is likely to

be by calling a face-to-face meeting, which may be at short notice. A trial's decision-making body (such as the TSC or sponsor) and its DMC should also consider planning in advance to allow a third group to arbitrate if they were later to disagree when the DMC recommends a change in protocol.

Should some DMC decisions be considered to be 'errors'? (Question 22)

While it is difficult to judge whether a DMC has made a good or poor decision, there is evidence of ways to minimise the chances of a poor decision. Concerns have been expressed about who would be deemed liable for an erroneous decision if a legal challenge were to be mounted, and this needs clarification.

Recommendation

DMCs should recognise that the chances of a decision error are likely to be reduced if they make a thorough review of the evidence, they have a clear understanding of how they should function, there is active participation by all group members, resolution of differences is through discussion, and there is systematic matching of the facts to the criteria for the various decision options.

What should the DMC's role be concerning publications? (Question 23)

The question of what role, if any, the DMC should play once interim analyses have been completed has received little attention. There are, however, good reasons for the DMC at least commenting on the draft trial report.

Recommendation

DMCs should be encouraged to comment on draft trial reports and this should be agreed at an early

DMC meeting. Trial reports should include information about the data monitoring procedures and processes, and about the DMC membership.

For further research on behavioural and organisational aspects of data monitoring in RCTs

- Widening of DMC membership beyond clinicians, trialists and statisticians (e.g. to include consumer representatives or ethicists) should be formally evaluated.
- Initiatives to train members of DMCs should be evaluated as they are introduced.
- Research is needed on methods of decision-making in DMCs, in particular the role of voting and of formal decision-making tools.
- The role of 'open' data monitoring requires further research.
- The advantages and disadvantages of DMCs covering a portfolio of trials (rather than single trials) should be clarified.
- There was inconsistency between the components of this study about what constituted the optimal size of a DMC. This warrants further study, incorporating issues of group dynamics.
- The generalisability of findings related to other small decision-making groups, such as juries, is questionable; this could be addressed by empirical research of DMCs and their decision-making.
- The question of which trials should or should not have a DMC remains controversial and further research could clarify this.



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Appendix I

Summary of statistical approaches to data monitoring

Introduction

It is universally accepted that monitoring of clinical trials will involve some form of statistical analysis, although the underlying statistical philosophy and the precise methods to be used remain controversial subjects. This appendix reviews the approaches of the main schools of statistical 'ideology', and summarises how they can be applied to the range of problems facing a DMC. No attempt is made to review comprehensively the large literature on statistical aspects of monitoring clinical trials, and the reader may refer to books by Whitehead¹¹² and Jennison and Turnbull,¹⁹² and less technical chapters such as that provided by Piantadosi.⁸⁰ In particular, Ellenberg and colleagues¹⁹ provide a range of worked examples, and the special issue of *Statistics in Medicine* in 1994¹⁹³ also contains a range of relevant papers to 'stopping rules'. Other review articles^{6,7,194-196} mainly focus on frequentist methods, although alternatives are increasingly being mentioned. In contrast, this brief review attempts to consider all potential methods without regard to their current popularity.

Statistical approaches

Four major statistical paradigms can be identified, and this section will first consider how each one tackles the issue of early stopping in the face of apparent benefit of an active intervention; their approach to other situations will be considered afterwards. Only a minimum of notation is required: at the i th interim analysis, it is assumed that the evidence is adequately summarised by a standardised test statistic z_i , typically based on the current estimate of the treatment effect divided by its standard error. Traditional values of interest include $z_i = 3$, corresponding to a two-sided p -value of around 0.001, and $z_i = 2$, corresponding to a two-sided p -value of around 0.05. However, these 'naive' p -values ignore the influence of the repeated analyses typically carried out when data monitoring, and such issues emphasise the careful attention paid to statistical methodology in this context.

Frequentist

This Neyman–Pearson approach is rooted in a theory of 'inductive behaviour', seeking procedures of hypothesis testing and estimation with guaranteed properties under repeated use. Specifically, clinical trials are generally designed to have fixed size (the chance of incorrectly rejecting the null hypothesis, or 'Type I' error), often taken as 5% or 1%, and fixed power (the chance of not detecting the alternative hypothesis, or one minus the 'Type II' error), often taken to be 80% or 90%.

The option of early termination of trials presents frequentist methods with a strong challenge, since all potential actions must be considered when establishing their repeated sample properties. Suggested protocols for early stopping can be well visualised as 'stopping boundaries' which describe, for example, critical values of the test statistic z_i that would be considered sufficient evidence for stopping and concluding efficacy. For example, a naive boundary would stop a trial for efficacy of $z_i > 1.96$: while this would provide a test with fixed Type I error of 0.025 for a fixed sample size, it is clear that the chance of crossing such a boundary at some point during the course of a trial can considerably exceed this nominal figure, owing to the well-known problems associated with repeated significance tests.

Stopping boundaries will generally be designed to have fixed Type I error over the planned maximum lifetime of the trial; open-ended schemes with no preset maximum sample size will not generally be considered practical. Within this class of boundaries there are many options that can be compared, for example, on the basis of their power to detect plausible alternatives or their expected sample size.

Major recommendations for frequentist schemes can be divided into two main classes: group sequential and continuous procedures.

Group sequential procedures assume a limited number of interim analyses at preset times. It is useful to focus on two of the most widely discussed proposals: the Pocock model in which a common

boundary for z_i is used at all interim analyses, with the boundary chosen to have the appropriate Type I error, and the O'Brien and Fleming boundary, which is much more conservative at the start of the trial, but comes near to the nominal level at the final analysis. O'Brien and Fleming boundaries are perhaps more popular in the USA. The boundaries for five interim analyses are shown in *Figure 7*.

Continuous procedures allow inspection of the data and therefore stopping to occur at any stage of a trial. Two approaches have been used in practice. First, the triangular test has linear boundaries on a plot relating estimated effect with information gained. Whitehead^{112,197} emphasises the generality of this approach and indicates adjustments for sampling at fixed times, over-running (in which information is received after having crossed the boundary¹⁹⁸) and so on. The alpha spending approach^{199,200} specifies a 'spending function', which is a smooth increasing function of information gained ranging from 0 to the overall Type I error, say 0.05. At any point in the trial, the boundary is set so that the probability of falsely rejecting the null hypothesis before that point is equal to the spending function. This increased flexibility carries with it a substantial computational burden.

The repeated confidence interval method²⁰¹ does not use an explicit boundary, but monitors whether an interval estimate (adjusted for repeated analyses) excludes the null hypothesis.

An important issue is the estimation of the treatment effect after early stopping in a sequential design. The naive estimate will be biased if the trial stops and publishes; informally, a contributory reason for crossing a boundary is likely to be a run of good or bad luck.²⁰² Techniques for producing unbiased estimates have been researched,¹¹² but they are complex and appear to have rarely been used in practice.

Likelihood approach

This Fisherian approach bases inference on the true underlying treatment effect solely on the likelihood function, which expresses the relative support given by the observed data to different values of the true underlying treatment effect. It would be possible to draw conclusions based solely on the relative support for null and alternative values of the true underlying treatment effect.^{203,204} If carried out after each observation this leads to the sequential probability ratio test, although Piantadosi⁸⁰ points out that this test becomes a frequentist procedure once its boundaries start being set on the grounds of its

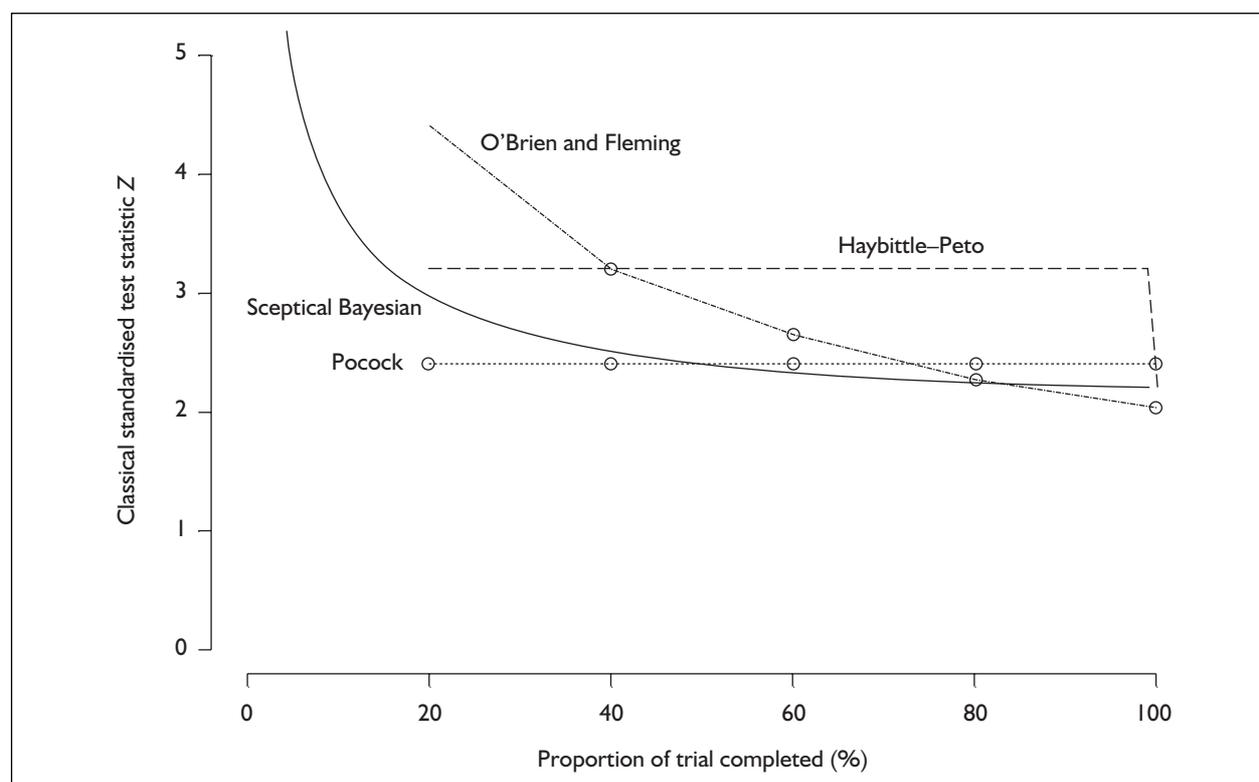


FIGURE 7 Haybittle-Peto, O'Brien and Fleming, Pocock and sceptical Bayesian stopping boundaries for five interim analyses

sampling properties. Fisher suggested that the evidence against a null hypothesis be summarised by a p -value (unadjusted for multiple looks at the data), which is the chance of observing such extreme data under the null hypothesis.

When monitoring trials, this somewhat informal approach is perhaps best exemplified by trials influenced by the Oxford school under Richard Peto,²⁰⁵ in which protocols generally state that the DMC should only alert the TSC to stop the trial on efficacy grounds if there is “both (a) ‘proof beyond reasonable doubt’ that for all, or for some, types of patient one particular treatment is clearly indicated ..., and (b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the results of other main studies”. There is no formal expression of what evidence is required to establish ‘proof beyond reasonable doubt’, although $|z_i| > 3$ and $p < 0.001$ have been mentioned as possible criteria. Also note the explicit, though again informal, appeal to the idea that the results should be convincing to a broad spectrum of opinion (see next section).

Although this approach is not intended as a formal stopping boundary, it may be considered as an informal continuous monitoring scheme, and is often termed the Haybittle–Peto rule: its form is displayed in *Figure 7*. Its precise frequentist properties are not explored, so it cannot be considered a formal frequentist method. It is perhaps more popular among UK trialists.

Bayesian approach

Bayesian methods extend the likelihood approach inference by including a ‘prior distribution’, which is intended to summarise evidence concerning the true underlying treatment effect arising externally from the trial. This is then combined with the likelihood using Bayes’ theorem to produce a posterior distribution, which expresses an updated belief having taken into account evidence from the study, and on which all inferences are based. Monitoring of the clinical trial is based on posterior distribution and hence Bayesian monitoring procedures explicitly use external evidence or judgement and are not solely based on data from the trial. The Bayesian approach to trials has been reviewed in detail by Spiegelhalter and colleagues.²⁰⁶ (See also reviews by Spiegelhalter,²⁰⁷ Berry,^{208,209} Freedman²¹⁰ and Fayers.²¹¹)

There is no formal necessity to preset stopping boundaries within the Bayesian approach, but

criteria such as ‘stop if the posterior probability that the treatment is beneficial is greater than 97.5%’ have been investigated. The following three issues immediately arise.

What prior to use?

Although the ideal Bayesian view is that the trial evidence revises one’s personal subjective beliefs, in practice it is generally accepted that a community of priors should be considered. This formalises the idea that “the purpose of a trial is to collect data that bring to conclusive consensus at termination opinions that had been diverse and indecisive at the outset”.²¹² Priors may include the opinions of enthusiasts for the new innovation or a sample of clinicians, or be based on a formal meta-analysis. In particular, before concluding efficacy, it has been argued that the data should be sufficient to overcome the handicap of a ‘sceptical prior’ centred on the null hypothesis. One suggestion is that such a prior reflect the opinion that the targeted alternative hypothesis is unlikely.²¹¹ Such a sceptical prior will tend to draw the estimated treatment effect towards the null hypothesis, inducing a degree of conservatism similar to that of frequentist stopping procedures. This is demonstrated in *Figure 7*, which shows a practical example of monitoring using a sceptical prior, reported by Parmar.²¹³ Other prior distributions may be appropriate in different circumstances (see below).

What are the sampling properties?

Repeated sampling properties are, officially, of no interest within the Bayesian paradigm, but it is inevitable that comparison is drawn with frequentist procedures. It has been shown that group-sequential schemes based on posterior tail areas and sceptical prior can have good sampling properties,²¹⁴ but there can be considerable sensitivity to the prior distribution.²¹⁵

What about null hypotheses?

Within the Bayesian paradigm there is no need for null hypotheses to remain fixed throughout the trial: the goalposts may move. Thus, it may be reasonable to specify a point of clinical equivalence, which may change as the trial progresses, and monitor the posterior probability that the true effect exceeds this.

Decision-theoretic approach

The decision-theoretic approach requires a specification of a formal loss or utility function which quantifies the desirability or otherwise of different outcomes, such as treating a patient with an inferior treatment or spending resources on

treatments. Decisions on whether to continue (or even to start) a trial are based on the potential losses (or gains) under the different options: both Bayesian (e.g. take the decision that minimises the expected loss) and non-Bayesian (e.g. take the decision that minimises the maximum potential loss) alternatives are available.²¹⁶ In support of this approach, Berry²¹⁷ states that “deciding whether to stop a trial requires considering why we are running it in the first place, and this means assessing utilities”, while Healy²¹⁸ considers that “in my view the main objective of almost all trials on human subjects is (or should be) a decision concerning the treatment of patients in the future”.

Although there has been substantial theoretical work in this area (see, for example, Berry and Pearson²¹⁹), the DAMOCLES group is unaware of any reported examples of prospective use.

Critical comparison of approaches

It is easy to emphasise the differences between the approaches outlined above, but Piantadosi⁸⁰ points out similarities such as the need for clearly stated objectives, proper design and conduct of the trial, and acknowledgement of additional context beyond the raw observed data, as well as the qualitative similarity of the various options, in that they all exhibit conservatism in protecting against a trial stopping inappropriately early. In addition, in spite of the technical formalism of the approaches, there is a general consensus that these statistical techniques should only be used as guidelines rather than as rules, and that a strong element of contextual judgement is always required. Nevertheless, there are some clear ideological differences between the paradigms.

Frequentist

Particularly strong attacks have been made against the (most commonly adopted) frequentist approach:

- The investigators may disobey the likelihood principle,²²⁰ in that the inference is based on the intentions of the investigator rather than simply the data observed. Hence, exactly the same data could lead to rejection or no rejection of a null hypothesis depending on what the investigator would have done had different data been observed earlier in the study.^{203,221} Meier²²² considers that “provided the investigator has faithfully presented his methods and all of his results, it seems hard

indeed to accept the notion that **I** should be influenced in my judgement by how frequently he peeked at the data while **he** was collecting it”.

- Cornfield²²⁰ points out that “the entire basis for sequential analysis depends upon nothing more profound than a preference for minimising β for given α rather than minimising their linear combination. Rarely has so mighty a structure, and one so surprising to scientific common sense, rested on so frail a distinction and so delicate a preference”.
- Anscombe²²³ says, “the concept of error probabilities of the first and second kinds ... has no direct relevance to experimentation”.
- Frequentist approaches have difficulty adapting to changes in the trial, for example a shift in null hypothesis brought about by findings of toxicity.
- Naive estimates following early termination are biased, since the data are more likely to be subject to a transient random extreme.^{6,7,202} This fact appears to be almost universally ignored when reporting results following early termination.

In response, it can be argued that when treatments are being recommended for general use or passed by regulatory authorities there is a need for quality control, and procedures that pre-specify rates of inappropriate conclusion provide a simple and communicable framework, with protection against inappropriate early stopping of a trial.

Likelihood

Objections include:

- the lack of formal assessment of possible Type I error
- the associated informality of the monitoring procedure.

Bayesian

Objections to the Bayesian approach include those associated with the likelihood approach, and in addition:

- Conclusions may depend strongly on the prior, and this necessarily involves a subjective judgement. Even with extensive sensitivity analysis, such input may be considered unacceptable to, for example, regulatory bodies.
- The techniques are generally more complex than frequentist and likelihood approaches, and may be seen as less transparent.
- There are generally no established sampling properties.

- There is little experience in their use, and limited understanding of their basis.

Decision-theoretic

Objections include:

- This approach is generally complex for monitoring trials owing to the difficulty in specifying an agreed loss function, particularly for the post-trial consequences of stopping a trial. For example, Peto,²²⁴ in the discussion of Bather,²¹⁶ states that “Bather, however, merely assumes ... ‘it is implicit that the preferred treatment will then be used for all remaining patients’ and gives the problem no further attention! This is utterly unrealistic, and leads to potentially misleading mathematical conclusions.”
- There are strong computational demands in calculating potential losses under all possible future actions. This ‘backwards induction’ requires dynamic programming techniques in all but the simplest circumstances. Nevertheless, advances are being made.²²⁵

Questions under consideration by a DMC

This section considers the different questions that could be asked by the DMC, using the same structure as for question 15 in the systematic review of published literatures on DMCs (see Chapter 2). Emphasis is placed both on frequentist and Bayesian methods.

The study should stop completely or partially

Apparent benefit of active treatment on primary outcome

The different approaches have already been outlined above.

Apparent benefit of control on primary outcome

Frequentist schemes require a lower boundary, which may well be asymmetric with the efficacy boundary because of the wish to detect quickly a potentially inferior active treatment. From a Bayesian perspective it may be reasonable to monitor with an ‘enthusiastic’ prior centred on the alternative hypothesis. Evidence against the active treatment could then be assessed on the basis of its capacity to convince an enthusiast that the treatment is ineffective, interpreted as a very low posterior probability that θ exceeds a clinically important effect. When investigating non-inferiority or equivalence, non-zero null

hypotheses will generally need to be specified (see below).

Safety concerns with secondary outcomes

These may be too rare or too diffuse to have formal stopping rules, although combinations of events could be used. Formal bivariate monitoring schemes have been explored.²²⁶

Small chance of eventually showing benefit

Futility calculations, also known as stochastic curtailment, can be carried out within a frequentist framework, by calculating the conditional probability of an eventual significant result, given the data so far and the null or alternative hypothesis.^{227,228} From a Bayesian perspective it makes more sense to average such conditional probabilities with respect to the current posterior distribution, which then produces an overall predictive assessment of the chance of eventual success.^{84,229} It is possible to make such predictions based on the current data alone and without using a prior distribution,²³⁰ and in this context there is essentially no difference between the frequentist and non-informative Bayesian approach.

Convincing evidence of equivalence or non-inferiority, in a trial with this objective

In this context it will be necessary to specify an effect demarcating non-inferiority or a range indicating equivalence. Frequentist designs that simultaneously monitor efficacy and non-inferiority have been suggested.²³¹ From a Bayesian perspective no special considerations are necessary, since at any time the posterior probability of lying in any region can be obtained and used for monitoring. However, as with looking for control benefit, one may want to be assured that the findings were convincing to an enthusiast for the new treatment.

Part of the study should stop

Stopping randomisation in a subgroup for one of the reasons given above

Frequentist approaches would require prespecification of tests of treatment by subgroup interaction, designed to have appropriate sequential properties, although these are likely to have low power. From a Bayesian perspective, it is standard to adopt a sceptical prior for between-subgroup differences, leading to shrinkage of estimates towards the overall effect to a degree decided by the empirical between-subgroup heterogeneity.²³² Individual subgroups can then be monitored using posterior tail areas.

Stopping randomisation in one arm of the trial for one of the reasons given above

Frequentist techniques exist for terminating one arm in a multiarm trial,^{106,233,234} which may be particularly appropriate in factorial designs.⁷³ Again, Bayesian analysis is unaffected by other arms unless the treatment effects are assumed to be correlated.

Factors that may be taken into account in statistical analysis include the following.

External evidence

This is clearly important,¹⁹ but formal meta-analysis is not recommended as a basis for monitoring within a frequentist framework.^{235,236} Thus, there is a strong element of subjectivity as to how external evidence is considered. Within the Bayesian paradigm it is natural to incorporate external evidence, possibly discounted, into one of the prior opinions being considered.

Need to influence clinical opinion

This can be handled informally within a likelihood approach (as noted by the Peto stopping rule) and the frequentist approach by making more stringent stopping criteria. The Bayesian paradigm can require data to overwhelm the handicap of a sceptical prior opinion. Both approaches can shift the null hypothesis in response to substantial clinical demands for efficacy.

The study should continue with modifications

Basic statistical analysis may be involved in many suggestions for improvement to a study, but the following are of particular interest.

Additional interim analyses

Group-sequential designs will have their properties changed by such a request, whereas continuing monitoring schemes, likelihood (Peto) and Bayesian methods will be unaffected.

Extending recruitment or follow-up time

Many factors may lead to wanting to change the planned sample size: slow recruitment, low event rate, change in alternative hypothesis, and so on. The effect of revising sample size calculations at an interim stage has been studied for frequentist designs.²³⁷⁻²³⁹ There is no effect on Bayesian procedures.

Conclusions

Currently, there is no single approach that can be considered both theoretically and practically ideal. The frequentist approach is currently the dominant philosophy, strongly influenced by the quality-control framework set up by the regulatory bodies. Bayesian approaches are rare in practice, but they are becoming increasingly discussed. Focus on cost-effectiveness and health policy is bringing decision-theoretic ideas away from purely theoretical constructs. Novel studies, such as complex adaptive dose-finding designs, are demanding increasingly flexible monitoring procedures. However, while it is likely that a somewhat wider range of statistical approaches will be used in future, the nature of their role is likely to make DMCs rather cautious and conservative in their use of experimental statistical techniques.

Appendix 2

Search terms used for the systematic review of published literature on data monitoring committees

Search terms used in MEDLINE, PREMEDLINE, EMBASE, CINAHL and HealthSTAR (all on OVID) for the systematic review of the published literature on DMCs

1. (data adj3 (committee\$ or board\$)).tw.
2. (interim adj2 analy\$).tw.
3. dmsb.tw.
4. (trial\$ adj2 monitor\$).tw.
5. (monitor\$ adj2 (committee\$ or board\$)).tw.
6. interim data.tw.
7. trial\$ adj1 halt\$.tw.
8. revis\$ adj2 recruit\$.tw.
9. or/1-8
10. safety committee\$.tw.
11. (dilemma\$ adj1 resol\$).tw.
12. (earl\$ adj1 stop\$).tw.
13. (stop\$ adj1 rule\$).tw.
14. or/10-13
15. controlled clinical trial.pt.
16. randomized controlled trial.pt.
17. randomized controlled trials/
18. random allocation/
19. double blind method/
20. single blind method/
21. clinical trial.pt.
22. exp clinical trials/
23. placebos/
24. placebo\$.tw.
25. random\$.tw.
26. research design/
27. volunteer\$.tw.
28. (clin\$ adj25 trial\$).tw.
29. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).tw.
30. factorial.tw.
31. cross-over studies/
32. crossover.tw.
33. latin square.tw.
34. (balance\$ adj2 block\$).tw.
35. (animal not human).sh.
36. or/15-34
37. 36 not 35
38. 37 and 14
39. 38 or 9

Key: .tw., textword search (i.e. searching in titles and abstracts); \$, wildcard; adj n , within n words either side; /, MeSH term all subheadings; sh, MeSH term; .pt., publication type.

Four of the terms (line 14) were combined, using the Boolean operator 'AND', with a set of terms to locate RCTs based on the Cochrane Highly Sensitive Search Strategy (line 37) [Appendix 5c.2, The Cochrane Handbook. In *The Cochrane Library* (Issue 2). Oxford: Update Software; 2002].

Date last search performed: 26 June 2001.

Years/dates covered by search: MEDLINE 1966 to Week 2 June 2001; PREMEDLINE 25 June 2001; EMBASE 1980 to Week 24 2001; CINAHL 1982 to May 2001; HealthSTAR 1975 to December 2000.

Search terms used in the Cochrane Library for review of literature relevant to DMCs

The following search terms were used for searching the Cochrane Controlled Trials Register and the Cochrane Methodology Register:

1. (DATA near COMMITTEE*)
2. (DATA near BOARD*)
3. (INTERIM near ANALY*)
4. DMSB
5. (TRIAL* near MONITOR*)
6. (MONITOR* near COMMITTEE*)
7. (MONITOR* near BOARD*)
8. (INTERIM next DATA)
9. (TRIAL* near HALT*)
10. (REVIS* near RECRUIT*)
11. (SAFETY next COMMITTEE*)
12. (DILEMMA* near RESOL*)
13. (STOP* near RULE*)
14. (EARL* near STOP*)
15. ((((((((((((((#1 or #2) or #3) or #4) or #5) or #6) or #7) or #8) or #9) or #10) or #11) or #12) or #13) or #14)

Key: *, wildcard.

Date of last search: 26 June 2001, Issue 2, 2001, (on CD-ROM) Update Software, Oxford.

Rejected terms for review of literature relevant to DMCs

The following terms were tested in MEDLINE but rejected as no (or very few) additional relevant articles were retrieved.

These terms were not combined with other terms:

(trial\$ adj25 futi\$).tw.
 (trial\$ adj1 effi\$).tw.
 (trial\$ adj25 oversight).tw.
 (trial\$ adj25 overse\$).tw.
 scientific integrity review.pt.
 (trial\$ adj1 (dilemma\$ or fiasco\$)).tw.
 equipoise.tw.
 Data adj1 monitor\$
 DMEC
 DMEB
 DMSC
 DSMC
 DSMB
 DMB
 DMC
 TMC
 TMB
 ID
 AMC
 Independent adj1 review
 Data adj1 (policy or policies) AND RCT terms
 Monitor\$ adj1 safety.tw.
 Trial\$ safety.tw.
 Oversight adj1 committee\$.tw.
 Institutional review board
 IRB
 Professional staff committees/
 Drug monitoring/
 Adverse drug reaction reporting systems/
 Utilization review/
 Trial\$ adj1 extend\$.tw.
 Extens\$ adj1 recruit\$.tw.
 Trial\$ adj3 stop\$.tw.
 Sn.fs. (ie statistical and numerical data as a floating subheading) AND RCT terms AND review terms
 (Trial\$ adj1 fail\$) not (heart failure\$).tw.

The terms below were combined, using the Boolean operator 'AND', with a set of review terms based on the Centre for Reviews and Dissemination's (CRDs) strategy for locating systematic and other reviews (short version)

1. review, academic.pt.
2. review tutorial.pt.
3. review literature.pt.
4. review multicase.pt.
5. review of reported cases.pt.
6. review.pt.
7. bibliography.pt.
8. (meta-analysis or review literature).sh.
9. meta-analy\$.tw.
10. metaanal\$.tw.
11. (systematic\$ adj4 (review or overview\$)).tw.
12. meta-analysis.pt.
13. case report.sh.
14. historical article.pt.
15. meta-analysis.ti.
16. or/1-15
17. (stop\$ adj1 rule\$).tw. – when combined with review, reject, useful when combined with RCT terms
18. (earl\$ adj1 stop\$).tw. – when combined with review, reject, useful when combined with RCT terms
19. (trial\$ adj3 stop\$).tw. – not useful when used alone either
20. (trial\$ adj1 discontinu\$).tw. – not useful when used alone either
21. (stop\$ adj1 recruit\$).tw. – not useful when used alone either
22. (stop\$ adj2 recruit\$).tw. – not useful when used alone either
23. (stop\$ adj3 recruit\$).tw. – not useful when used alone either
24. (revised\$ adj1 recruit\$).tw. – not useful when used alone either
25. (revis\$ adj2 recruit\$).tw. – not useful when used alone either
26. (extens\$ adj2 recruit\$).tw. – not useful when used alone either
27. earl\$ adj1 terminat\$.tw. – not useful when used alone either
28. trial\$ adj25 terminat\$.tw. – not useful when used alone either
29. trial\$ adj1 continu\$.tw.

This term below was combined, using the Boolean operator 'AND', with a set of RCT terms based on the Cochrane Highly Sensitive Search Strategy to locate RCTs (see the MEDLINE search above for these RCT terms):

(stop\$ adj3 enroll\$).tw.

Appendix 3

Number of quotes found per question in *Box 1* in the systematic review of the published literature on data monitoring committees

Question	No. of quotes	File size (kb)
1	279	444
2	56	106
3	135	230
4	36	63
5	94	171
6	199	289
7	165	209
8	143	226
9	70	103
10	14	38
11	305	497
12	13	38
13	12	40
14	26	51
15	89	145
16	118	185
17	143	214
18	9	35
19	32	70
20	112	162
21	8	32
22	34	101
23	32	67
Total	2124	3516

Since the number of quotes does not take into account the length of the quotes highlighted, the eventual plain ASCII text file size is displayed as a measure of overall length. Relevant quotes may have been included under more than one question.

Appendix 4

List of included references in the systematic review of published literature on data monitoring committees

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Appendix 5

Summary of databases searched for the review of small group processes

PsycINFO (on WebSPIRS, the Web interface of SilverPlatter)

Years searched: 1887 to April 2001. Date of search: June 2001.

Some terms only (indicated on list of search terms) 1996 to August 2001. Date of search: November 2001.

ASSIA PLUS (Applied Social Sciences Index and Abstracts Plus) (on Bowker Saur on A&I Plus CD-ROM, now published and distributed by Cambridge Scientific Abstracts, E. Grinstead, UK)

Years searched: spring 2001 (covers 1987 to present). Date of search: August/September and November 2001.

SSCI (Social Science Citation Index) (Institute for Scientific Information, Philadelphia, PA, USA) (on ISI Web of Science on MIMAS)

Years searched: 1996 to 11 November 2001. Date of search: 12 November 2001.

MEDLINE (on OVID on Digital Island, web interface)

Years searched: 1966 to week 2 May 2001. Date of search: May 2001.

PREMEDLINE (on OVID on Digital Island, web interface)

Search covered: 24 May 2001. Date of search: 29 May 2001.

EMBASE (on OVID on Digital Island, web interface)

Years searched: 1980 to week 22 2001. Date of search: May/June 2001.

CINAHL (on OVID on Digital Island, web interface)

Years searched: 1982 to April 2001. Date of search: May 2001.

HealthSTAR (on OVID on Digital Island, web interface)

Years searched: 1975 to December 2000. Date of search: May 2001.

HMIC (Health Management Information Consortium database) (on WinSPIRS)

Years searched: DHdata and Kings Fund Database 1979 to current; HELMIS 1984 to current. Date of search: 20 November 2001.

Appendix 6

Electronic databases with search terms used for the review of small group processes

PsycINFO

Years searched: 1887 to April 2001 for reviews (some terms only 1996 to August 2001, indicated beside individual term). Date of last search: November 2001.

All terms limited to publication type = Literature review – research review, unless otherwise stated; all fields searched unless otherwise stated.

Useful terms:

Decision* NEAR error* (dates searched: 1996 to August 2001)
 Exp teams in DE
 Team* NEAR (task* or decision*)
 Group* process*
 3020 in CC (ie Group-and-Intepersonal Processes)

Rejected terms:

(Small NEAR group*) AND (task* or decision*) (dates searched: 1999 to April 2001)
 Group* NEAR decision* (dates searched: 1999 to April 2001)
 Group* NEAR task* (dates searched: 1999 to April 2001)
 Complex* decision* (dates searched: 1999 to April 2001)
 Small NEAR group* NEAR research* (Team* or group*) NEAR error*
 Organizational-behaviour in DE
 3630 in CC (ie Personnel Evaluation and job performance)
 exp Interpersonal interaction in DE
 Individual differences in DE
 Groupthink (dates searched: 1996 to August 2001)
 Decision* NEAR disaster* (dates searched: 1996 to August 2001)
 (Exp Leadership in DE OR leadership) AND task* (dates searched: 1996 to August 2001)
 leadership NEAR decision* (dates searched: 1996 to August 2001)
 Decision* NEAR strateg* (dates searched: 1996 to August 2001)
 Decision* NEAR technique* (dates searched: 1996 to August 2001)

Decision* NEAR process* (dates searched: 1996 to August 2001)
 (Decision* OR task*) AND committee* (dates searched: 1996 to August 2001)
 complex* NEAR task* (dates searched: 1996 to August 2001)
 Exp Group decision making in DE (dates searched: 1999 to April 2001)
 Exp Group dynamics in DE (dates searched: 1999 to April 2001)
 Group problem-solving in DE (dates searched: 1999 to April 2001)

Key: *, wildcard; DE, descriptor; CC, concept code; exp, exploded search; AG, age group field.

ASSIA PLUS (on Bowker Saur on A&I Plus CD-ROM)

Spring 2001 (goes back to 1987). Date of search: August/September and November 2001.

Review terms, all combined with review\$ in keyword field (words in any order):

1. Group\$ Task\$
2. Group\$ AND Decision\$
3. Group\$ dynamic\$
4. Groupthink
5. Groupwork\$
6. Leadership AND decision\$
7. Leadership AND task\$
8. Decision\$ AND disaster\$
9. Task\$ AND disaster\$
10. Child protection AND decision\$
11. Team\$ AND process\$
12. Team\$ AND task\$
13. Team\$ AND decision\$
14. Complex\$ AND decision\$
15. Decision\$ AND (error\$ OR bias\$)
16. (Team\$ OR group\$) AND error\$
17. Decision\$ AND strateg\$
18. Decision\$ AND technique\$
19. Decision\$ AND process\$
20. (Decision\$ OR task\$) AND committee\$
21. Complex\$ AND task\$

Key: \$, wildcard.

MEDLINE, CINAHL, HealthSTAR

Years searched: MEDLINE (1966 to April/week 2/3 May 2001), CINAHL (1982 to April 2001), HealthSTAR (1975 to December 2000). Dates of searches: May 2001

All terms combined with review terms, given below, unless otherwise stated:

Team\$ adj2 process\$. tw
 Complex\$ adj1 decision\$.tw
 Conflict\$ adj1 resolv\$.tw.
 Group processes/
 Groupthink.tw (not combined with review terms)
 (majority or minority) adj1 influence\$.tw. (not combined with review terms)

Terms tested in MEDLINE and rejected, not run in CINAHL and HealthSTAR (dates searched: mid 1998 to April/week 2/3 May 2001).

All combined with review terms, given below, unless otherwise stated:

(team adj25 (task\$ or decision\$)).tw.
 Group processes/
 Group structure/
 Committee\$ and (decision\$ or task\$).tw
 (Group\$ adj1 process\$).tw.
 Expert\$ adj1 panel\$) and process\$).tw.
 Group\$ adj25 decision\$.tw.
 Group\$ adj25 task\$.tw.
 Group\$ adj1 task\$.tw.
 Group\$ adj1 dynamic\$. tw
 Leadership/
 Decision\$ adj2 strateg\$.tw.
 Task performance and analysis/
 Decision support techniques/
 Complex\$ adj1 task\$ tw.
 Task\$ adj1 perform\$.tw.
 Decision\$ adj1 technique\$.tw.
 Decision adj1 making.tw.
 ((Decision adj1 making) AND complex\$).tw
 Interprofessional relationships/
 Interprofessional relationships/AND decision making/
 Communications/ AND interprofessional relations/
 Decision\$ adj1 process\$.tw.
 Dilemma\$ adj1 resolv\$.tw.
 Decision\$ adj1(bias\$ or error\$)
 Decision making/
 Critical adj1 incident\$.tw.

EMBASE

Years searched: 1980 to week 22 2001. Dates of searches: May/June 2001.

All combined with review terms, given below, unless otherwise stated:

Group dynamics/
 Teamwork/ AND (decision\$ or task\$)
 Psychodynamics/
 Group psychology/
 Team\$ adj2 process\$. tw
 (team\$ and (task\$ or decision\$))tw.
 Complex\$ adj1 decision\$.tw
 Conflict\$ adj1 resolv\$.tw.
 Interpersonal Communication/ AND (group\$ or team\$).tw.
 Group processes/
 (majority or minority) adj1 influence\$.tw. (not combined with review terms)
 Groupthink.tw (not combined with review terms)

CRD

Search Strategy for Systematic and Other Reviews (Short Version) Terms used for searching for reviews in MEDLINE, CINAHL, EMBASE and HealthSTAR:

1. Review, academic.pt.
2. Review tutorial.pt.
3. Review literature.pt.
4. Review multicase.pt.
5. Review of reported cases.pt.
6. Review.pt.
7. Bibliography.pt.
8. (meta-analysis or review literature).sh.
9. meta-analy\$.tw.
10. metaanal\$.tw.
11. (systematic\$ adj4 (review or overview\$)).tw.
12. meta-analysis.pt.
13. (case report).sh.
14. historical article.pt.
15. meta-analysis.ti.
16. or/1-15

Key: ti, term in title; tw, textword, i.e. term in title or abstract; pt, publication type; sh or /, MeSH (medical subject heading) (with all subheadings); \$, wildcard; adj(*n*), word within *n* words either side of another word.

SSCI (on Web of Science)

Years searched: 1996 to 11 November 2001. Date of search: 12 November 2001.

All in textword (i.e. title, abstract and author assigned keywords):

(Decision* AND disaster*) AND review*
(Decision* SAME group*) AND review*

HMIC (on WinSPIRS)

Years searched: DHdata and Kings Fund Database
1979 to current; HELMIS 1984 to current. Date of
search: 20 November 2001.

Search terms used:

((decision* or task*) NEAR (group* or team*))
AND review*
(leadership NEAR (decision* or task*)) AND
review*

PREMEDLINE

Year searched: 24 May 2001. Date of search:
29 May 2001.

All terms rejected, no review terms used:

Team\$ adj2 process\$. tw
(team\$ and (task\$ or decision\$))tw.
Complex\$ adj1 decision\$.tw
Groupthink.tw.
Conflict\$ adj1 resolv\$.tw.
(majority or minority) adj1 influence\$.tw.
group\$ adj1 process\$.tw.

Appendix 7

Number of review papers identified at each stage of the review of small group processes

Source	Field	No. of abstracts assessed	No. of abstracts potentially relevant (1st assessment)	Reassessment of abstracts (2nd assessment)	No. of full papers assessed	No. of papers included in the review
Electronic sources						
PsycINFO	Psychology	810	117	67	62	36
ASSIA PLUS	Social sciences	482	64	42	40	9
SSCI	Social sciences	112	14	10	10	4
MEDLINE	Clinical	1230	17	13	13	1
PREMEDLINE	Clinical	58	0	0	0	0
EMBASE	Clinical	302	0	0	0	0
CINAHL	Nursing and allied health professions	50	1	1	1	0
HealthSTAR	Health services research and health management	9	0	0	0	0
HMIC	Health management	134	0	0	0	0
Electronic sources: total		3187	213	133	126	50
Other sources						
Experts		7	7	7	7	7
Total		3194	220	140	133	57

Appendix 8

Summary of review articles included in the review of small group processes

Authors and year	Focus	Type of studies	Description of review
Aldag and Fuller, 1993 ¹⁶³	Reappraisal of groupthink and a new model of group decision processes	Laboratory and field	Narrative review and conceptual integration/new model
BarNir, 1998 ¹⁴¹	Meta-analysis of research on group decisions about life dilemmas (group polarisation/choice shift). Aim to identify moderators of choice shift	Laboratory research (14 studies), 1974–1994	Search strategy and eligibility criteria specified. Meta-analytical review
Bettenhausen, 1991 ²⁴⁰	Primary purpose, to review the literature on groups published in the past 5 years. Second goal is to provide insight into the dynamics of group behaviour for academics and practitioners	Laboratory research and case studies, all types ($n = 250$), 1986–1989	Search strategy and eligibility criteria specified. Narrative review
Blumberg, 1994 ¹⁴⁵	Reviews studies on group discussion and decision-making: predominantly choice shift and simulated juries	Laboratory research, 1973–1988	Narrative review
Bonito and Hollingshead, 1997 ¹⁸⁰	Studies on participation in small groups	Laboratory and field	Specified inclusion criteria. Narrative review
Chemers, 2002 ²⁴¹	Effects of leadership	Laboratory and field	Conceptual review
Chertkoff and Mesch, 1997 ¹⁷³	Effects of contingent reward systems on task performance in groups	Experimental studies, laboratory only	Strict methodological quality criteria for inclusion. Narrative review
Davies, 1994 ¹⁸²	Review of research on personality and interpersonal/group behaviour	Laboratory and field studies	Search strategy specified
De Dreu, 1999 ¹⁸³	Relationship between conflict and performance in groups	Laboratory and field	Narrative and conceptual review
Devine <i>et al.</i> , 2001 ¹⁴⁰	Reviews empirical research on jury decision-making	Laboratory and field (206 studies), 1955–1999	Tabulated data. Narrative review
Dukerich <i>et al.</i> , 1990 ¹⁵¹	Investigation into how groups reason about moral dilemmas	Laboratory research, 4 members per group in empirical studies	Narrative review driven by theories of moral reasoning plus two experimental studies testing theoretically based hypotheses
Esser, 1998 ¹⁵⁷	Summary of empirical research on groupthink theory	Case studies (17 articles, 16 cases), laboratory tests (11 articles, 13 experiments), 1971–1996	Tabulated data and narrative review
Frey, 1996 ¹⁷⁶	History of research on communication and small group decision-making	Laboratory and field, 1920–1990	Historical narrative review
George and Jessup, 1997 ²⁴²	Studies of groups using group support systems technology and working over time on common tasks	Laboratory (7), quasi-laboratory (3) and field (2)	Tabulated data (12 studies)

continued

Authors and year	Focus	Type of studies	Description of review
Gill <i>et al.</i> , 1984 ¹⁷⁵	Reviews member characteristics and conditions that increase the likelihood of participation in small groups	Laboratory and field	Narrative review
Gigone and Hastie, 1997 ¹³⁶	Methodology in research on group judgement accuracy	Laboratory and field	Tabulated data and conceptual integration
Gist <i>et al.</i> , 1987 ¹²⁹	Review of role of groups in organisations	Field	Narrative
Griffith and Vaitkus, 1999 ²⁴³	Develops a framework for organising variables related to group cohesion and task performance in military groups	Field (military settings)	Narrative review and conceptual integration
Guerin, 1986 ¹⁷⁴	Review of literature on social facilitation (mere presence effects)	Experimental, laboratory research (85 studies)	Search strategy and eligibility criteria specified. Tabulated data. Narrative review and vote counting
Gully <i>et al.</i> , 1995 ²⁴⁴	Investigates the hypothesis that task interdependence moderates the relationship between cohesion and performance in groups	Laboratory and field, (46 studies, 51 effect sizes)	Search strategy and eligibility criteria specified. Meta-analysis
Guzzo and Dickson, 1996 ^{188a}	Reviews recent research investigating factors that influence the effectiveness of teams at work in organisations	Studies conducted in organisational settings in 1990s	Narrative review
Hartman and Nelson, 1996 ¹⁴³	Studies on group decisions in the negative domain (prospect theory/framing)	Not clear, 1961–1993	Tabulated data/vote-counting based narrative review
Hollingshead, 2002 ²⁴⁵	Communication technologies and group performance	Laboratory and field	Narrative
Honeywell-Johnson and Dickinson, 1999 ¹⁷²	Effects of small group incentives on performance	Experimental studies in laboratory (9) and field (3), 1952–1997	Tabulated data
Isenberg, 1986 ^{142a}	Review of group polarisation studies. Comparison of two major explanatory hypotheses	21 studies (33 effect sizes), 1974–1982	Meta-analysis
Jones and Roelofsma, 2000 ¹³¹	Critical review of social contextual and group biases relevant to team decision making in command and control situations	Laboratory and field	Narrative review
Kagehiro, 1990 ²⁴⁶	Reviews literature on jury comprehension of instructions and standard of proof	Laboratory	Narrative review and summary of five experiments
Larson, 1997 ²⁴⁷	Studies on sharing of information in decision-making groups	Laboratory research	Narrative review and new model
Levine and Moreland, 1990 ¹²⁶	Comprehensive overview of research on small groups	Laboratory research and natural groups	Narrative review
Levine and Moreland, 1998 ¹²⁷	Updates Levine and Moreland (1990) ¹²⁶	Laboratory research and natural groups (672 refs)	Narrative review
Maass and Clark, 1984 ^{150a}	Reviews and evaluates literature on minority influences in small groups	Laboratory	Narrative review and conceptual integration
MacCoun, 1989 ¹⁶⁷	Reviews experimental research on jury decision-making	Laboratory	Narrative review
Martin and Hewstone, 2002 ¹⁴⁹	Reviews literature on majority and minority influence. Updates Maass and Clark (1984) ¹⁵⁰	Laboratory, predominantly 1980–2000	Narrative review and conceptual integration
Matsatsinis and Samaras, 2001 ¹³⁹	Effects of group decision support systems	Laboratory and field	Narrative review
McLeod, 1992 ¹⁷⁹	Relationship between electronic group support systems and group processes and outcomes	Experimental studies (13) 1980–1990	Search strategy and eligibility criteria specified Meta-analytical review

continued

Authors and year	Focus	Type of studies	Description of review
Miranda, 1994 ¹⁷¹	Explores the potential role of group support systems in avoiding groupthink	Empirical studies of groupthink and decision quality, empirical studies of group support systems	Tabulated data Narrative review
Mohamed and Wiebe, 1996 ²⁴⁸	Aims to identify the theoretical nature of groupthink theory and consider how it should be tested	Case studies and experimental studies	Conceptual and methodological review
Moorhead <i>et al.</i> , 2002 ¹⁶⁵	Application of groupthink theory to self-managing teams: does groupthink have relevance to organisations in the twenty-first century?	Laboratory research and case studies	Narrative review
Mullen <i>et al.</i> , 1994 ¹⁶²	Effects of group cohesiveness on quality of decision-making	Experimental studies, laboratory or field (9 papers, 17 effect sizes, 1382 participants), 1960–1992	Search strategy and eligibility criteria specified. Meta-analysis
Murphy <i>et al.</i> , 1998 ¹²⁸	To identify factors that affect the decisions that emerge from consensus development methods and make recommendations for groups developing clinical guidelines	Empirical articles and reviews, with emphasis on studies undertaken in the health sector ($n = 177$), 1966/1974–1996	Search strategy and inclusion criteria specified. Narrative review driven by key questions
Neck and Moorhead, 1995 ¹⁵⁶	Reviews research on groupthink and effects of time pressure on group decision-making	Case studies (4 articles, 4 cases), experimental studies (11 articles), 1977–1992	Tabulated data. Narrative review. Conceptual integration
Park, 1990 ¹⁵⁹	Review of empirical studies on groupthink	Laboratory research (7) and natural groups case studies (9), 1974–1990	Narrative and vote counting
Pavitt, 1993 ^{184a}	Do formal group discussion procedures result in better quality decisions?	Laboratory research	Narrative and vote counting
Phills, 1998 ¹⁷⁰	Review of literature on group composition with respect to relevance to real-life groups	Laboratory research and case study of theatre group	Narrative review and qualitative case study
Postmes and Lea, 2000 ¹⁸⁶	Evaluation of group decision support systems	Quasi-experimental field studies and experimental laboratory studies (12 independent studies, 1432 participants in 332 groups)	Search strategy and criteria for eligibility specified Meta-analytical review
Postmes <i>et al.</i> , 1998 ²⁴⁹	Studies of impact of characteristics of computer-mediated communication on social influence	Laboratory research	Narrative review
Raven, 1998 ¹⁵⁵	Reanalysis of groupthink case studies (Bay of Pigs and Watergate)	Case studies	Qualitative analysis and conceptual review
Robertson and Callinan, 1998 ²⁵⁰	Personality factors in work performance (including group performance)	Field	Narrative review
Salazar, 1995 ¹⁷⁷	Development of theory on effects of communication on group outputs (including decision quality)	Unclear	Theoretical development

continued

Authors and year	Focus	Type of studies	Description of review
Shelly, 1995 ²⁵¹	Reviews one theory of interaction with respect to task groups	Not clear	Narrative review
Stasser and Dietz-Uhler, 2002 ¹⁴⁴	Reviews studies of collective choice, judgement and problem solving in cooperative groups	Laboratory	Narrative review
Tindale <i>et al.</i> , 2002 ¹⁶⁸	Reviews literature on socially shared cognitions in groups and effects on process and performance	Laboratory	Conceptual review
Tindale <i>et al.</i> , 2002 ²⁵²	Reviews studies of procedural mechanisms and jury behaviour		
Turner and Horvitz, 2001 ¹⁶⁶	Overview of literature relevant to understanding how groups perform under external threat	Laboratory research and natural groups, 1952–1998	Narrative
Wekselberg, 1996 ¹⁶⁰	Critical review of groupthink theory	Laboratory research and case studies, analysis of social psychology textbooks, 1973–1995	Theoretical critique
Whyte, 1998 ¹⁶⁴	Develops a non-groupthink framework for explaining decision fiascos	Laboratory research and case studies of decision fiascos	Conceptual review
Zander, 1979 ²⁵³	General overview of group processes, including decision-making	Laboratory and field	Narrative review

^a Reviews included in the Murphy *et al.* (1998) *Health Technology Assessment* report.¹²⁸

Appendix 10

Data extraction form (cross-sectional review of reported use of data monitoring committees in main published reports of randomised controlled trials)

Microsoft Access - [Cross Section Study]

File Edit View Insert Format Record Sort Window Help

Address: []

ADMIN
Computer Library Drive

Publication Details

Journal: []
Year: []
Volume: []
Issue Number: []
Pages: [] to []

Find

Trial Details

Trial/Subject area: []
Primary endpoint: []
Planned sample size: [] to []
Actual sample size: []
Planned analysis time (m): []
Planned FU length (m): []
Double Blind: []
Placebo Controlled: []
Cross Over Trial: []
Number of Arms: []
Multi-centre trial: []
Country/Region of trial: []
 blinded Analysis: []
 Use of DMC: []

Notes

Sample Check
Title Lead
Emergent Issues

Drug Company Funding: []

DMC DETAILS (if applicable) Do not complete this section.

Form of (first) analysis rule: []
Planned number of analyses: []
Actual number of analyses: []
Did this trial stop early? []
Review conclusions: []
DMC membership accepted: []
Size of DMC: []
Name: []
Explicitly 'Independent': []

More Info

Show Duplicates Remove Duplicates Accept Transfer

Formid: 141 807 1 14 143 01 001
Protocol and/or methods published elsewhere

Taken copy of paper: [] Cancelled []

Appendix II

Sampling strategy for completed trials in surveys of policies and practice

	Mention of DMC in the article		Total
	Yes	No	
Single-centre trials	0	15	15
Multicentre trials	7	23	30
Total	7	38	45

	Disease area			Total
	Cancer	Cardiovascular/respiratory	Other	
Single-centre trials	1	5	9	15
Multicentre trials	8	10	12	30
Total	9	15	21	45

In addition, there were 15 trials from the UK, 15 from North America (i.e. the USA and Canada) and 15 from the rest of the world.

Appendix 12

Letter to principal investigator(s) for the survey of data monitoring in recently completed trials

Dear Sir or Madam

Data Monitoring Committees: Lessons, Ethics and Statistics (DAMOCLES)

I am writing to you in relation to a survey we are conducting on data monitoring committees in the context of randomised controlled trials (RCTs) which we are conducting with colleagues at the MRC Clinical Trials Unit and the Health Services Research Unit in Aberdeen. An outline of the project is attached. This letter relates to part C ii), practices relating to data monitoring committees in recently completed trials.

We have selected your trial, *ref* from a list of trials published during 2000. We are aware that editorial constraints often do not allow space for many details. If you would like to take part, we would be most grateful if you would be kind enough to **send us a copy of the trial protocol** in the envelope provided. If you would prefer to attach the protocol to an e-mail response, the e-mail address is given on the letterhead.

Please would you also tell us whether the trial data were monitored as detailed in the protocol, or whether there were any circumstances which necessitated a change from those plans. If so, would you be willing to answer a few questions about this by telephone? Please include your telephone and e-mail contact details on the attached sheet. If you are not able to help, please let us know who would be the most appropriate person to contact.

All information will be treated in confidence, and any publications will be based on aggregated data (unless you specifically request that your contribution be acknowledged by name). If you have any questions about this survey in the meantime, please feel free to contact us.

Thank you for your help.

Yours sincerely

Ms Felicity Clemens, Prof. Diana Elbourne, Prof. Stuart Pocock, London School of Hygiene and Tropical Medicine; Prof. Janet Darbyshire, MRC Clinical Trials Unit
On behalf of the DAMOCLES group

Encl. Summary of the DAMOCLES study
Return envelope

Appendix 13

Proforma for recent trials identified (part III) in surveys of policies and practice

DMC policies in recent trials

Trial name and reference	
Area of clinical interest (delete two)	Cardiovascular or respiratory/Cancer/Other
Number of centres	Single/Multi
Contact Name of PI	
Address/phone/e-mail	

This information on the role of DMCs in a recent trial will be collated mainly from the trial protocol, with some extra space for feedback following a telephone interview with PIs if they are happy to give one (their contact details should be returned with the protocol)

If there was a DMC, how many times did it meet over the course of the study?

	Was there a provision? (delete as necessary)	If yes, what was this provision?
1. Did the trial have a DMC?	Not applicable	Yes/No
2. What guidelines were used to draft the protocol provisions relating to the DMC, and who gave input to the provisions?	NA	
3. Why was a DMC planned for this trial?	NA	
4. Was there a provision governing the terms of reference of the DMC?	Yes/No	
5. Was there a provision for the time point during the trial when the DMC was formed (e.g. prior to final protocol draft)?	Yes/No	
6. Was there a provision governing the planned membership of the DMC (range of fields of expertise and the selection of members), and the role of the chairman if applicable?	Yes/No	
7. Was there a provision governing the position of the DMC with respect to trialists, sponsors, etc.; was conflict of interest addressed?	Yes/No	
8. Was there a provision on the conduct of meetings – open, closed, mixed; would investigators be allowed to participate, and what would happen to the papers after the meeting?	Yes/No	
9. Was there a provision describing the planned practical arrangements – timing and frequency of meetings, face-to-face or remote meetings?	Yes/No	
10. Was there a provision about the amount of experience necessary to DMC members, or a provision on the training of potential members?	Yes/No	
11. Was there a provision governing who was to provide the information for the DMC to consider?	Yes/No	
12. Was there a provision for the type of information to be provided to the DMC (baseline information, blinded/unblinded, etc.)?	Yes/No	
13. Was there a provision governing interactions with other DMCs or otherwise sharing the information presented at an interim analysis?	Yes/No	

continued

If yes, what was this provision?	Was there a provision? (delete as necessary)	Yes/No
14. Was there a provision discussing the scope of decision-making open to DMCs – for example extending recruitment, stopping part or all of the trial, making protocol changes?	Yes/No	Yes/No
15. Was there a provision governing whether the DMC's role was advisory or binding ?	Yes/No	Yes/No
16. Was guidance provided about the ways in which the DMC could reach a decision ?	Yes/No	Yes/No
17. Was there a provision governing whether the DMC should operate with reference to guidelines or a stopping rule ?	Yes/No	Yes/No
18. Was there a provision for the discussion of ethical issues ?	Yes/No	Yes/No
19. Was there a provision about who received the DMC's report , and the form this report took?	Yes/No	Yes/No
20. Space for discussion of practical difficulties encountered by the investigator in setting up the DMC		
21. Space for discussion of difficulties in implementing the provisions for data monitoring – data quality, freezing the data and other issues		
22. Was it worth setting up the DMC – was its work valuable? What recommendations did it make?		
23. Having finished the study, what would the investigators have changed about its data monitoring provisions?		

Appendix I4

Sampling strategy for survey of ongoing trials in surveys of policies and practice

	Number of centres ^a		Industry/non-industry			Disease area			Total
	Single (1 centre)	Multicentre (>1 centre)	Industry-funded	Publicly funded	Cancer	Cardiovascular/ respiratory	Other		
MRC (as at April 2001)	3	9	–	12	3	3	6	12	
HTA (as at November 2001)	3	9	–	12	2	2	8	12	
Trent MREC (excluding HTA/MRC)	–	10	6	4	3	3	4	10	
GOS LREC (excluding HTA/MRC and MREC trials)	5	1	4	2	2	2	2	6	
Total	11	29	10	30	10	10	20	40	

^a As it is not always possible to ascertain initially whether a trial is single-centre or multicentre from MRC listings, HTA trials are classified as single-centre if there are fewer than three centres, and some trials approved by the LREC may have two to four centres, the authors initially oversampled from the list of trials for which the number of centres is not known, in order to fill the cells as indicated above.

Appendix 15

Letter to principal investigator(s) for the survey of current data monitoring practices

Dear Sir or Madam

Data Monitoring Committees: Lessons, Ethics and Statistics (DAMOCLES)

I am writing to you in relation to a survey we are conducting on data monitoring committees in the context of randomised controlled trials (RCTs) in conjunction with colleagues at the MRC Clinical Trials Unit and the Health Services Research Unit in Aberdeen. An outline of the project is attached. This letter relates to part C ii), practices relating to data monitoring committees in ongoing trials.

We have selected your current trial, *name, from a database made available to us by collaborators at the HTA/from the register of MRC-funded trials publicly available on the Internet*. We would be most grateful if you would be kind enough to **send us a copy of the trial protocol** in the envelope provided/by mail to the address below or as an e-mail attachment to the address below.

Please would you also tell us whether the data monitoring is working in practice as detailed in the protocol, or whether circumstances have necessitated a change from these plans. If so, would you be willing to answer a few questions about this by telephone? Please include your telephone and e-mail contact details on the attached sheet. If you are not able to help, please let us know who would be the most appropriate person in the trial for us to contact.

All information will be treated in confidence, and any publications will be based on aggregated data (unless you specifically request that your contribution be acknowledged by name). If you have any questions about this survey in the meantime, please feel free to contact us.

Thank you for your help.

Yours sincerely

Ms Felicity Clemens, Prof. Diana Elbourne, Prof. Stuart Pocock, London School of Hygiene and Tropical Medicine; Prof. Janet Darbyshire, MRC Clinical Trials Unit
On behalf of the DAMOCLES group

Encl. Summary of the DAMOCLES study
Sheet for contact details
Return envelope

Name of principal investigator	Title of trial	HTA reference number where applicable

Are the data being monitored as detailed in the protocol?

Yes

No (circumstances necessitated a change)

If you would be willing to provide a brief outline of how the monitoring process has changed over the course of the study, please do so in the box below:

--

If you would prefer to be interviewed about this briefly by telephone, please provide contact details below:

E-mail address	Telephone contact details

Appendix 16

Proforma for data extraction from the studies sampled (part II) in surveys of policies and practice

DMC policies in current trials

Trial name and ref. number if applicable	
Area of clinical interest (delete two)	Cardiovascular or respiratory/Cancer/Other
Sponsor (delete two)	MRC/HTA/MREC/LREC
Contact Name	
Address/phone/e-mail	

This information on the role of DMCs in a current trial will be collated mainly from the trial protocol, with some extra space for feedback following a telephone interview with PIs if they are happy to give one (their contact details should be returned with the protocol)

For trials that have a DMC, has it met yet? If so, how many times?

	Was there a provision? (delete as necessary)	If yes, what was this provision?
1. Does the trial have a DMC?	Not applicable	Yes/No
2. What guidelines were used to draft the protocol provisions relating to the DMC, and who gave input to the provisions?	NA	
3. Why was a DMC planned for this trial?	NA	
4. Was there a provision governing the terms of reference of the DMC?	Yes/No	
5. Was there a provision for the time point during the trial when the DMC was formed (e.g. prior to final protocol draft)?	Yes/No	
6. Was there a provision governing the planned membership of the DMC (range of fields of expertise and the selection of members), and the role of the chairman if applicable?	Yes/No	
7. Was there a provision governing the position of the DMC with respect to trialists, sponsors, etc.; was conflict of interest addressed?	Yes/No	
8. Was there a provision on the conduct of meetings – open, closed, mixed; would investigators be allowed to participate, and what would happen to the papers after the meeting?	Yes/No	
9. Was there a provision describing the planned practical arrangements – timing and frequency of meetings, face-to-face or remote meetings?	Yes/No	
10. Was there a provision about the amount of experience necessary to DMC members, or a provision on the training of potential members?	Yes/No	
11. Was there a provision governing who was to provide the information for the DMC to consider? Was the analysis to be performed by the trial statistician or an independent statistician?	Yes/No	
12. Was there a provision for the type of information to be provided to the DMC (baseline information, blinded/unblinded, etc.)?	Yes/No	
13. Was there a provision governing interactions with other DMCs or otherwise sharing the information presented at an interim analysis?	Yes/No	

continued

If yes, what was this provision?	Was there a provision? (delete as necessary)	If yes, what was this provision? (delete as necessary)
14. Was there a provision discussing the scope of decision-making open to DMCs – for example extending recruitment, stopping part or all of the trial, making protocol changes?	Yes/No	
15. Was there a provision governing whether the DMC's role was advisory or binding ?	Yes/No	
16. Was guidance provided about the ways in which the DMC could reach a decision ?	Yes/No	
17. Was there a provision governing whether the DMC should operate with reference to guidelines or a stopping rule ?	Yes/No	
18. Was there a provision for the discussion of ethical issues ?	Yes/No	
19. Was there a provision about who receives the DMC's report , and the form this report will take?	Yes/No	
20. Space for discussion of practical difficulties encountered by the investigator in setting up the DMC		
21. Space for discussion of difficulties in implementing the provisions for data monitoring – data quality, freezing the data and other issues		
22. Was it worth setting up the DMC – was its work valuable?		
23. How far along is the study in terms of a fraction – i.e. $\frac{1}{4}$ of the way through, etc.?		
24. Having set up the protocol, what would the investigators change about its data monitoring provisions?		

Appendix 17

Proforma used to gather policy information from funding organisations in surveys of policies and practice

DMC policies

Organisation	
Website Address	
Contact Name	
Address	

The questions on the following pages ask about whether your organisation has a policy about particular issues to do with Data Monitoring Committees (DMCs), and if so, what this policy is.

If there are policy documents available, please attach them.

If there is no policy, who makes decisions regarding data monitoring?

Note: to save your time, we have already completed some sections from the website(s) cited above, but please amend these details if we have interpreted them incorrectly *This line is omitted for those organisations for which we don't have any information*

This form contains five columns. Column 1 contains each policy question. Column 2 asks if there is a policy in place dealing with each question; if Y, go to columns 3 and 4; if N, go to column 5.

1	2	3	4	5
	Is there a policy? If Y → columns 3&4 If N → column 5	If yes, please give details of the policy	Is the policy statement attached? (delete as required)	If no policy, how are decisions taken and by whom?
1.	Is there a policy about which trials should have a DMC?		Yes/No	
2.	Are there (a) Standard terms of reference for the DMC, and (b) are its recommendations advisory to or binding on the trial executive?		Yes/No	
3.	Is there a policy about (a) at what point a DMC should be initiated and (b) whether it should have input into the trial protocol before recruitment?		Yes/No	
4.	Is there a policy about the size and composition (range of professional expertise +/- consumer input) of the DMC?		Yes/No	
5.	Is there a policy about who should decide the names of the members of particular DMCs?		Yes/No	
6.	Is there a policy about the position the DMC should have with respect to the sponsor, trialists and participants?		Yes/No	
7.	Is there a policy about whether DMC members should be paid?		Yes/No	
8.	Is there a policy for how to deal with conflicts of interest?		Yes/No	
9.	Is there a policy about whether the meetings are open, closed or mixed (that is, whether non-members of the DMC are allowed to attend)?		Yes/No	

continued

1	2	3	4	5
	Is there a policy? If Y → columns 3&4 If N → column 5	If yes, please give details of the policy	Is the policy statement attached? (delete as required)	If no policy, how are decisions taken and by whom?
10.	Is there a policy about who has access to the accumulating data during the trial (in addition to the DMC members)?		Yes/No	
11.	Is there a policy about who receives the DMC's report ?		Yes/No	
12.	Is there a policy about disposal of the DMC's papers after their meeting?		Yes/No	
13.	Is there a policy about (a) the timing and frequency of the DMC meetings, and (b) the means of communication used (personal contact, teleconference, e-mail, etc.)?		Yes/No	
14.	Is there a policy about training the DMC members for their role?		Yes/No	
15.	Is there a policy about who produces the data considered by the DMC?		Yes/No	
16.	Is there a policy about what information is provided to the DMC, and whether relevant information external to the trial is included in DMC meeting discussions?		Yes/No	
17.	Is there a policy about how the DMC should reach its decisions?		Yes/No	
18.	Is there a policy about differently addressing the issues of safety and efficacy (for example, giving separate guidelines for stopping)?		Yes/No	
19.	Is there a policy about whether issues of patient recruitment are discussed?		Yes/No	

continued

1	2	3	4	5
	Is there a policy? If Y → columns 3&4 If N → column 5	If yes, please give details of the policy	Is the policy statement attached? (delete as required)	If no policy, how are decisions taken and by whom?
20.	Is there a policy on discussion of ethical issues?		Yes/No	
	<i>Finally, how long have these policies been in place?</i>			
	<i>Are there any plans to change them?</i>	Yes/No <i>If yes, please give details:</i>		
	<i>Please give details about any other policy issues related to DMCs not mentioned above.</i>			
	<i>Would you like to be sent a copy of the report of the study when it is completed in 2002?</i>			Yes/No

Appendix 18

Classification of organisations included in the survey of data monitoring policies and summary of response in surveys of policies and practice

Organisation	Website	Question subject	
		Types of trials which should have DMCs	Terms of reference
<i>Charities</i>			
British Heart Foundation (BHF)	www.bhf.org.uk	-	-
Cancer Research Campaign (CRC) (now part of Cancer Research UK)	www.crc.org.uk www.cancerhelp.org.uk	-	✓
Imperial Cancer Research Fund (ICRF) (now part of Cancer Research UK)	www.icnet.uk	-	-
<i>UK Governmental health departments</i>			
Chief Scientist Office of the Scottish Executive Health Department (CSOSEHD)	www.show.scot.nhs.uk/cso/	-	-
Department of Health (DH) (England)	www.dh.gov.uk/research/rd3/nhsrandd/researchgovernance/govhome.html	✓	✓
Department of Health, Social Services and Public Safety (DHSSPSNI) (Northern Ireland)	www.dhsspsni.gov.uk/index.html	-	-
Health and Social Services Committee (HSSC) (Wales)	www.wales.gov.uk/subihealth/index.htm	-	-
<i>Industry</i>			
Association of the British Pharmaceutical Industry (ABPI)	www.abpi.org.uk	✓	✓
International Conference on Harmonisation/International Federation of Pharmaceutical Manufacturers' Associations (ICH/IPMA)	www.ifpma.org http://www.ich.org/pdf/ICH/e9.pdf	✓	✓
<i>International</i>			
Community Research and Development Information Service (CORDIS) (EU)	www.cordis.lu/life/src/iv2_64.htm	✓	✓
World Health Organisation (WHO)	http://www.who.int/medicines/library/par/ggcp/GCPGuidePharmaterials.pdf	✓	✓
<i>Regulatory</i>			
European Agency for the Evaluation of Medicinal Products (EMA)	www.emea.eu.int www.europa.eu.int/comm/enterprise/policy_en.htm	✓	✓
Food and Drug Administration (FDA) (USA)	www.fda.gov/cder/guidance/91698.pdf	✓	✓
Medicines Control Agency (MCA) (UK)	www.mca.gov.uk/	✓	✓

continued

Organisation	Website	Question subject	
		Types of trials which should have DMCs	Terms of reference
Research and development: governmental bodies and research councils			
Canadian Institutes of Health Research (CIHR)	www.cihr.ca www.nserc.ca/programs/ethics/english/sec07.htm www.eortc.be	✓	✓
European Organisation for Research and Treatment of Cancer (EORTC)	www.mrc.ac.uk/PDFs/ctg.pdf www.mrc.ac.za www.nchta.org/ www.nci.nih.gov www.cancertrials.nci.nih.gov/understanding/indepth/protections/monitor.html www.cancertrials.nci.nih.gov/researchers/dsm/html/essential.html www.health.gov.au/nhmrc/research/policy.htm	✓	✓
Medical Research Council (MRC) (UK)		✓	✓
Medical Research Council of South Africa (MRC – SA)		✓	✓
Health Technology Assessment (HTA) Programme (UK)		✓	✓
National Cancer Institute (NCI) (USA)		✓	✓
National Health and Medical Research Council (NHMRC) (Australia)		✓	✓
National Heart, Lung and Blood Institute (NHLBI) (USA)	www.nhlbi.nih.gov/funding/policies/dsmb_est.htm www.nhlbi.nih.gov/funding/policies/dsmb_othr.htm www.niaid.nih.gov/ncn/pdf/clinterm.pdf www.nichd.nih.gov/funding/datasafety.htm www.grants.nih.gov/grants/guide/notice-files/not98-084.html	✓	✓
National Institute for Allergies and Infectious Diseases (NIAID) (USA)		✓	✓
National Institute for Child Health and Human Development (NICHD) (USA)		✓	✓
National Institutes of Health (NIH) (USA)		✓	✓
Total number of respondents to each question		19	20
Of these organisations, those whose remit is primarily to fund trials are: BHF, CRC, ICREF, DH (through the HTA), CORDIS, WHO, CIHR, MRC, MRC-SA, HTA, NCI, NHMRC, NHLBI, NIAID, NICHD and NIH.			

Organisation	Question subject							Total number of respondents to each question	continued
	Role: advisory or executive	Whether the DMC should have input into the trial protocol	Access to the interim data	Who the DMC reports to	Disposal of the DMC papers after the meeting	Timing and frequency of meetings	Means of communication used		
<i>Charities</i>									
BHF	-	-	-	-	-	-	-	-	-
CRC	-	-	-	-	-	-	-	-	-
ICRF	-	-	-	-	-	-	-	-	-
<i>UK governmental health departments</i>									
CSEHED	-	-	-	-	-	-	-	-	-
DH	✓	-	✓	✓	✓	✓	✓	✓	✓
DHSSPSNI	-	-	-	-	-	-	-	-	-
HSSC	-	-	-	-	-	-	-	-	-
<i>Industry</i>									
ABPI	✓	-	✓	✓	-	✓	-	-	-
ICH/IFPMA	✓	-	✓	✓	-	✓	-	-	-
<i>International</i>									
CORDIS	✓	-	✓	✓	-	✓	-	-	-
WHO	✓	-	-	✓	✓	-	✓	-	-
<i>Regulatory</i>									
EMA	✓	-	✓	✓	-	✓	-	-	-
FDA	✓	✓	✓	✓	-	✓	-	-	-
MCA	✓	-	✓	✓	-	✓	-	-	-
<i>Research and development: governmental bodies and research councils</i>									
CIHR	✓	-	-	-	-	-	-	-	-
EORTC	✓	✓	✓	✓	✓	✓	✓	✓	✓
MRC	✓	-	✓	✓	✓	✓	✓	✓	✓
MRC – SA	✓	-	✓	✓	✓	✓	✓	✓	✓
HTA	✓	-	✓	✓	✓	✓	✓	✓	✓
NCI	✓	✓	✓	✓	✓	✓	✓	✓	✓
NHMRC	✓	-	✓	✓	-	✓	-	-	-
NHLBI	✓	✓	✓	✓	✓	✓	✓	✓	✓
NIAID	✓	✓	✓	✓	✓	✓	✓	✓	✓
NICHD	✓	✓	✓	✓	✓	✓	✓	✓	✓
NIH	✓	✓	✓	✓	✓	✓	✓	✓	✓
Total number of respondents to each question	19	7	17	18	8	17	5		

Organisation	Question subject					
	Training of DMC members	Size and composition of the DMC	Who decides the membership of the DMC	Position of the DMC with respect to sponsors, trialists and participants	Payment of DMC members	Dealing with conflicts of interest for DMC members
<i>Charities</i>						
BHF	-	-	-	-	-	-
CRC	-	-	-	-	-	-
ICRF	-	-	-	-	-	-
<i>UK governmental health departments</i>						
CSOSEHD	-	-	-	-	-	-
DH	-	✓	✓	✓	✓	✓
DHSSPSNI	-	-	-	-	-	-
HSSC	-	-	-	-	-	-
<i>Industry</i>						
ABPI	-	✓	✓	✓	-	-
ICH/IFPMA	-	✓	✓	✓	-	-
<i>International</i>						
CORDIS	-	✓	✓	✓	-	-
WHO	-	✓	-	✓	-	-
<i>Regulatory</i>						
EMEA	-	✓	✓	✓	-	-
FDA	-	✓	✓	✓	✓	✓
MCA	-	✓	✓	✓	-	-
<i>Research and development: governmental bodies and research councils</i>						
CIHR	-	-	✓	✓	✓	✓
EORTC	-	✓	✓	✓	✓	✓
MRC	✓	✓	✓	✓	✓	✓
MRC – SA	-	✓	✓	✓	-	-
HTA	-	✓	✓	✓	✓	✓
NCI	-	✓	✓	✓	✓	✓
NHMRC	-	✓	✓	✓	✓	✓
NHLBI	✓	✓	✓	✓	✓	✓
NIAID	-	✓	✓	✓	✓	✓
NICHD	-	✓	✓	✓	✓	✓
NIH	-	✓	✓	✓	-	✓
Total number of respondents to each question	2	18	18	19	10	11

continued

Organisation	Question subject						
	Conduct of the meetings (open, closed, mixed)	Production of the interim information considered by the DMC	Information contained in the interim report, and consideration of external data	Decision-making within the DMC	Separate consideration of safety and efficacy	Discussion of patient recruitment	Discussion of specifically ethical issues
Charities							
BHF	-	-	-	-	-	-	-
CRC	-	-	-	-	-	-	-
ICRF	-	-	-	-	-	-	-
UK governmental health departments							
CSEHD	-	-	-	-	-	-	-
DH	✓	✓	✓	-	-	✓	✓
DHSSPSNI	-	-	-	-	-	-	-
HSSC	-	-	-	-	-	-	-
Industry							
ABPI	-	-	-	-	✓	-	-
ICH/IFPMA	-	-	-	-	✓	-	-
International							
CORDIS	-	-	-	-	✓	-	-
WHO	✓	-	-	-	-	-	-
Regulatory							
EMEA	-	-	-	-	✓	-	-
FDA	✓	-	-	-	✓	✓	-
MCA	-	-	-	-	✓	-	-
Research and development: governmental bodies and research councils							
CIHR	✓	-	-	-	-	-	-
EORTC	✓	✓	✓	-	-	✓	✓
MRC	✓	✓	✓	-	-	✓	✓
MRC – SA	-	-	-	-	✓	-	-
HTA	✓	✓	✓	-	-	✓	✓
NCI	✓	✓	✓	-	-	✓	-
NHMRC	-	-	-	-	✓	-	-
NHLBI	✓	✓	✓	✓	-	✓	✓
NIAID	✓	✓	✓	✓	-	✓	✓
NICHD	✓	✓	✓	✓	✓	✓	✓
NIH	✓	-	✓	-	-	✓	✓
Total number of respondents to each question	12	8	9	3	9	10	8

Appendix 19

Letter to key organisations involved with randomised controlled trials

Dear Sir or Madam

Data Monitoring Committees: Lessons, Ethics, and Statistics (DAMOCLES)

We are writing to you in relation to a research project on data monitoring committees in the context of randomised controlled trials (RCTs) which we are conducting with colleagues at the MRC Clinical Trials Unit and the Health Services Research Unit in Aberdeen. The project is funded by the HTA. Brief details of the different components of the project are given on the attached summary sheet. We are responsible for component C (i), surveys of the policies about data monitoring committees from major organisations (such as *organisation name*) that support RCTs.

We have consulted your website to see if we can obtain the information we need for your organisation, but not all the details were available from this source. We are therefore attaching a partially completed proforma, and would be very grateful if you would:

- (a) **check that the information we have included is correct**, and
- (b) **add the details which are currently missing**. If all this information is already available in written policy statements, please send us these instead if this would be easier for you.

Please return the checked and completed proforma (and policy statements, if available) in the envelope provided. If you would prefer to complete the form electronically, please e-mail us and we can send it to you as a word or rtf attachment. If you are not able to help, please let us know who would be the most appropriate person for us to contact within your organisation, or forward the proforma to them. We would be very grateful if you could reply **within the next 10 days**.

We will send you a copy of the findings of the study when completed but if you have any questions about the survey in the meantime, please feel free to contact us.

Thank you very much for your help.

Yours sincerely

Ms Felicity Clemens, Prof. Diana Elbourne, Prof. Stuart Pocock, London School of Hygiene and Tropical Medicine; Prof. Janet Darbyshire, MRC Clinical Trials Unit

On behalf of the DAMOCLES group

Enc. Summary of the DAMOCLES study; Proforma; Return envelope

Appendix 20

Summary of the DAMOCLES study in surveys of policies and practice

Data Monitoring Committees: Lessons, Ethics and Statistics (DAMOCLES)

BACKGROUND

Randomised controlled trials (RCTs) are a major component in the evaluation of interventions in health care. RCTs are essential to identify the best way to manage a particular health condition, but they can be costly and can raise difficult ethical issues. RCTs are only worthwhile if their findings are sufficiently robust to enhance future health care; and they are only ethical if the possibility of being harmed as a result of being in the trial is minimised. To ensure that this is the case, most RCTs incorporate a data monitoring (or safety) committee to assess the data as they accumulate and decide whether or not a trial should continue. The quality of the decision made by a data monitoring committee is crucial, and concern has been raised that 'wrong' decisions may occur because of the ways in which data monitoring committees are conducted.

AIM

To develop recommendations for the conduct of data monitoring committees in RCTs in order to minimise the risk that 'wrong' decisions will occur.

PLAN OF INVESTIGATION

The proposed study will have four components:

- (A) A systematic review of available information about the conduct of data monitoring committees
- (B) A review of the relevant literature on decision-making processes in other types of task-orientated small groups
- (C) Surveys of (i) the policies about data monitoring committees from major agencies which support RCTs, and (ii) practices relating to data monitoring committees in recently completed and ongoing trials
- (D) Case studies of particular trials drawn from the sample survey and experiences of members of the study group

Two of these pieces of work (A & C) will be conducted by London members of the research team based in the London School of Hygiene and Tropical Medicine and the MRC Clinical Trials Unit. A team at the Health Services Research Unit, Aberdeen, will undertake components B & D.

TIMETABLE

Start date: 1 February 2001
Completion date: 31 July 2002

FUNDING

NHS R&D Health Technology Assessment Programme

Appendix 2I

Letter to experienced data monitoring committee members requesting a general interview

Dear

NHS R&D FUNDED PROJECT ON DATA MONITORING COMMITTEES: LESSONS, ETHICS & STATISTICS (DAMOCLES)

The NHS R&D HTA programme have funded a project to explore practical issues related to monitoring accumulating data in randomised controlled trials. An outline of the project is attached.

As part of the project we hope to interview a number of experienced DMC members with a view to identifying possible advantages and disadvantages of alternative models of working. Given that you have served on a number of DMCs the DAMOCLES team (see below) suggested you as a key person in this regard.

If you were agreeable, it would involve a relatively short telephone interview, to discuss your experience of DMCs. It is hoped interviewing would take place towards the beginning of May.

I look forward to hearing from you, however if you require any further information please do not hesitate to contact me directly on 01224 551100 or e-mail skm@hsru.abdn.ac.uk

Yours sincerely

Sharon McLeer
(*on behalf of the DAMOCLES group*)

Enc. Summary of the DAMOCLES study

The DAMOCLES group:
Prof. Stuart Pocock, Prof. Diana Elbourne, Prof. Janet Darbyshire, Prof. Adrian Grant, Prof. Doug Altman, Dr David Spiegelhalter, Dr Mahesh Parmar, Dr Abdel Babiker, Dr Anne Walker, Marion Campbell, Matthew Sydes, Felicity Clemens, Sharon McLeer, Sheila Wallace

Appendix 22

Semistructured interview schedule used for general interviews and case studies

1. Membership of DMC

- (a) Can you begin by telling me about the members of the DMC?
(lead into discussion about group size, how they were chosen, range of expertise, status, familiarity, etc.)
- (b) Was there a chairperson and, if so, how were they selected?
(probe into committee satisfaction with chairperson selection)
- (c) What was the role of the chairperson (and statistician)?
(probe into opinions about responsibilities, influence, abilities)

2. Training and expertise

- (a) Did you or any of the other members have any prior training or experience of DMCs?
(probe familiarity with standard DMC procedures and small group decision-making. If training provided, by whom?)

3. Accountability and role of DMC

- (a) What position did the DMC have with respect to sponsor, trialist and participant?
(probe independence, payment, incentives)
- (b) Were the DMC deliberations open or closed?
(lead into discussion about who was present during discussions, who outside the committee saw the interim analysis, and who was informed about the decisions reached)
- (c) Was a terms of reference available for the DMC?
(probe scope and value of terms of reference, perceived role and responsibilities of the DMC)
- (d) What recommendations were open to the DMC?
(probe decision versus recommendation, early stopping, extending subgroups, trial organisation)
- (e) Did the DMC have any role before or after the trial recruitment phase?
(probe input to protocol, e.g. changing outcome measures and sanctioning changes)

4. Practical arrangements

- (a) How frequent were the meetings?
(probe timing of meetings, attendees, format of meetings, etc.)
- (b) What communication media were used?
- (c) What material was available to the DMC?
(probe what was produced, who produced it and what was available before and during the meeting)
- (d) Was any external evidence included; if so, how?
(probe when and who circulated external evidence, e.g. systematic reviews, other trials)

5. Decision-making

Issues relating to decision-making in the DMC

- (a) What were the main issues under consideration by the DMC?
(lead into discussion to clarify events leading up to the decision)
- (b) Was the DMC decision difficult to reach, and if so, why?
(probe task complexity)
- (c) In your opinion, what factors impacted on the decision-making process?
(e.g. probe for group composition and size, leadership, communication, time constraints, external influence/accountability, trial design, formal statistical methods)
- (d) How was the decision reached in the DMC?
(probe for methods and criteria for guiding deliberations e.g. role of the chairperson, formal statistical methods versus guidelines)
- (e) Was there any formal method of achieving consensus?
(probe member satisfaction with outcome)
- (f) What factors impacted on the decision-making process?
(e.g. probe for group composition and size, leadership, communication, time constraints, external influence/accountability, trial design, formal statistical methods)
- (g) Was there a role for consumer members on the DMC?

6. Ethical issues

- (a) Were ethical issues made explicit in the handling of the DMC deliberations?
(probe the nature of issues and who raised them)
- (b) How were these issues handled?
(probe general principles underlying decision, weights given to different end-points)

7. DMC recommendations and reporting

- (a) How did the DMC make its recommendations?
(probe who it reported to, advisory or executive, and whether form or report)
- (b) Did the DMC approve any publications, especially in relation to reporting any DMC recommendations regarding the termination of the trial?
(probe what information was included in published trial reports in light of the CONSORT report)

Appendix 23

Letter to principal investigator(s) requesting permission to include a trial in case-study interviews

Dear

NHS R&D FUNDED PROJECT ON DATA MONITORING COMMITTEES: LESSONS, ETHICS & STATISTICS (DAMOCLES)

The NHS R&D HTA programme have funded a project to explore practical issues related to monitoring accumulating data in randomised controlled trials. An outline of the project is attached.

To facilitate this study, members of the project team (see below) have identified a number of trials that faced difficult DMC monitoring decisions about whether the trial should continue or not. The [name of trial] has been suggested as one such possible case study. As the principal investigator, we would like to ask for your permission to include this trial in our study.

If you were agreeable this would involve a telephone interview with you, and with members of the data monitoring committee. It is hoped interviewing could take place in the next couple of weeks.

I look forward to hearing from you, however if you require any further information please do not hesitate to contact me directly on +44 1224 551100 or e-mail skm@hsru.abdn.ac.uk

Kind regards

Sharon McLeer
(on behalf of the DAMOCLES group)

The DAMOCLES group:
Prof. Stuart Pocock, Prof. Diana Elbourne, Prof. Janet Darbyshire, Prof. Adrian Grant, Prof. Doug Altman, Prof. David Spiegelhalter, Prof. Mahesh Parmar, Dr Abdel Babiker, Dr Anne Walker, Marion Campbell, Matthew Sydes, Felicity Clemens, Sharon McLeer, Sheila Wallace

Appendix 24

Letter to data monitoring committee members requesting an interview for case studies

Dear

NHS R&D FUNDED PROJECT ON DATA MONITORING COMMITTEES: LESSONS, ETHICS & STATISTICS (DAMOCLES)

The NHS R&D HTA programme have funded a project to explore practical issues related to monitoring accumulating data in randomised controlled trials. An outline of the project is attached.

To facilitate this study, members of the project team (see below) have identified a number of trials that faced difficult data monitoring decisions about whether the trial should continue or not. The [name of trial] has been suggested as one such possible case study.

I have already spoken to [name of PI(s)] as one of the principal investigators, who has kindly given his permission for me to contact you as one of the DMC members involved in this trial. If you were agreeable, I would like to interview you to discuss your experience as a DMC member. It is hoped that a telephone interview would take place in the next couple of weeks.

I look forward to hearing from you, however if you require any further information please do not hesitate to contact me directly on 01224 551100 or e-mail skm@hsru.abdn.ac.uk

Yours sincerely

Sharon McLeer
(on behalf of the DAMOCLES group)

Enc. Summary of the DAMOCLES study

The DAMOCLES group:
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Health Technology Assessment Programme

Prioritisation Strategy Group

Members

Chair, Professor Tom Walley, Director, NHS HTA Programme, Department of Pharmacology & Therapeutics, University of Liverpool	Professor Bruce Campbell, Consultant Vascular & General Surgeon, Royal Devon & Exeter Hospital	Dr John Reynolds, Clinical Director, Acute General Medicine SDU, Radcliffe Hospital, Oxford
	Professor Shah Ebrahim, Professor in Epidemiology of Ageing, University of Bristol	Dr Ron Zimmern, Director, Public Health Genetics Unit, Strangeways Research Laboratories, Cambridge

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Professor Ann Bowling, Professor of Health Services Research, Primary Care and Population Studies, University College London	Professor Fiona J Gilbert, Professor of Radiology, Department of Radiology, University of Aberdeen	Professor Tim Peters, Professor of Primary Care Health Services Research, Division of Primary Health Care, University of Bristol	Professor Simon G Thompson, Director, MRC Biostatistics Unit, Institute of Public Health, Cambridge
Professor Andrew Bradbury, Professor of Vascular Surgery, Department of Vascular Surgery, Birmingham Heartlands Hospital	Professor Adrian Grant, Director, Health Services Research Unit, University of Aberdeen	Professor Ian Roberts, Professor of Epidemiology & Public Health, Intervention Research Unit, London School of Hygiene and Tropical Medicine	Ms Sue Ziebland, Senior Research Fellow, Cancer Research UK, University of Oxford
	Professor F D Richard Hobbs, Professor of Primary Care & General Practice, Department of Primary Care & General Practice, University of Birmingham	Professor Peter Sandercock, Professor of Medical Neurology, Department of Clinical Neurosciences, University of Edinburgh	

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<p>Ms Norma Armston, Freelance Consumer Advocate, Bolton</p>	<p>Dr David Elliman, Consultant in Community Child Health, London</p>	<p>Dr Edmund Jessop, Medical Adviser, National Specialist Commissioning Advisory Group (NSCAG), Department of Health, London</p>	<p>Professor Lindsay Wilson Turnbull, Scientific Director, Centre for MR Investigations & YCR Professor of Radiology, University of Hull</p>
<p>Professor Max Bachmann, Professor Health Care Interfaces, Department of Health Policy and Practice, University of East Anglia</p>	<p>Professor Glyn Elwyn, Primary Medical Care Research Group, Swansea Clinical School, University of Wales Swansea</p>	<p>Dr Jennifer J Kurinczuk, Consultant Clinical Epidemiologist, National Perinatal Epidemiology Unit, Oxford</p>	<p>Professor Martin J Whittle, Head of Division of Reproductive & Child Health, University of Birmingham</p>
<p>Professor Rudy Bilous, Professor of Clinical Medicine & Consultant Physician, The Academic Centre, South Tees Hospitals NHS Trust</p>	<p>Dr John Fielding, Consultant Radiologist, Radiology Department, Royal Shrewsbury Hospital</p>	<p>Dr Susanne M Ludgate, Medical Director, Medical Devices Agency, London</p>	<p>Dr Dennis Wright, Consultant Biochemist & Clinical Director, Pathology & The Kennedy Galton Centre, Northwick Park & St Mark's Hospitals, Harrow</p>
<p>Dr Paul Cockcroft, Consultant Medical Microbiologist/Laboratory Director, Public Health Laboratory, St Mary's Hospital, Portsmouth</p>	<p>Dr Karen N Foster, Clinical Lecturer, Dept of General Practice & Primary Care, University of Aberdeen</p>	<p>Dr William Rosenberg, Senior Lecturer and Consultant in Medicine, University of Southampton</p>	
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	<p>Dr Karen A Fitzgerald, Pharmaceutical Adviser, Bro Taf Health Authority, Cardiff</p>	<p>Dr Frances Rotblat, CPMP Delegate, Medicines Control Agency, London</p>	

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Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (<http://www.ncchta.org>) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.