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Lay public's understanding of equipoise and randomisation in randomised controlled trials

EJ Robinson, CEP Kerr, AJ Stevens, RJ Lilford, DA Braunholtz, SJ Edwards, SR Beck and MG Rowley

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Lay public's understanding of equipoise and randomisation in randomised controlled trials

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Abstract

Lay public's understanding of equipoise and randomisation in randomised controlled trials

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Objectives: To research the lay public's understanding of equipoise and randomisation in randomised controlled trials (RCTs) and to look at why information on this may not be not taken in or remembered, as well as the effects of providing information designed to overcome barriers.
Design: Investigations were informed by an update of systematic review on patients' understanding of consent information in clinical trials, and by relevant theory and evidence from experimental psychology. Nine investigations were conducted with nine participants.
Setting: Access (return to education), leisure and vocational courses at Further Education Colleges in the Midlands, UK.
Participants: Healthy adults with a wide range of educational backgrounds and ages.
Investigations: Participants read hypothetical scenarios and wrote brief answers to subsequent questions. Sub-samples of participants were interviewed individually to elaborate on their written answers. Participants' background assumptions concerning equipoise and randomisation were examined and ways of helping participants recognise the scientific benefits of randomisation were explored.
Main outcome measures: Judgments on allocation methods; treatment preferences; the acceptability of random allocation; whether or not individual doctors could be completely unsure about the best treatment; whether or not doctors should reveal treatment preferences under conditions of collective equipoise; and how sure experts would be about the best treatment following random allocation vs doctor/patient choice. Assessments of understanding hypothetical trial information.
Results: Recent literature continues to report trial participants' failure to understand or remember information about randomisation and equipoise, despite the provision of clear and readable trial information leaflets. In current best practice, written trial information describes what will happen without offering accessible explanations. As a consequence, patients may create their own incorrect interpretations and consent or refusal may be inadequately informed. In six investigations, most participants identified which methods of allocation were random, but judged the random allocation methods to be unacceptable in a trial context; the mere description of a treatment as new was insufficient to engender a preference for it over a standard treatment; around half of the participants denied that a doctor could be completely unsure about the best treatment. A majority of participants judged it unacceptable for a doctor to suggest letting chance decide when uncertain of the best treatment, and, in the absence of a justification for random allocation, participants did not recognise scientific benefits of random allocation over normal treatment allocation methods. The pattern of results across three intervention studies suggests that merely supplementing written trial information with an explanation is unlikely to be helpful. However, when people manage to focus on the trial's aim of increasing knowledge (as opposed to making treatment decisions about individuals), and process an explanation actively, they may be helped to understand the scientific reasons for random allocation.
Conclusions: This research was not carried out in real healthcare settings. However, participants who could correctly identify random allocation methods, yet judged random allocation unacceptable, doubted the

possibility of individual equipoise and saw no scientific benefits of random allocation over doctor/patient choice, are unlikely to draw upon contrasting views if invited to enter a real clinical trial. This suggests that many potential trial participants may have difficulty understanding and remembering trial information that conforms to current best practice in its descriptions of randomisation and equipoise. Given the extent of the disparity between the assumptions underlying trial design and the assumptions held by the lay public, the solution is unlikely to be simple. Nevertheless, the results suggest that including an accessible explanation of the scientific benefits of randomisation may be beneficial provided potential participants are also enabled to reflect on the trial's aim of advancing knowledge, and to think actively about the information presented. Further areas for consideration include: the identification of effective combinations of written and oral information; helping participants to reflect on the aim of advancing knowledge; and an evidence-based approach to leaflet construction.

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List of abbreviations

ANOVA	analysis of variance
ARTQ	Attitudes to Randomised Trials Questionnaire
CERES	Consumers for Ethics in Research
CI	confidence interval
CM	conventional management
DCCT	Diabetes Control and Complications Trial
DICCT	Deaconess Informed Consent Comprehension Test
ECMO	extracorporeal membrane oxygenation
HRT	hormone replacement therapy
IF	industry form
IRB	Institutional Review Board
LSU	Louisiana State University
MacCAT	MacArthur Competence Assessment Tool for Clinical Research
MANOVA	multivariate analysis of variance
MF	modified form
MREC	Multicentre Research Ethics Committee
NCI	National Cancer Institute
ns	not significant
QuIC	quality of informed consent in cancer trials
RCT	randomised controlled trial
SD	standard deviation
SLT	speech and language therapy
SWOG	Southwestern Oncology Group

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 understand why, despite efforts to make trial information clear, participants in RCTs are at risk of failing to take in or remember information about random allocation and equipoise.
- To investigate the background knowledge about randomisation and equipoise that members of the public are likely to bring to bear if invited to take part in an RCT.
- To explore in the context of hypothetical trials the effects of providing information designed to overcome barriers to understanding and recall of randomisation and equipoise.

Methods

Reviews

The investigations were informed by an update of an earlier systematic review on patients' understanding of consent information in clinical trials, and by relevant theory and evidence from experimental psychology.

Investigations

Nine investigations were conducted, involving healthy adult participants with a wide range of educational backgrounds and ages. Use of hypothetical scenarios allowed precise comparisons to be made between conditions in ways that would be both impractical and unethical in real clinical settings, but which could produce results relevant to real trial consent procedures. Investigations 1–6 (n between 67 and 130) examined participants' background assumptions concerning equipoise and randomisation. Investigations 7–9 (n = 128) explored ways of helping participants to recognise the scientific benefits of randomisation.

Results

Reviews

Recent literature continues to report trial participants' failure to understand or remember information about randomisation and equipoise, despite the provision of clear and readable trial information leaflets. Within the context of research in experimental psychology this is unsurprising. Patients' expectations about normal treatment decisions may make it hard for them to take in information about randomisation and equipoise. Even if patients realise that normal treatment decision-making is not going to take place, they may lack appropriate scientific background knowledge to interpret trial information as intended. In current best practice, written trial information describes what will happen without offering accessible explanations. As a consequence, patients may create their own incorrect interpretations and consent or refusal may be inadequately informed.

Investigations

Investigations 1–6 addressed the following questions.

- *Do members of the public understand and accept randomisation?*
  In investigation 1, participants judged which methods of allocation were random. The majority judged correctly. However, most judged the random allocation methods to be unacceptable in a trial context.

- *Do members of the public assume that new treatments are better?*
  In investigation 2, the mere description of a treatment as new was insufficient to engender a preference for it over a standard treatment.

- *Do they accept doctors' individual equipoise?*
  In investigations 3 and 6 around half of the participants denied that a doctor could be completely unsure about the best treatment.

- *Do they accept doctors' suggestions of random allocation given equipoise?*
  In investigations 3 and 6, a majority of participants judged it unacceptable for a doctor to suggest letting chance decide when uncertain of the best treatment. Randomising for research purposes may be judged less unacceptable.

- *Do they believe that random allocation has scientific benefits?*
  In investigations 4–6, in the absence of a justification for random allocation (none is

currently recommended for real trial information leaflets), participants did not recognise scientific benefits of random allocation over normal treatment allocation methods: they failed to judge that doctors would be more sure about which of two treatments was better when allocation was at random rather than by doctor/patient choice.

Investigations 7–9 examined the consequences of explaining the reasons for randomising. In investigation 7 a pre-existing brief justification for randomisation did not help participants to recognise the scientific benefits of random allocation. With more demanding procedures used in investigations 8 and 9, both this brief justification and an extended explanation led participants to recognise that more certain knowledge would arise with random allocation than with doctor/patient choice. The pattern of results across investigations 7–9 suggests that merely supplementing written trial information with an explanation is unlikely to be helpful. However, when people manage to focus on the trial's aim of increasing knowledge (as opposed to making treatment decisions about individuals), and process an explanation actively by answering test questions, they may be helped to understand the scientific reasons for random allocation.

Conclusions

This research was not carried out in real healthcare settings. However, participants who could correctly identify random allocation methods, yet judged random allocation unacceptable, doubted the possibility of individual equipoise and saw no scientific benefits of random allocation over doctor/patient choice, are unlikely to draw upon contrasting views if invited to enter a real clinical trial. This suggests that many potential trial participants may have difficulty understanding and remembering trial information that conforms to current best practice in its descriptions of randomisation and equipoise.

Given the extent of the disparity between the assumptions underlying trial design and the assumptions held by the lay public, the solution is unlikely to be simple. Nevertheless, the results suggest that including an accessible explanation of the scientific benefits of randomisation may be beneficial provided potential participants are also enabled to reflect on the trial's aim of advancing knowledge, and to think actively about the information presented.

Recommendations for research

The findings of this study raise the following questions:

- How is participants' understanding of written trial information influenced by different forms of oral accompaniment? A leaflet may be understood and remembered more or less well depending on what is said during recruitment. Effective combinations of written and oral information need to be identified.
- How can potential trial participants be helped to take a research perspective and thereby improve their chances of understanding about random allocation and equipoise? Participants tend to construe a trial as aiming to identify the best treatment for each recruit. Informed decision-making may be more likely if participants can reflect on the aim of advancing knowledge.
- Can (and should) research ethics committees expect trialists to have evaluated information leaflets on relevant patient groups? The current emphasis is on leaflets' adherence to national guidelines. An evidence-based approach to leaflet construction may be valuable.

Chapter 1

Objectives

The objectives of this study were as follows.

- To understand why, despite efforts to make trial information clear, participants in RCTs are at risk of failing to take in or remember information about random allocation and equipoise.
- To investigate the background knowledge about randomisation and equipoise that members of the public are likely to bring to bear if invited to take part in an RCT.
- To explore in the context of hypothetical trials the effects of providing information designed to overcome barriers to understanding and recall of randomisation and equipoise.

Chapter 2

Literature reviews

Overall strategy for literature reviews

The broad aim of the reviews was to inform and guide empirical work on the lay public's understanding of equipoise and randomisation in randomised controlled trials (RCTs). Therefore, all papers relevant to understanding of randomisation and equipoise were retained even when they did not directly relate to patient understanding of consent information. All papers were read by one author (CK) and sorted for relevance to patients' understanding, understanding of randomisation, attitudes towards randomisation and equipoise. The aims, methods, sample(s) and main relevant findings of studies are summarised in Appendices 1–4 under the same headings. Articles that hold relevance for more than one appendix are cross-referenced, but repetition of methods has been avoided by summarising in a particular appendix only method details that are relevant to the findings reported in that appendix.

To increase the usefulness of the review for empirical work, comments on the quality of each paper were favoured over a rigid quality checklist (as used in the 1998 review[1]), although the aim in all cases was to comment on response rate and quality of the measures of understanding. Comments on quality made within the papers are included where relevant, and additional comments made by the authors of this review are shown in italics in Appendices 1–4.

This more informal and flexible approach to assessing the quality of studies allows qualitative and quantitative studies to be included side by side in the review tables. Traditionally, qualitative research has been excluded from systematic reviews. This has been either because researchers have applied standard quantitative quality criteria of reliability, validity, objectivity and generalisability, which has resulted in qualitative research being evaluated as inadequate and inferior, or because researchers have contended that there can be no criteria for judging the quality of qualitative research. However, there is increasing recognition of the value of qualitative research in answering questions that are not easily addressed exclusively by experimental methods. In light of this, some researchers have argued that formal synthesis of both qualitative and quantitative forms of research in systematic reviews is essential.[2] To evaluate quantitative and qualitative studies equally in this review a third approach was adopted, as presented by Popay and colleagues.[3] All studies were evaluated on the basis that some quality issues may be equally applicable to the evaluation of any research product, even if applying the same criteria would be inappropriate, for example appropriate sampling methods and reliability checks. At the same time it is recognised that the type of knowledge generated and the way in which it can be used are importantly different.

Appendix 1 and the associated text below summarise studies on patients' understanding published between 1996 and 2001 and not encompassed by the 1998 review. Appendices 2–4 and the associated text sections below focus on topics central to the aims of the current research, understanding about randomisation and equipoise. To give a comprehensive picture of all research on understanding and attitudes towards randomisation and equipoise, all earlier papers held by the authors, including the relevant articles from the 1998 review, are included, in addition to the more recent ones.

After one author (CK) had drafted the four appendices, three other authors (ER, SB and SE) examined the entries in all four for relevance, consistency and coherence. In addition, two of three authors (ER and SB) read 36.9% of the summarised papers in full and checked that the information and the comments on quality were correct.

Update of 1998 literature review on patients' understanding of consent information in clinical trials, 1997–2001

This review updates and extends specific sections of the HTA systematic review on ethical issues in the design and conduct of RCTs.[1] In the 1998

review, studies on patients' understanding were not brought together in a single table, but that review lists relevant studies in the text sections headed 'What is the "best" method for obtaining informed consent?' (pp. 36–41), and 'What is the quality of informed consent in practice?' (pp. 41–4). The former section relates to the 14 studies in Table 7a, Methods of obtaining informed consent for real trials (pp. 92–3), and Table 7b, Methods of obtaining informed consent in hypothetical trial scenarios (pp. 94–6). The latter section relates to the 24 studies in Table 10, Audit of the quality of communication (pp. 97–102).

Literature search strategy and retrieval

A search of the literature relating to patient understanding of consent information in clinical trials was carried out. The aim was to identify descriptive and comparative empirical studies published since the previous systematic review. The main method used was an electronic literature survey. This was conducted on six databases, MEDLINE, Bath Information Data Services (BIDS), PsycINFO and IBSS online, EBSCO academic, business and trial databases, Web of Science, ECO World CAT and the Combined Health Information Database (CHID). Although the previous review was published in 1998, few papers reviewed were published in 1997 or later, and so the searches were set for the years 1996–2001 to ensure a small overlap. On all databases searches in titles and abstracts were carried out using combinations of the terms: informed consent, trials, randomised, understanding, comprehension, randomisation, equipoise, perceptions, attitudes, views, willingness, participation, medical and clinical research. The search strategies were deliberately broad in order to retrieve a large variety of papers and to be as exhaustive as possible.

Inevitably, such a broad search revealed many false positives, so all search results were scanned by title to extract the broadly relevant articles and then by abstract to extract the directly relevant articles. MEDLINE and PsychINFO yielded the largest number of broadly and directly relevant articles. The other databases yielded only a few more and many that had already been identified in other searches. The electronic survey identified 30 empirical articles relevant to patient understanding of consent information in clinical trials and a further 11 relevant to patient attitudes towards randomisation and new treatments, or general understanding of randomisation without consent information.

The electronic survey identified two papers,[4,5] that reviewed some recent relevant empirical studies, yielding eight more articles not already identified by the searches. Five articles cited in recent papers (one passed to the authors by colleagues before publication), as well as six included in an annotated bibliography,[6] further augmented the collection. Although the electronic survey identified three abstracts and three letters whose authors indicated that they had relevant findings to report, MEDLINE and PsychINFO searches of the authors' names did not reveal any relevant papers reporting the data in full.

As a final strategy the contents pages of the journals that had published several of the relevant articles recently and in the previous review were handsearched. *Social Science and Medicine*, *Journal of Medical Ethics*, *British Medical Journal*, *Hastings Center Reports*, *Controlled Clinical Trials* and *Patient Education and Counselling* were all searched in this way. Only two articles were identified that had not been found by the other strategies.

The total number of new articles found that were relevant to patient understanding of consent information in clinical trials was 45, with a further 18 that were relevant to patient attitudes towards randomisation and new treatments, or general understanding of randomisation without consent information.

Review results: patients' understanding of consent information in the context of clinical trials (papers published 1996–2001)

The 45 recent studies relating to patient understanding were published in 36 different journals. Thirty-two papers were purely quantitative, two used both quantitative and qualitative methods, one described itself as qualitative but all interview data had been transformed into quantitative findings, and nine were purely qualitative. Lists of the studies, along with their methods, main results and comments, are summarised in Appendix 1.

Level of patient understanding of consent information

Twenty-four of the studies related to patients' understanding of trials that they had been invited to join. These included treatments for psychiatric problems,[7,8] various forms of cancer,[9–13] prostatic disease,[14] herpes,[15] prevention of cancer,[16,17] contraception,[18,19] anti-infective agents,[20] anaesthesia,[21] attention deficit hyperactivity disorder[22] and myocardial infarction.[23–25] Several

studies sampled a number of types of trials.[26–30] Eight of the studies related to surrogates' understanding of trials to which they had been asked to consent on behalf of someone else. In seven cases the surrogates were parents giving consent for their children to participate in trials of speech and language therapy,[31] diabetes or cancer,[32,33] an influenza vaccine,[34] prevention of recurrence of febrile seizures[35] and various neonatal trials.[36,37] In the eighth case identified surrogates were asked for their consent on behalf of patients with advanced dementia to a trial of palliative approaches.[38]

Overall understanding of consent information

Five studies gave an indication of overall understanding of consent information. Appelbaum and colleagues[7] found a seemingly good overall level of understanding among patients with depression, with a mean score of 23.33 out of a maximum of 26, and nobody scoring below 20. However, this is not easy to interpret as the authors did not define criteria for an acceptable score on this or the other three dimensions of informed consent. Mason and Allmark[37] judged that only 29.5% of parents that they studied had given valid consent or refusal, and this was partly because 20% of parents were judged to have problems with understanding. Similarly, Baskin and colleagues[38] found that for 19% of patients with advanced dementia, informed consent could not be obtained because their surrogate could not understand the research protocol. Van Stuijvenberg and colleagues[35] found a better level of understanding among parents, with 73% of them aware of the major study characteristics, although this is at odds with the finding by Schaeffer and colleagues[28] that overall research participants retained less than 35% of information disclosed to them.

Understanding of specific areas of consent information

Fourteen studies gave measures of understanding, recall, knowledge or awareness of specific areas of information.

Right to withdraw

Cox and Avis[9] found that although accounts of the initial consultation were poor, one of three aspects consistently recalled by participants in early trials of anticancer drugs was their right to withdraw from the trial. Fleissig and colleagues[10] reported that over 95% of their sample knew they could leave the trial or study at any time and still be treated. Likewise, Joffe and colleagues[12] showed a similarly good recollection of the right to withdraw: 89.7% of their sample of participants drawn from several trials knew they could withdraw; and Sugarman and colleagues[29] found that 78% of an outpatient sample who reported participating in research believed that the policy for dropping out of the project was that they could withdraw at any time for any reason. Fortney[18] found a slightly lower percentage of awareness in her sample of women participating in a clinical trial assessing the effectiveness of a contraceptive in four sites, one in the USA, two in Latin America and one in Africa. Overall, 67% "thought it would be fine with them [the clinic staff]" if they withdrew from the study; however, in the African site, this proportion was only 27%.

Voluntary nature of participation

Schaeffer and colleagues[28] found a very high awareness of the voluntary nature of participation in trials; 97% of healthy research volunteers and patients participating in Phase I, II and III were aware of this aspect of consent. In a similarly heterogeneous sample of trial participants, Joffe and colleagues[12] found that 99% knew they could decline participation. Likewise, Mongomery and Sneyd[21] found that 97% of anaesthesia trial participants realised that participation was voluntary, Fogas and colleagues[22] found that over 89% of children believed that they could have said no when first asked to participate, and 73% at the time of the procedure, and Searight and Miller[15] reported that all of those interviewed in their study viewed their participation as voluntary. However, Cox and Avis[9] reported that in early trials of anticancer drugs where no standard treatment was available, patients felt in reality that they had no choice because not participating was equated with death. Kass and colleagues[27] found a similar feeling reported by outpatients who had tried other interventions without success. They felt that there were no alternatives left and characterised the decision to participate as a matter of little choice. The participants in RCTs of acute myocardial infarction interviewed by Agard and colleagues[23] also reported that in the circumstances in which they were asked, they felt they had little choice but to participate. Van Stuijvenberg and colleagues[35] found that 25% of parents who had volunteered their children in a trial felt obliged to participate, and while Hayman and colleagues[36] found that 100% of their sample of parents who had consented for their child to participate in a trial felt free to refuse participation, 10% thought that taking part was part of their infants' treatment.

Side-effects and risks

Leach and colleagues[34] found that 53% of parents who gave consent for their children to participate

in a vaccine trial were aware of possible side-effects. Fortney[18] found that although 83% of the women who were asked remembered about possible side-effects of the trial method of contraception, when they were asked whether 'anything bad' might happen as a result of participation, side-effects were not mentioned. The only fear anyone mentioned was the risk of becoming pregnant. They found that participants poorly recalled the estimated risk of pregnancy, with 19% estimating too high and 41% too low. Only 27% correctly perceived the level of risk of pregnancy of the trial contraceptive method as high. Kass and colleagues[27] report that outpatients in their sample were so trusting of their hospital, physician and the research that they believed that no harm could be done.

Research purpose
Fortney[18] found that 55% of women in a contraceptive trial correctly understood the research purpose, whereas Sanchez and colleagues[19] reported that the objectives of a contraception trial were one of the least understood aspects by women at their clinic. In contrast, Hayman and colleagues[36] found that 100% of parents who had consented for their babies to participate in a research study felt that they understood the research purpose and 98% the research process, and 96% summarised the research study accurately. Outpatients in the Kass and colleagues[27] sample were able to articulate broad goals of the research, but viewed their own participation as simply another treatment option. Searight and Miller[15] were concerned to find that trial participants made little distinction between research and treatment, none of those interviewed believing that they were in any way limited by receiving their care as part of a research protocol. In Pletsch and Stevens'[32] study interviewing mothers of children with cancer or diabetes, the authors expressed a similar concern over participants' confusion between research and treatment. However, in a study reporting only the mothers whose children had diabetes,[33] the authors found that they were able to describe accurately the purpose and nature of trial participation, were certain about which aspects of their children's care were part of the study and which were not, and could state clearly the differences between a clinical trial and standard medical care.

Availability of alternative methods of treatment
Fortney[18] found that 79% of women in a contraceptive trial recalled being offered alternative methods of contraception. Joffe and colleagues[12] found that 88.3% of participants in a variety of trials recalled being offered alternatives to trial participation.

Awareness of placebo
Leach and colleagues[34] found that, in general, awareness of the placebo-controlled design was very low, with only 10% of parents who consented being aware of the placebo. In marked contrast, Searight and Miller[15] found that all of the participants whom they interviewed could provide a reasonable description of a placebo and about one-third verbalised a more sophisticated rationale for using placebos in drug-trial studies.

Random allocation of treatment
Only 23% of the patients asked by Heitenan and colleagues[13] perceived that their treatment had been chosen randomly. Other studies found much higher levels of awareness. Joffe and colleagues[12] found that 90.6% of participants in Phase III trials were aware of being randomly allocated to treatment. Likewise, Featherstone and Donovan[14] found that almost all participants interviewed were aware of some aspects of randomisation, and the majority acknowledged the involvement of chance in the allocation of treatment. However, despite this awareness, participants found the concept hard to understand, apparently because of their expectation that clinicians would assign them to treatment based on their specific symptoms, clinical findings and age. Glogowska and colleagues[31] found a similar view expressed by parents who had given consent for their child to participate in a randomised trial of speech and language therapy. In contrast, Searight and Miller[15] found that their sample consistently demonstrated an understanding that assignment of the placebo or active drug was randomly determined, with some referring to concrete analogies such as rolling a dice.

Awareness of trial participation
Four studies showed that not all participants in research were aware that they had been enrolled in a clinical trial. Sugarman and colleagues[29] showed that for 6% (69 patients) of those in their outpatient sample who reported that they were not or never had been participants in medical research, there was clear evidence from records that they had been or were participating in research. Likewise, for 6% (36 patients) of those who reported that they were or had been participants in research, there was strong evidence that they were not. Agard and colleagues[23] also found that 6% (two patients) of their sample did not know they had been included in an RCT of

acute myocardial infarction, while Hayman and colleagues[36] reported that 98.4% of their sample knew they were participating in a research study. Ferguson[26] found that while many women in a trial of pain relief in labour may have been aware that they had been asked to participate in some research, they were unaware that this involved a clinical trial of a new drug. This explained the 12% of the sample who could not comment on their motivation to participate in the trial.

Patients' perceptions of their own understanding

Six studies asked participants to assess their understanding of information. Ferguson[26] found that 100% of participants in various pharmaceutical trials and 91% of women who participated in a labour trial felt that they had understood all or most of the information. All nine of the mothers of children with diabetes in Pletsch and Stevens' Study[33] reported they had understood the clinical research. Montgomery and Sneyd[21] found that 90% of participants in six anaesthesia trials felt that they had understood everything. In contrast, Yuval and colleagues[25] found that 31% of patients reported having full comprehension of the randomised trial in acute myocardial infarction in which they had participated, 50% reported partial understanding and 19% little or no understanding. Agard and colleagues[23] found that according to some participants in trials of acute myocardial infarction, their knowledge about the trial was almost non-existent. When evaluating the information they had been given, van Stuijvenberg and colleagues[35] found that 97% of parents evaluated the verbal information they had received as easy to understand, and 95% evaluated the written information and consent form as easy to understand. Heitenan and colleagues[13] found that 91% of their sample of breast cancer patients regarded the consent information provided as easy or quite easy to understand, and 76% of those who read the written information evaluated it as easy or quite easy to understand. Gotay[16] found that 46% of a sample of healthy trial participants could not remember whether the consent form was understandable, but of the 37 who could remember, 29 rated it as easy or very easy to understand. Similarly, while 52% did not remember the amount of information in the consent form, 30 out of the 32 who did remember reported that the information was 'just right'. Williams and colleagues[24] found the overall reported comprehension of verbal consent information in a sample of consenters and refusers to be 70%, compared with 43% for the written consent information. A further three studies reported that over 90% of their samples felt that they were adequately informed or had been told what they needed to know about the trial.[8,10,15] However, in the development of their measure of understanding of informed consent information, Joffe and colleagues[11] reported that their pilot sample scored higher on subjective (or perceived) understanding than objective (or measured) understanding, although when used with a sample of participants from various trials[12] they found that the knowledge and self-assessment scores were significantly associated. This higher level of perceived to actual understanding was noted too by Miller and colleagues[20] in their study assessing the reliability of their measure to assess comprehension of informed consent information.

Correlates of understanding

A large proportion of the new studies identified and examined correlates of (and possible influences on) understanding. Thirteen studies revealed characteristics of participants that may be relevant to their understanding, ten reported aspects of the informed consent procedure that may be relevant and 25 reported findings relevant to the effect on understanding of differences in the information given at consent.

Participant characteristics

Level of education

Six studies reported differences in levels of understanding related to the level of education of participants. Verheggen and colleagues[30] found that the higher a patient's level of education, the better a patient appeared to understand written information. Heitenan and colleagues[13] found that better educated participants had a better understanding that they had been randomised, more frequently reported having received and read written information, and found it more understandable than less well-educated patients. Schaeffer and colleagues[28] found that higher educational level was associated with more information being retained by symptom-free Phase III participants and healthy volunteers, but not by sicker participants (patients with cancer participating in Phase I and II studies). Miller and colleagues[20] found a positive correlation between comprehension of consent information and educational level. Joffe and colleagues[12] found that having a college education was associated with higher knowledge scores. Using hypothetical trial information with non-clinical samples, Bjorn and colleagues[39] found that understanding increased with level of education among an older sample considering a hypertension trial leaflet, but not among a younger, predominantly female, sample considering a sterilisation trial leaflet.

Cognitive ability
Carpenter and colleagues[40] found that cognitive measures were highly predictive of performance on the understanding, reasoning and appreciation scales of a measure of informed consent capacity [the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR)] in both psychiatric and normal samples. Sanchez and colleagues[19] reported that women processed informed consent information according to their cognitive abilities (among other factors). Using hypothetical trial leaflets, Davis and colleagues[41] found that regardless of the complexity of the form used, participants' comprehension scores were related to their reading ability. Adults reading at or above ninth grade level (equates to a minimum ability of reading fairly difficult pieces of text such as *Reader's Digest* articles) had significantly higher comprehension of both forms than those reading at or below eighth grade level (equates to a maximum ability of reading standard pieces of text such as *Newsweek* articles).

Severity of diagnosis
In addition to differences in the effect of level of education on information retention reported above, Schaeffer and colleagues[28] found that healthy volunteers retained the most risk information and Phase I participants the least; and Phase I and II participants retained the most information about procedures 4–6 weeks after consent, and healthy volunteers the least. It should be noted, however, that the quantity and content of information given to participants differed between the groups.

Consenters versus refusers
Five studies looked at differences in understanding of information between those who consented to participate in a clinical trial and those who refused to participate. Leach and colleagues[34] found that overall refusers knew less of the subject matter than acceptors, and specifically that much larger proportions of acceptors compared with refusers were aware of the purpose of the trial vaccine, possible side-effects of the vaccine and placebo control group. Lovegrove and colleagues[17] found that women who had refused to participate in a trial of a drug to prevent breast cancer assessed the information they had been given about the drug as harder to understand than did those who had consented. Fleissig and colleagues[10] found that a larger proportion of those who accepted trial entry felt that they were given enough information compared with those who declined. However, Verheggen and colleagues[30] found no differences in the level of understanding of written information disclosure between patients who consented to participate in trials and those who refused. Williams and colleagues[24] found a different pattern: 35% of consenters compared with 100% of decliners reported comprehending the written consent information, and 69% of consenters compared with 83% of decliners reported understanding the verbal consent information; however, the sample of decliners comprised only six people.

Using information from other sources
Sanchez and colleagues[19] found that women processed information about contraception trials according to information previously obtained from different sources, and that sometimes mistaken beliefs were not modified by new information received, especially when they came from a significant source such as a mother or friends. Joffe and colleagues[12] found that use of supplemental pamphlets, information found on the Internet, books or magazines was associated with higher knowledge scores.

Consent procedures

Timing of consent
Ferguson[26] attributed the differences between participants in a labour trial and a comparative group of participants in various pharmaceutical trials to the timing of when information was given and consent asked for. Although 65% of the participants in the labour trial felt that they had been given the right amount of information, this was because the information was given after they had gone into labour and were in pain. They could not see the point in having any more detailed information in that situation. Only 58% of the labour sample felt that they had plenty of time to ask questions, compared with 96% of the comparison group. Agard and colleagues[23] found that most participants in acute myocardial infarction trials felt that at the time when they were asked to consent they had too low levels of consciousness or too much pain to understand the information given.

Time to discuss/consider
Yuval and colleagues[25] found that participants' reported comprehension was related to patients' recollection that there was an opportunity to ask questions and their estimations of the duration of the explanation. Schaeffer and colleagues[28] found that the more time researchers took explaining the protocol and consent document, the greater the immediate and long-term retention of information

about the purpose of the study and long-term retention of risk information. Leach and colleagues[34] found that awareness of the placebo group was higher among participants who had received the information sheet at least a week before consent was requested, compared with those who had not received a sheet in advance (15% compared with 4%). Joffe and colleagues[12] found that higher knowledge scores were associated with not signing the consent form at the initial trial discussion. Heitenan and colleagues[13] found with their sample that in addition to being less likely to understand, older and less well-educated patients were more likely to feel that they needed more time to decide.

Educational programmes to improve capacity to give informed consent

Three studies focused on the capacity of patients with mental health problems to understand consent information and therefore give valid consent. Carpenter and colleagues[40] showed that although initially 20 out of the 30 patients with schizophrenia scored below the median understanding score of the comparison 'normal' control group, after an educational process of reviewing the trial protocol they showed considerable improvements in understanding. After the educational process 70% of the previously poorly performing patients with schizophrenia scored higher than the median understanding score of the comparison 'normal' control group. Wirshing and colleagues[8] similarly improved the scores of patients with schizophrenia on an informed consent survey from the time that consent forms were read and explained to patients. They did this by looking at which questions patients answered wrongly on the first informed consent survey, repeating the relevant information to patients and then retesting them. This process was repeated until patients scored 100%. Stiles and colleagues[42] also used this method of presentation and discussion of consent information followed by testing, feedback and retesting, and compared it with a 'facilitated' method of information giving. In this, a second researcher sitting in on the presentation of information used strategies to maximise patients' understanding while the information was being presented. Patients with depression and those in the control group did better with the facilitator than with the feedback, whereas the reverse was true for patients with schizophrenia. In samples of participants from various cancer trials Joffe and colleagues[12] found that having a nurse present at the consent discussions was associated with higher knowledge scores.

Information given at consent

Written consent information

- **Format of written consent information**: five studies compared the effects on understanding of varying the format of written consent information. Bjorn and colleagues[39] compared two information leaflets that had been used in trials with versions of the same leaflets that they had simplified by shortening sentences and replacing professional language with lay terms. Using two samples from the general public, they found that people perceived the simplified forms as easier to understand and that perceived comprehensibility was related to their level of understanding of the information. However, understanding of key consent issues such as the voluntary nature of participation and the right to withdraw, or that chance decided which treatment they received, was not related to which version of the leaflet they received. Nearly everyone, regardless of the leaflet, understood the former, while the random allocation was poorly understood by those in one trial (regardless of whether they received the simplified leaflet for that trial), but well understood by those in the other trial. Davis and colleagues[41] carried out a similar study comparing an original trial leaflet assessed as being of 16th grade readability (level of reading required to read very difficult text such as an article in the *New England Journal of Medicine*) with a version of the same which they simplified to seventh grade readability (level of reading required to read a standard text such as an article in *Newsweek*). They tried these out with a clinical sample and a sample from the general public. Those with lower reading ability preferred the simplified form, but comprehension of the information was unimproved with the simpler form. In another very similar study, Dresden and colleagues[43] modified an industry consent form by focusing only on providing the minimum required information, increasing readability and taking into account comments made by physicians, nurses and patients. The modified form resulted in significantly higher scores on purpose, randomisation, length, risks/side-effects, benefits, alternative treatments, confidentiality and voluntary participation. However, scores on some of the questions were still as low as 54% even with the modified form. Kruse and colleagues[44] designed three versions of the same written information and found that the version designed to be the simplest and the most appealing did not significantly increase knowledge scores. The version that both

increased knowledge scores significantly and resulted in the largest increase in people obtaining an acceptable knowledge score (>50% correct) paid increased attention to logical composition and presentation of condensed information. Although they found that a more detailed version increased positive attitude towards the trial, knowledge and attitude scores were not significantly associated. Joffe and colleagues[12] found that although knowledge scores were higher for trials using a consent information template mandated for use by the review board, knowledge scores were not significantly correlated with consent form readability.

- **Terms used**: Waggoner and Sherman[45] found that many medical terms used in patient information and consent documents were very poorly understood by members of the lay public. Similarly, Featherstone and Donovan[14] found lay interpretations of the terms 'trial' and 'at random' that differed from clinicians'. Sugarman and colleagues[29] found that outpatients in their sample held different beliefs about levels of risk and the use of unproven treatments depending on whether 'medical research', 'medical studies', 'medical experiments', 'clinical investigations' or 'clinical trials' were used to describe a trial.
- **Use of written information**: Ferguson[26] found that 54% of participants in a labour trial compared with 99% of participants in various pharmaceutical trials could recall receiving written information. Gotay[16] found that 68% of healthy participants in a cancer prevention study could recall reading a consent form and a similar proportion could recall someone explaining the consent form, but the rest denied receiving a consent form or could not remember. Heitenan and colleagues[13] found that 76% of their sample of patients in a breast cancer trial reported receiving written information, 6% did not read it and 55% felt that it had contributed to their decision-making. Jenkins and Fallowfield[46] found that in observed consultations discussing consent to take part in randomised trials, information leaflets were only given in 67.1% of cases. Mason and Allmark[37] found that 90.7% of clinicians reported using an information sheet in consent, which corresponded with only 9% of parents stating that they had not received an information sheet. Verheggen and colleagues[30] found that 58% (198) of patients in their sample drawn from 26 clinical trials indicated that they had received written information from the trial clinician. Of these, 82% (163 patients) reported having read the written information thoroughly, 11.7% (23 patients) had read it only globally and 6.3% (12 patients) said that they had not read it at all. Many participants in Kass and colleagues'[27] sample assumed that they need not pay attention to what was written in a consent form because they had already decided to participate based on their physician's recommendation and their general trust that no harm would come to them. Searight and Miller[15] found that it was extremely rare for participants to describe the informed consent form as having educational benefit, seeing it primarily as a legal document designed to prevent litigation.

Video or computer presentation

Weston and colleagues[47] gave a clinical sample written information about a trial for which they were ineligible and then, in addition, showed an information video to half of their sample. In the short term there was no difference in the number of women in the two groups that showed adequate knowledge, but the video group appeared to retain the information better a few weeks later, and those in the video group were more willing to participate in the trial. Fureman and colleagues[48] also evaluated supplementing written information with an information video about HIV vaccine trials. They presented the information to injecting drug users and found that the video did not increase knowledge compared with just written information. However, those who had seen the supplementary video retained more information when tested 1–2 months later. In this study the video did not affect attitudes to the trial. Rather, in this sample, willingness to enter the trial was associated with trust in government. Dunn and colleagues[49] compared a computerised presentation (enhanced) of consent information with written (routine) consent information in a sample of participants enrolled at a research centre for psychosis in older people. They found that a higher number of people who had the enhanced procedure scored 100% on the first presentation of a comprehension test compared with the routine group, and again after receiving feedback on wrong answers and taking the test for a second time. However, normal comparison subjects did not differ across the conditions.

Framing of information

Wragg and colleagues[50] gave participants both written and video presentation of information. The content of the information was either framed in a way that emphasised the current state of uncertainty about costs and benefits of treatment

(similar to information commonly given to participants at consent), or contained numerical details of known facts about the treatment (similar to information commonly given to clinicians to justify a trial). Participants' knowledge about the treatment was unaffected by framing of information, but those who had received the information containing facts and figures were more likely to express a strong preference for or against the treatment, and more likely to refuse entry to the hypothetical trial.

Information from clinicians and researchers

- **Content of information from clinicians**: four studies gave information from the clinicians' perspectives on what type of information they discussed with patients. Mason and Allmark[37] judged only 2.8% of clinicians whom they interviewed as having no problem with obtaining consent satisfactorily. Jenkins and colleagues[51] found that in a high proportion of observed consultations doctors described the treatments, side-effects, uncertainty about treatment decisions and collective (rather than personal) uncertainty, and described randomisation implicitly. Less often they mentioned randomisation explicitly with reasons for randomising, checked patients' understanding of randomisation or mentioned the patients' right to withdraw at any time. Leach and colleagues[34] explained the low awareness of the placebo-controlled design among parents whose children were participating in a vaccine trial in terms of trial workers' avoidance of issues that were complicated or controversial. Verheggen and colleagues[30] found that while 84.4% of clinicians thought that their explanation about the clinical trial was comprehensible for patients, they emphasised aspects of the trial that they expected a patient to understand easily, and did not emphasise issues that they expected patients to have more difficulty understanding. They expected patients to find it difficult to understand the type of study and study objective, treatment alternatives, collection of data, privacy and confidentiality of data, and study design of the trial, including randomisation and selection procedure.
- **Clinicians' awareness of patient information preferences or understanding**: Fleissig and colleagues[10] introduced an intervention in which doctors had access to the information preferences and attitudes towards trials of their patients for half of the consultations, and in the other half the doctors carried out their consent procedures as usual. There was no association between doctors' ratings of the consultations or patients' satisfaction with the consultation, and doctors' access to patient information preferences and attitudes. Although differences were not tested for significance, doctors' access to patient information preferences and attitudes did not appear to result in differences in patients' understanding of the information discussed in the consultation. Joffe and colleagues[12] found that while providers' ratings of participants' understanding were significantly correlated with participants' knowledge scores, they did not predict the knowledge scores of individual participants whose consent they had obtained.
- **Content of information from researchers**: Titus and Keane[52] gathered information from unwitting researchers applying for Institutional Review Board (IRB) approval, about how they intended to explain their trial and gain consent from participants, although no information was gathered about what actually happened. Researchers intended to focus their verbal information on the study purpose and procedures, but often failed to give this information in a meaningful way. Meaningful discussion on areas such as risks, benefits, alternatives, costs, confidentiality, non-participation or withdrawal was rarely planned. In the main, researchers did not plan to give time for the participants to ask questions or think about participating.
- **Importance of oral information**: Mason and Allmark[37] found that 47% of parents in neonatal trials relied mainly on information provided verbally by the clinician for their decision. Hayman and colleagues[36] found that 82.5% of parents in their sample felt that the researcher's verbal explanation was the most useful source of information, whereas 10.5% felt that the written information sheet was the most useful. Yuval and colleagues[25] found that 71% of participants recalled the oral explanation of the trial, 32% recalled having both an oral explanation and a written explanation, and 5% recalled only the written description of the project.

Overview of review: patients' understanding of consent information in the context of clinical trials (papers published 1996–2001)

See Appendix 1.

Methods of measuring understanding

Studies used various methods to assess participants' understanding, knowledge, awareness and recall of consent information. Twenty-six used questionnaires, including two which involved structured interviewer-led questionnaires, and 13 used interviews that varied in terms of how structured they were. Baskin and colleagues[38] gave no indication as to how they assessed surrogates' understanding of research protocol.

Questionnaires

Of the studies that used questionnaires, ten used multiple-choice or forced-choice measures.[13,21,29,39,41–44,48,50] Dunn and colleagues[49] used a mixture of forced-choice and short-answer questions. Miller and colleagues[20] used a set of open-ended questions. Stiles and colleagues[42] compared open-ended questions, which measured free recall, to a multiple-choice questionnaire measuring recognition; they found that overall, the mean recall scores were lower than the recognition scores. Of the other studies that used questionnaires, Joffe and colleagues[12] used the QuIC (Quality of Informed Consent in cancer trials), a brief questionnaire developed by the same authors[11] using response formats of disagree/unsure/agree on knowledge questions and Likert scales for subjective understanding items. Likewise, Lovegrove and colleagues[17] used a visual analogue scale on which participants (acceptors and refusers) indicated their perceived ease of understanding of information. Schaeffer and colleagues[28] used a questionnaire to test retention of information in seven areas and then calculated an overall retention score by dividing the total number of items recalled by the total number possible. Wirshing and colleagues[8] used an informed consent survey, which was a list of questions with specific correct answers that participants had to volunteer. In the interviewer-led questionnaires, Verheggen and colleagues[30] used a questionnaire where patients indicated their answers on Likert scales, and Fogas and colleagues[22] used items with predetermined response options, Likert scales and open-ended answers. Gotay,[16] Hayman and colleagues,[36] van Stuijvenberg and colleagues[35] and Yuval and colleagues[25] all used postal surveys containing structured and open-ended questions. Three studies that used questionnaires to test knowledge or understanding did not report the type of questionnaire used.[24,45,47]

Reporting reliability and validity of questionnaires was rare, with only six studies including figures.[11,12,20,22,28,30,44] When reliability measures are reported, they are often quite low (e.g. Cronbach's alpha <0.7). Similarly, only four studies reported any development through piloting,[11,29,41,44] although unreported piloting could have taken place in other studies.

Interviews

Of the 13 studies that used interviews (other than to present a questionnaire), eight used largely unstructured interviews and qualitative analysis of data,[9,14,15,19,27,31–33] three used a more structured approach to elicit both quantitative and qualitative data[23,26,34] and two used structured interviews to elicit quantitative data.[18,37]

The majority of the interview studies failed to specify in any detail how the data were analysed and four failed to mention the method of analysis at all.[9,18,26,27] Only six of the interview studies reported the use of reliability checks of data collection or analysis.[7,15,33,34,37,40]

Development of specific measures of informed consent comprehension/capacity

Two studies reported the development of questionnaires aimed at measuring reliably the quality of informed consent, and the comprehension of informed consent information. Joffe and colleagues[11] aimed to develop a brief questionnaire to evaluate the quality of informed consent in cancer trials (QuIC) and they report in detail the development of the measure through piloting and reliability testing. However, the scores were not interpreted and no criteria were set by which acceptable informed consent could be judged. The QuIC was used with a sample of cancer patients participating in a variety of clinical trials.[12] Miller and colleagues[20] tested out the reliability and validity of their measure of comprehension of informed consent information [the Deaconess Informed Consent Comprehension Test (DICCT)] in their study, and obtained basic descriptive statistical data in a large sample of clinical trials participants. However, the authors were cautious about generalising their reliability and validity data to other samples owing to the relatively young and well-educated nature of the tested sample. Two other studies[7,40] used the MacCAT-CR. This instrument assesses the capacity of individuals to consent to research using a semistructured interview format. It assesses understanding of disclosed information about the nature of the research project and its procedures, appreciation of the effects of research participation on subjects' own situations, reasoning about participation and ability to communicate choice.

Time of assessment

The studies also differed in the time after consent that understanding, knowledge, awareness or recall was assessed. Nine studies carried out their assessments immediately after information or consent had been given.[20,39,41–43,45,49,50] A further six tested immediately or within 24 hours and again a certain number of weeks later.[7,8,28,40,47,48] Two studies carried out their assessments within days of consent,[9,34] although the latter found it harder to arrange interviews with refusers than with acceptors. Joffe and colleagues[12] evaluated the quality of informed consent 3–14 days after consent, whereas Kruse and colleagues[44] assessed knowledge 2 weeks after information was given, and Verheggen and colleagues[30] within 4 weeks of consent. Several studies asked participants about consent information a substantial time after the event: Yuval and colleagues[25] posted their questionnaire 1–3 months after the acute event, Ferguson[26] interviewed women in the labour sample 7–12 months later, Fogas and colleagues[22] carried out their telephone interviews at least 8 months after the trial procedure, Fortney[18] interviewed women up to 289 days after consent (although the study was not originally designed that way), Glowgowska and colleagues[31] interviewed parents 12 months into their trial participation, Heitenan and colleagues[13] posted questionnaires to participants 5–17 months after consent, Hayman and colleagues[36] posted their questionnaire to participants 2 weeks to 19 months after their trial involvement ended, Gotay[16] posted questionnaires to participants who were 2 years into a 7-year trial, and Montgomery and Sneyd[21] posted their questionnaire to patients 6 months to 2 years after their trial participation. Fourteen studies did not report when assessment of understanding, recall, awareness or knowledge was carried out in relation to receiving information or giving consent.[12,14,15,17,23,24,26,27,29,32,33,35,37,38]

Comparison with findings from Edwards and colleagues' (1998) review

The findings of this review of recent papers are compared with the findings of the previous review[1] in three areas: the level of patient understanding of consent information in practice, influences on patient understanding of consent information, and methodological issues.

Level of patient understanding in practice

Edwards and colleagues[1] concluded that certain areas of consent such as medical details, particularly concrete information about side-effects, were better understood than others. Other factual information such as the right to withdraw and available treatment alternatives was also familiar to respondents. More 'conceptual' or 'abstract' information, such as the concept of randomisation, was less accessible to patients. The findings of the present review tend to support this conclusion, bar one qualitative study which found uncharacteristically high levels of understanding of randomisation and other scientific concepts.[15] Unfortunately, the authors did not comment on this aspect of their findings or offer any explanations of why this might be. However, no one study has measured all areas of understanding within the same group of trial participants. Hence, any conclusion about the relative difficulty of understanding different areas arises from comparisons between studies and between different groups of patients who will have received different information about different trials. The current review also reveals that there can be problems with understanding even in the areas that seem generally to be better understood by patients. Although awareness of side-effects is generally high, Fortney[18] found that this did not reflect an accurate understanding of risk of the side-effects or possible negative consequences of trial participation. Furthermore, although a number of studies showed a high level of awareness of the voluntary nature of participation, it cannot be assumed that patients feel no pressure to participate.

Correlates of patient understanding of consent information

Studying the correlates of and possible influences on patient understanding of consent information appears to have become a much more active area of research in recent years. In the 1998 review, the major influence on understanding studied was the effect of quantity of information. The findings suggested that giving participants more information resulted in greater understanding of the concept of a clinical trial and the research nature of treatments, but at a possible cost of a lower consent rate. The studies did not test effects on other aspects of consent, and improvements in understanding may reflect increased quality (e.g. supplementary telephone interview with a research nurse[53]) rather than quantity of consent information. There appeared to be an optimal level of information about side-effects where patients were not overburdened by detail, but were informed of the more important risks. However, findings about the effect of more information about randomisation on understanding were contradictory. The authors of the 1998 review commented that the effect of different formulations of the same information had not been investigated fully in comparative studies.

The more recent studies included in the current review focus on the quality of consent information rather than the quantity, possibly reflecting recommendations made around the time of the last review. Kent[54] reviewed aspects of the social and cognitive psychological literature that were relevant to this and called for improved readability. In his paper he claims that readability of consent forms had not improved despite research (see LoVerde and colleagues[55]) and recommended using specific features, such as a minimum point size of 10, avoiding italics, using unjustified text and improving comprehensibility by using concrete words and active verbs and structuring information. Similarly, the need to improve the information given to patients in general and the application of research in this area was highlighted in a review by Arthur.[56] Dixon-Woods[57] questioned the use of readability testing to achieve this. Readability scores are based primarily on the length of sentences and the use of words with more than two syllables. The score gives an indication of the level of education or reading age that a piece of writing requires a reader to possess to be able to comprehend it. Dixon-Woods[57] noted that readability testing has been heavily criticised by disciplines outside medicine and its value undermined by some empirical studies (e.g. Hawkey and Hawkey[58]).

In general, the current review shows that changes made to the readability of written information, the framing of information or the mode of presentation have not been sufficient to improve knowledge of the information provided. Some efforts seemed to have a level of success (e.g. Dresden and Levitt,[43] Fureman[48] and Kruse[44]) and participants often preferred the simplified written material, although the changes made to the consent information seemed more effective in influencing participants' attitudes towards participation in trials. One study clearly found that readability of consent forms was not correlated with knowledge scores, whereas the use of a recommended template for information was.[12] Detailed written information[44] and a supplementary video[47] both increased positive attitudes towards the trial. This appears to be at odds with the effect of quantity of information on consent rate reported in the 1998 review. However, another study in the current review found that participants who had received information containing numerical details of known facts about a treatment, rather than information focusing on the current state of uncertainty about the costs and benefits of the treatment, were less willing to participate in a hypothetical, randomised trial of the treatment.[50]

Additional difficulties have arisen from the use of certain words, which were perhaps not viewed as jargon by the researchers but have been reported as having different lay meanings to the subjects;[14,29,45] for example, a patient questioning whether a routine treatment could be involved in a 'trial' as this involved things that were being tried out.[14] This form of misunderstanding has been highlighted before by Appelbaum and colleagues,[59] giving examples such as a patient rejecting the idea that she was involved in an "experiment" (as this would involve drugs whose effects were unknown), and preferring to describe herself as being involved in "research" where doctors "were trying to find out more about you in depth". It is interesting to note here that somewhere along the line of rejecting the word experiment and trying to describe her own experience, the patient has introduced the idea that the trial is designed to benefit her. Further misunderstanding with aspects of the experimental process may arise from the use of the word 'treatment' when it is referring to an experimental procedure, rather than something that is done solely to improve the health of the individual (suggested by Schaeffer and colleagues[28]). Concerning random allocation of treatment, Snowdon and colleagues[60] found that some parents had difficulty with the terminology that a computer would decide which treatment their baby would receive. They may have interpreted the word 'decide' as meaning 'reach a reasoned decision' rather than 'allocate'.

In spite of the focus on improving written information, it appears that some patients were not given information sheets by their clinicians,[37,51] and some did not read the written information they were given.[27,30] In such circumstances the oral presentation of information by the clinician or researcher became the only source of consent information. Yet clinicians may avoid discussing aspects of the trial that they expect to be hard to understand, and focus on the concrete medical information.[30] In addition, researchers did not plan meaningful discussions of consent information and did not plan to allow patients time to ask questions or consider their participation.[52] The 1998 review concluded that information needed to be tailored to the individual so that they would have enough information to be informed without being overloaded. An attempt was made to do this by Fleissig and colleagues,[10] who provided clinicians with a measure of a patient's preference for level of information as well as a measure of his or her attitudes towards trials. However, there was no

measurable impact on consultation style or outcome; clinicians did not appear to make use of the information or alter their consultation accordingly.

Findings in the current review highlight the importance of aspects of the informed consent procedure, particularly the aspects of timing of presentation of information and the amount of time spent discussing the consent information. The 1998 review found that consent in emergency situations was more forthcoming than in circumstances where patients had more time, although studies in the current review reported a high level of dissatisfaction with consent given under such circumstances.[23,26] Other studies generally found that the more time taken in discussing the consent information with patients,[25,28] or the more time patients had to consider the information,[12,34] the better the patients' understanding. In addition, studies using educational programmes to improve the capacity of mental health patients to give consent have successfully used tools to identify areas of poor understanding followed by further discussion of the identified areas to increase patient understanding. It should be noted that the same methods did not work equally well with all types of patients.[42]

It is clearly important to consider both what information is presented and how this is done, but the circumstances and characteristics of the person to whom the information is given are also important factors in the level of understanding achieved. Considerable efforts to improve written information have had only a limited impact on patient understanding, and patients' level of education and cognitive or reading ability may partly explain why (e.g. Davis[41]). Achieving sufficient understanding with individuals with low levels of education and low cognitive or reading ability may require intensive efforts such as those described above, designed to increase the capacity to consent among individuals at high risk of poor understanding (such as some patients with mental health problems). Understanding or recall may also vary with age: Bjorn and colleagues[39] found differences in levels of understanding of written consent information between two samples that differed greatly in age, particularly understanding the role of chance in treatment allocation, suggesting an age or a cohort effect. The circumstances surrounding patients' being asked to join a trial may cause stress or emotional distress, the extent of which could be a further influence on understanding of trial information.[28]

Methodological issues

At the beginning of this section the types and quality of methods of measuring understanding in recent studies were discussed. There was widespread use of measures of unreported validity or reliability. Many studies did not report how long after consent the awareness or understanding of consent issues was being assessed, and several that reported substantial timelags or a wide range of timings of assessment did not consider the impact of intervening time on understanding. As noted earlier, recent articles have been published in a large number of journals from different clinical specialities, and the apparent lack of sophistication or rigour in many of the methods used may be related to this. Studies do not appear to build on the findings, methods or limitations of earlier studies. Rather, work conducted in particular clinical contexts appears to be carried out in isolation from largely similar work already conducted in others.

The 1998 review expressed concern over the use of recall (there used broadly to include both free recall and recognition measures) as a measure of understanding, noting examples such as randomisation where memory may have been good but understanding poor. Similarly, the review noted that using patients' estimates of their own understanding as a measure of understanding would be likely to lead to an overestimate, as patients may not be aware of what there is to know. There is further discussion of the implications of using various methods to measure understanding in the section 'Reflections drawing on theory and evidence from experimental psychology' in Chapter 2.

The authors of the 1998 review were also concerned that studies investigating patient understanding of informed consent information should include patients who refused to participate in trials as they might be systematically different from those who accepted. Three studies out of the four in the current review that compared acceptors with refusers found differences. Refusers were less knowledgeable about consent information, perceived information as harder to understand and were less likely to feel that they had been given enough information. One possible interpretation of the findings is that the problems with understanding found in acceptors may be even greater in those who declined, with the implication that they may not have given informed refusal.

Another methodological concern expressed in the 1998 review was how to interpret the findings of hypothetical studies. The effect of the stress of a

clinical trial situation on cognition was discussed earlier and it is highly likely that such factors may influence informed consent in real trials to a greater extent than in hypothetical trials. However, research involving hypothetical trials has an important role to play in making comparisons in a carefully controlled way, and in examining factors that are difficult to manipulate in an ethically acceptable manner in real trial situations. In the current review, there have been some areas of study where both hypothetical trial and real trial studies have been carried out, allowing a rough comparison of findings. In assessments of the relationship between education and cognitive or reading ability and understanding, hypothetical trials and real trials have produced similar results. These effects may differ with severity of diagnosis, as reported by Schaeffer and colleagues,[28] although it was difficult to compare understanding validly across different real trials owing to the variation in the quality and quantity of information received by patients. With the advent of informed consent guidelines for written information, it should become more feasible to compare understanding between patients with different levels of severity of diagnosis, participating in different trials, yet having received similar information about aspects common to the trials involved. It also becomes easier for hypothetical trials to model and test real trial information more effectively, even if they cannot re-create the added stressors and personal involvement in a real clinical situation.

Conclusions of review: patients' understanding of consent information in the context of clinical trials (papers published 1996–2001)

There is still a problem of patients' failure to understand consent information in clinical trials, and hence of being able to give consent that is genuinely informed. Clinicians' awareness of patients' difficulty understanding certain aspects of the trial may lead them to focus instead on other aspects when they invite patients to participate. Understanding of design features such as random allocation to treatment arms is still problematic and perhaps cannot be solved purely by simplifying consent forms or using non-technical words. The nature of patients' problems with understanding such aspects of trial design needs to be examined.

The lack of reliable and valid measures of understanding was apparent in both the 1998 and the current review. However, good progress has been made recently in developing measures that can be used at the time of informed consent to measure understanding or capacity to give informed consent (see the section 'Methods of measuring understanding', p. 12).

Recent studies have highlighted the importance of considering not only what information is presented and how this is done, but also the characteristics of the person to whom the information is given. Some education programmes carried out with groups of patients at high risk of poor understanding show promise, although the apparent failure of clinicians to take into account information about their patients' preferences for information or attitudes to trials is disappointing. The feasibility of tailoring information to the needs of the individual in current trial settings remains unclear.

Extracted studies on understanding of randomisation in the context of clinical trials (all papers, pre-1997 to 2001)

Fifteen new studies were found during the literature search, eight studies were included in Edwards and colleagues'[1] review and two other papers held by the authors also contained findings relevant to the understanding of randomisation in the context of clinical trials. All are included in this review to give as detailed and as comprehensive a picture as possible. Seven of the studies used qualitative methods and the other 17 were quantitative studies. Lists of the studies, along with their methods, main results and comments, are summarised in Appendix 2.

Real trial participants' understanding of randomisation

Studies varied greatly as to when participants' understanding of randomisation was assessed and few authors commented on how understanding might change over time. Five of the studies, all quantitative, reported levels of understanding of the randomisation procedures used to allocate treatment immediately after or within days of consent.[7,53,59,61,62] However, another six studies reported levels of understanding of randomisation in real trial contexts some time later (Heitenan,[13] 5–17 months after consent; Gallet,[63] 5–21 months after consent; Davis,[41] 12 months after consent; Jensen,[64] 3 months after receiving consent information; Snowdon,[60] 11–24 months after consent; and van Stuijvenberg,[35] at the end of the trial). One study reported levels of understanding

of randomisation among trial participants 2 weeks to 15 months after consent, but did not report any analysis of the effect of time after consent on recall,[64] and two further studies did not specify how long after consent trial participants were interviewed.[14,15]

The studies conducted in real trial contexts present a varied picture of participants' levels of understanding of randomisation. Three studies reported understanding of randomisation among fewer than 28% of participants,[13,59,62] four studies reported understanding of randomisation among 42–54% of participants[35,53,63,65] and two reported that over 73% of participants understood randomisation.[61,64] The latter study reported a considerably higher level of understanding than any other study, possibly because their volunteers had participated in a 2–4-month educational programme before giving consent, and were tested by a multiple-choice questionnaire. Other studies found an increase in awareness of randomisation procedures with modified informed consent procedures. Aaronson and colleagues,[53] for example, found that 54% of a standard informed consent group were aware of random allocation, compared with 75% of a second group who received a supplementary, telephone-based contact with an oncology nurse. They also found that when they tested another group of trial participants at the same institute who had not been involved in the intervention study, but had supposedly had the same consent procedure as the standard informed consent group, only 17% were aware of the use of randomisation procedures. This raises the possibility that levels of understanding of randomisation among trial participants outside these studies could be even lower.

Some studies found that while a proportion of participants had some awareness of aspects of trial design related to randomisation, their understanding appeared to be incomplete. Howard and colleagues[65] found that 83% of trial participants recognised that some patients took the experimental drug and others took a placebo, but only 42% knew that allocation of treatment was based on chance. Similarly, van Stuijvenberg and colleagues[35] found that while 88% of parents of children in a double-blind, randomised, placebo-controlled trial were aware of the 50% chance of being assigned a placebo, only 50% were aware of the random allocation procedure.

When studies went beyond testing for awareness of randomisation and questioned participants' understanding a little further, many found that participants held other ideas about methods of treatment allocation. Gallet and colleagues[63] found that while 42.8% of participants correctly replied that treatment had been randomised through 'drawing lots', the majority, 55.9%, thought instead that treatment allocation was based on individual circumstances such as the seriousness of the condition, the age of the patient or their psychological state. Appelbaum and colleagues,[59] drawing on a number of studies, found that only 28% of participants had complete understanding of the randomisation procedure, while 69% had no comprehension of the actual basis for their random assignment to treatment. Instead of random allocation, 32% of participants stated their explicit belief that assignment would be made on the basis of therapeutic needs and 44% of participants failed to recognise that some patients who desired treatment would receive the placebo. The authors use the term 'therapeutic misconception' to describe the phenomenon where patients believe that every aspect of a research project has been designed to benefit those who participate. To maintain this therapeutic misconception, many participants constructed elaborate but entirely fictional means by which treatment assignment would be made that was in their best interests.

Further evidence of this therapeutic misconception was found in the qualitative studies. Featherstone and Donovan[14] report that awareness of randomisation procedures did not indicate understanding. While almost all participants were aware of some aspects of randomisation, their awareness was often confused with pre-existing lay beliefs that treatment allocation is based on specific symptoms, clinical findings and age. Glogowska and colleagues[31] found that in a trial where a therapy was being compared with watchful waiting, parents of children who participated assumed that allocation would take their circumstances into account. For example, they believed that if the therapist detected certain symptoms, then their child would receive therapy rather than be monitored. Snowdon and colleagues[60] also found that although parents of newborn babies enrolled in a neonatal trial responded to terms such as random and randomisation as if they were familiar, they constructed their own theories as to how and why treatment allocation took place. Instead of randomised allocation, some parents felt that the treatment decision was made on therapeutic grounds and that their baby was given a treatment appropriate to his or her need. In some interviews

parents held apparently contradictory views of the allocation procedure, in that their references to chance coexisted with accounts of non-random processes. Searight and Miller,[15] in contrast to the other qualitative studies, found a consistently good level of understanding among their participants that assignment of the placebo or active drug was randomly determined, with some using concrete analogies in their descriptions of randomisation. Despite such good levels of understanding, and an acknowledgement that there may be a distinction between research care and receiving care from their physician, none believed that they were in any way short-changed by receiving care as part of a research protocol.

For many of the studies involving real trials, it is unclear just what written or oral information participants were given about randomisation, but two studies focus on this. The first, by Verheggen and colleagues,[30] relied on interviews with clinicians who obtained informed consent in 26 clinical trials. They found that while 96.8% of clinicians believed that patients do not understand the design of the trial (randomisation, placebo and control group selection procedure), 70% of clinicians reported that they did not emphasise the design of the trial in informed consent discussions with patients. Consistent results are reported by Jenkins and Fallowfield,[46] who analysed taped interviews of clinical oncologists and patients discussing randomisation into a treatment trial. Randomisation was often mentioned implicitly (95.1% of consultations), for example, by stating that patients would be allocated to receive the treatment or not, and the decision would not be made by the doctor or the patient. Less often, there was explicit mention of randomisation with a rationale (62.2%), for example stating that patients would be randomised so that half would receive the treatment and half would not, and the decision would not be made by the doctor to avoid introducing bias. In 82.9% of consultations the clinicians did not check their patients' understanding of randomisation at all.

Understanding randomisation in hypothetical trial contexts

Three studies reported the levels of understanding in the contexts of hypothetical trials and all used only written information. Bjorn and colleagues[39] used written information from two previous trials and simplified versions of the same information. They found that understanding of randomisation was better for one trial than for the other. Only 26% of participants with the original hypertension trial leaflet and 42% with the revised hypertension leaflet correctly identified that chance decides which treatment they would receive. Most participants thought that it was the responsible doctor who decided. In the sterilisation study, by contrast, most participants answered this correctly. The authors suggest that this might be an age or cohort effect reflecting the difference in ages between their two samples. In their modification of an industry standard consent form, Dresden and Levitt[43] found that the modified version had an effect on correct responses to the question "will I definitely get the drug if I enrol in the study?"; 44% of those with the standard form compared with 78% of those with the modified form answered this correctly. However, neither version of the form was included in the article, and it is unclear how the form was modified to inform participants better about this.

Davis and colleagues[41] also used an original trial information leaflet and compared it with a simplified version, but the effect they found was related to the reading ability of their sample rather than the version of the questionnaire they received. Overall, 41% of participants correctly answered the question "what determines which treatment you get?" However, only 12% of participants reading at or below eighth grade level answered this item correctly, compared with 75% of those reading at or above ninth grade level.

General understanding of randomisation without consent information

Five studies assessed people's general understanding of randomisation without giving them any information. Ellis and Butow[66] carried out a qualitative study with a community sample and an outpatient sample of women, and found that while most were aware that clinical trials involved a comparison of treatments they were unsure how this would happen. The reason why treatment would be allocated at random was poorly understood. In a further study, developed from this pilot work, Ellis and colleagues[67] found that in an outpatient sample 31% of participants were unaware that treatment is allocated by chance in a randomised trial. Furthermore, 74% thought that the doctor would ensure that they received the best of the treatments offered in a randomised trial. Kjoergaard and colleagues[68] also carried out a survey of outpatients and using a multiple-choice questionnaire found that while only 37.7% knew what a randomised trial was, 47% correctly identified the reason for using randomisation. However, as the authors did not include their

questionnaire in the published paper there is no indication as to what this correct reason was considered to be or what other reasons participants could choose. Waggoner and Mayo,[69] in a sample of the general public, assessed the understanding of 25 words or phrases commonly used in clinical research consent forms, one of which was "if the drug you were to take was chosen *randomly* what does this mean?" They report that only 22% overall, 28% of college-educated participants and 4% of high-school or lower educated participants knew the meaning of the word 'randomly'. In their focus groups with African–Americans, exploring the barriers to participation in clinical research, Friemuth and colleagues[70] found that the term randomisation was poorly understood by most people, and gave two examples of misunderstanding as 'not giving any thought' or 'no specific target group'. In a qualitative study in which women with breast cancer and health professionals in the breast cancer field were interviewed about their experiences, Madden[71] found that confusion over the meaning of terms such as randomisation and equipoise was shared by health professionals and patients alike.

Extracted studies on attitudes towards randomisation in the context of clinical trials (all papers, pre-1997 to 2001)

Sixteen new studies found in the literature search, five studies included in Edwards and colleagues'[1] review and one earlier study cited in a recent paper contained findings relevant to attitudes towards randomisation in the context of clinical trials. Five of the studies used qualitative methods and the other 17 were quantitative studies. Lists of the studies, along with their methods, main results and comments, are summarised in Appendix 3.

Attitudes towards research in general and randomised trials in particular

The studies reported an overwhelmingly positive attitude towards research among outpatients,[67] cancer patients[10,71,72] and enrolees in managed care organisations.[73] The only concern expressed about research in general was made by women who had been treated for preliminary breast cancer who perceived the risks of taking part in research as very high and only worth taking if the potential benefit was of the highest kind.[71]

Attitudes towards randomised trials in particular were less positive. Ellis and colleagues[67] found that 88% of outpatients believed that patients should be asked to take part in trials testing new treatments. In contrast, only 51% agreed that randomised trials were the best way of finding out whether one treatment was better than another. Among participants of different types of trial, Madsen and colleagues[74] found that 71.9% of participants in a randomised trial sample had a positive view towards randomisation, compared with 44.7% of participants in a consecutive diagnostic study, 46.9% of an outpatient sample and 55.7% of a general public sample having a positive view of randomisation. Participants stated that drawing lots was the most just and fair method to ensure a random distribution between groups. The authors interpreted this to mean that they acknowledged randomisation as the most just and fair way to distribute patients between test treatments, but that does not necessarily follow from the result reported. Less positively, McQuellon and colleagues[75] found that 90% of breast cancer patients considering a hypothetical trial scenario would not allow the flip of the coin to determine which treatment they received. However, this strong finding may be a result of the fact that the trial scenario was presented as a treatment choice rather than cast in a research context, and it contained no statement of uncertainty about the relative benefits of the two treatments.

Snowdon and colleagues[76] found that parents who had consented to their children's participation in a randomised neonatal trial recognised difficulties in assigning treatments when there is uncertainty over treatment efficacy. Yet randomisation seemed unfair to them, and when the trial results were fed back to them, they found it hard to accept that chance had denied babies the better treatment. In interviews with parents of children who had participated in a randomised trial, Glogowska and colleagues[31] found that their attitudes were very negative, with some parents considering it unethical to withhold a treatment even when its value was unproven and equipoise existed. The random allocation of treatment, and the uncertainty or experimental nature of clinical trials, were perceived as major negative aspects of clinical trials by focus groups of breast cancer patients and women in the community.[66] Similarly, in a sample of cancer outpatients one of the two least appealing aspects of clinical trials was the fact that the treatment was decided by the trial rather than the doctor or the individual, with nearly half of patients finding this unappealing.[77]

Willingness to participate in a randomised trial

Surveys found that people were often unwilling to participate in randomised trials even when they held a positive attitude towards research in general.[10,67,71–73] In two studies, over 90% of cancer patients sampled thought that patients should be asked to take part in medical research. In one sample 69%, and in the other 77%, said that they would be prepared to take part in a study comparing two treatments. These percentages fell to 34% and 45% if the treatment was to be chosen at random,[10,72] Fallowfield and colleagues[72] found that the Attitudes to Randomised Trials Questionnaire (ARTQ) discriminated among three categories of patients: those who were comfortable with the concept of randomisation, those who had some concerns but with fuller explanation were prepared to consider randomisation, and those who were firmly against randomisation and participation in such trials whatever information was provided. When further information was given about randomisation (such as the existence of clinical equipoise, the right to leave the study if the treatment did not suit them, and being told by the doctor all about the two treatments before allocation), 68% and 70% of those who initially responded 'no' or 'don't know' to taking part in a trial where treatment would be chosen at random said that they would change their mind and be willing to participate. Reported willingness to participate in a randomised trial was lower when the two treatments were very different. Tambor and colleagues[78] surveyed women who were at increased risk for developing breast or ovarian cancer, where the three treatment options were surveillance, chemoprevention and prophylactic surgery. They found that only 18.7% and 16.9% of women would be willing to participate in a randomised breast or ovarian cancer trial, respectively; this rose to 84.8% and 75.9% if the proposed trial was not randomised.

In surveys of outpatients, over half of patients who indicated that they would not participate in research if or when invited referred to randomisation and specifically the lack of their own or their doctors' ability to choose their treatment as contributing to their refusal.[29,77] However, even when the fact that the treatment was decided by the trial rather than the doctor or the individual was seen as one of the most unappealing aspects of clinical trials, 97% of a sample of outpatients ranked reasons other than this as the most important aspect of research trials[77] and 95% of a sample of adolescents gave reasons other than randomisation for why they refused participation in a trial.[79] In a study assessing patients' willingness to participate in a number of hypothetical trial scenarios, Llewellyn-Thomas and colleagues[80] found that over half of patients said they would not consent to enter a randomised trial, and 63% of these reported aversion to randomisation as their primary reason for non-participation.

In a real trial setting, Jenkins and Fallowfield[46] found that nearly one-fifth of patients who declined entry into randomised cancer trials gave their most important reason for declining as worry about randomisation, and a further 9% gave their most important reason as being that they wanted the doctor to choose their treatment instead. Over one-third of those who agreed to take part were also concerned about randomisation and would have preferred their doctor to choose the treatment. Albrecht and colleagues[81] studied physician behaviour in relation to patient accrual to a clinical trial and found that more explanations of randomisation were recorded in interactions when patients were accrued to a trial (53%) than in interactions when patients were not accrued (40%). Similarly, random procedures were more often described in interactions when patients were accrued to a trial (89%) than in interactions when patients were not accrued (50%). This may indicate that being told about randomisation is related to being willing to participate in a trial, or it could be due to physicians not offering trial information after a patient has made it clear that they did not want to participate. It is also unclear whether the absence of a description or an explanation of randomisation meant that it was not mentioned at all, or mentioned but not described or explained.

Attitudes towards the description of randomisation

Corbett and colleagues[82] offered seven descriptions of randomisation and asked members of the public and medical students to evaluate how good they were (without assessing their understanding of the concept of randomisation). Participants preferred statements about randomisation that were not explicit and played down the role of chance, and disliked more concrete descriptions such as tossing a coin or names being pulled out of a hat. Members of the public particularly disliked the description which emphasised that the decision would not be made by the patient or doctor.

Attitudes towards other methods

Jensen and colleagues[64] identified two patients in their sample of 34 women with breast cancer who

reported that receiving detailed information about a clinical trial made them very anxious and they would have preferred, if randomisation were necessary, that it had been carried out without their knowledge. It is not clear what conclusion can be drawn from such a small data set. Snowdon and colleagues[83] asked parents who had consented to their children's participation in a neonatal trial, comparing a new treatment to conventional management, what they thought about Zelen randomisation or prerandomisation. In a Zelen method eligible patients are randomised to receive a standard or new treatment before being asked for their consent. Only those randomised to receive the new treatment are asked for their consent and if they refuse they are given the standard treatment. Those randomised to receive standard treatment are not asked for consent, as they are receiving the treatment that they would have received if no trial was being run. In this case the design had been considered as a way of protecting parents with seriously ill babies who were told about a new treatment but did not receive it. Parents were split as to whether they were for or against this design, but the group of parents whom it was proposed to benefit (those whose children had been randomised to receive conventional management) were more likely to reject it for reasons such as missing out on the benefits of deciding to participate in a trial (commitment to the trial, involvement at follow-up, making an altruistic decision) and the unacceptability of doctors going behind patients' backs.

Extracted studies on equipoise in the context of clinical trials (all papers, pre-1997 to 2001)

Twelve new studies found in the literature search, ten studies included in Edwards and colleagues'[1] review and one further paper held by the authors contained findings relevant to equipoise in the context of clinical trials. Eight of the studies used qualitative methods and 15 were quantitative studies. Lists of the studies, along with their methods, main results and comments, are summarised in Appendix 4.

Awareness and acceptance of equipoise

In trial consent information, equipoise is most often expressed in terms of uncertainty about which treatment is best, or about the benefits of a new treatment. In research into participants' understanding of equipoise, it is awareness of this uncertainty, rather than understanding of the term equipoise itself, that is assessed. Not all consent information includes such a statement of uncertainty (see Appendix 5), and the evidence suggests that even when it does appear, potential participants often remain unaware of uncertainty. White and colleagues[84] found that almost two-thirds of breast cancer patients receiving consent information that included a statement about equipoise remained unaware that the best chemotherapy regimen was not known. Gallo and colleagues[85] found that only 38.2% of a general public sample asked to participate in a hypothetical trial understood the supposed theoretical equipoise, even though the written information stated that "there is no evidence that one drug is better than the other. If we knew that one was better than the other, we would not be conducting the trial". Furthermore, among the subgroup who were apparently aware of equipoise, refusal to enter the trial was more common among those prerandomised to standard treatment than among those prerandomised to the experimental treatment. This suggests that they may not have accepted the theoretical equipoise. Other studies show that about one-quarter of outpatient and general public samples believe that doctors would know which treatment is best in a clinical trial.[67,86] Jenkins and colleagues[51] report that during discussions with patients about randomisation into a treatment trial, clinical oncologists expressed uncertainty about treatment decisions in virtually all of the consultations, although only in 14.6% of consultations was the uncertainty expressed as personal; more commonly, only general uncertainty was expressed.

Ellis and colleagues[67] also asked their sample of oncology outpatients what they would prefer to happen if there was no evidence to suggest that one treatment was better than another. Most wanted their doctor to tell them about the uncertainty, but to give an opinion about which was better, and less than one-third wanted the doctor to tell them about the uncertainty and invite them to take part in a trial to find out which was better. Alderson[87] found that among a sample of health professionals, 25% thought that women preferred to be informed of current uncertainty about the nature and treatment of breast cancer, while 15% thought that women were too distressed and preferred not to know. In contrast, among the sample of women who had been treated for breast cancer, 68% said that they would want to be informed about current uncertainty if they were asked to take part in a trial, and 4% said that they would not. Millon-Underwood and colleagues[88]

found that their sample of cancer patients and members of the public held views about the circumstances in which the best treatment is received. Twenty per cent believed that cancer patients who take the treatment that their physician recommends received the best treatment (interestingly, only 26% of this group believed that the physician knew which treatment was the most effective), 8% believed that those who participated in trials received the best treatment and 17% believed the treatments to be the same either way.

Johnson and colleagues[89] asked lay people to judge whether or not a trial would be ethical given a certain disparity of views among imaginary groups of experts. Eighteen per cent of the original sample could not understand the concept of equipoise or found the judgement task too demanding. Among those who could make judgements, 97% regarded a trial as substantially unethical if equipoise were disturbed above 80:20 (i.e. 80% of experts favoured treatment A and 20% favoured treatment B). The greatest tolerated inequality in this ratio was for treatments of less serious conditions. If the issues were highly emotive then equipoise must be much nearer 50:50 for a trial to be deemed ethical.

Beliefs about which treatment is best

Investigations of views about clinical trials have suggested that both lay people and clinicians may hold views about trial treatments even without being given any substantive information about them: the default assumption seems not to be one of equipoise. Alderson[87] found that only 25% of a sample of health professionals working with breast cancer patients thought that an individual doctor could achieve equipoise (defined by Alderson as a state of uncertainty, characterised by the belief that, in a trial, no arm is known to offer greater harm or benefit than any other arm), 13% thought that the whole breast care team could share equipoise and 18% thought that patients could achieve equipoise. Twomey[90] found that doctors emphasised the benefits of participating in a trial owing to possible access to an experimental treatment; the established treatments were considered far from perfect, so benefits from new treatments could be expected. Joffe and colleagues[12] found that only 30% of cancer patients participating in various clinical trials disagreed with the statement that "the treatment being researched in my clinical trial has been proven to be the best treatment for my type of cancer", while 82% of providers (who had presented the consent information to the participants) correctly disagreed with the statement. In contrast, Ellis and Butow[66] found that female patients and members of the community thought that current treatments were generally successful and that new treatments were only tested on terminally ill patients with no other treatment options. In a second study, this time with oncology outpatients, Ellis and colleagues[67] found that 19% agreed that clinical trials test treatments that nobody knows anything about.

Slevin and colleagues[77] found a distinction in the minds of their sample of cancer patients between new treatments and experimental treatments. The majority of their sample found the higher chance of obtaining new treatments an appealing aspect of clinical trials, but the higher chance of obtaining experimental treatments was one of the two least appealing aspects of clinical trials. Madsen and colleagues[74] found that more participants in a randomised trial (87.5%) and more participants in a consecutive diagnostic study (83.0%) rated the wish to receive the new drug/investigation as either important or very important to their decision to participate in the trial, than rated the wish to help future patients by testing new drugs or investigations as important or very important to their decision (75.1% and 73.5%, respectively).

A sample of AIDS patients in a study by Tindall and colleagues[91] was highly optimistic of benefits of new treatments: 79% felt that unproved treatments should not be restricted to trials, but that people should be able to choose between receiving them within and outside the trial mechanism. In telephone interviews with proxies who had given consent for dementia patients to participate in clinical research, Sugarman and colleagues[92] found that they had consented in the belief that there was nothing else available or they hoped that the experimental medicine would be better than medications available at the time.

The appeal of new over standard treatments has been noted in qualitative studies in real trial settings. Snowdon and colleagues[60] found that parents of severely ill babies in a neonatal trial considered assignment to the new treatment to be the desired outcome of treatment allocation. After the results of the trial were fed back to the parents,[76] it was found that retrospectively some parents felt that researchers had been pretty sure before the start that the new treatment, which was found to increase the likelihood of babies leaving hospital alive compared with the conventional treatment, would be likely to come out better. Mohanna and Tunna[93] found that women who

had declined entry to a clinical trial felt that the placebo design was unfair; the drug should be given to all women rather than denying half of participants a new treatment.

The possibility that people believe that new treatments will be more effective than standard treatments is supported by findings from hypothetical trials. Gallo and colleagues[85] enrolled 2035 healthy subjects who were visiting a scientific exhibition in a hypothetical trial of experimental versus standard treatment. More than half believed that the new treatment was better than the standard one. This finding is difficult to interpret, however, as in the information sheet participants were given an indication of the efficacy of the standard treatment, and this was varied from 20–80% survival to 5 years. The authors do not tell us whether the variation in proposed efficacy of the standard treatment affected the participants' beliefs about which treatment was better. However, they did find that the worse the prognosis with the standard treatment, the lower the refusal rate to participate in the hypothetical trial, with the exception of those who were prerandomised to the standard treatment (so by refusing they could ask for the experimental treatment). Their refusal rate rose with the worse prognosis. The inference from this is that people assumed that with only a 20% chance of survival with the standard treatment, the new treatment has plenty of scope to be better and is unlikely to be worse. Myles and colleagues[94] proposed a hypothetical trial to a sample of hospitalised patients due to have surgery, and found that 44.7% thought that the new treatment was better than the standard one. They also found that consent rates were higher in patients who thought that the experimental treatment was the better treatment. However, Sheldon and colleagues[95] found the opposite effect with vignettes of a hypothetical cancer trial among a sample of female cancer patients. They found that many patients grossly overestimated the actual benefit expected of the standard treatment and that those who did were significantly less likely to choose trial participation.

Several studies showed a common perception of new treatments as low in risk. Joffe and colleagues[12] found that only 37% of cancer trial participants disagreed with the statement "compared with standard treatments for my type of cancer, my clinical trial does not carry any additional risks or discomforts", while 71% of their providers correctly disagreed with the statement. Sugarman and colleagues[92] found that proxies felt that there was nothing to lose by consenting for a dementia patient to participate in a drug trial, and said that a drug must be safe if it was being tested on patients. Mothers in Pletsch and Stevens'[33] sample revealed similar beliefs when they reasoned that research medicine would have been tried many times in numerous studies before being offered to their children. They associated ideals of precision, competence and honour with research, and felt that mothers need not worry about harm to their children as researchers would have thought of everything.

Verheggen and colleagues[30] examined patients' attitudes in detail and found that patients with a generally positive attitude towards medical experiments expected low risks from the new, untested treatment procedures during a clinical trial. Similar expectations were held by those who valued the benefit that other patients might gain from the results of the clinical trial. Verheggen and colleagues[96] found that patients were likely to decline participation in a clinical trial if they associated high risks with the new, untested diagnostic procedures or treatment.

Implications of reviews for further empirical work

It seems clear from the reviews of the literature in the previous review sections that patients in trials are still at risk of failing adequately to understand about random allocation and equipoise, and even if they do understand adequately at the time of consent, they may lose sight of this information in the light of subsequent events. Hence, consent or refusal to participate in a trial might not be adequately informed. Even if consent is adequately informed, participants may subsequently come to believe that deliberate treatment decisions were made that were not in their best interests and/or to which they did not consent.

The published literature suggests lists of variables that can be relevant to patients' level of understanding. It does not, however, lead to a coherent picture of when and why problems of understanding arise or of how they can be reduced. As mentioned earlier, there are serious shortcomings with the methods used by many of the studies, and studies rarely build on previous findings in a way that genuinely advances generalisable knowledge. Often researchers appear to take a pragmatic approach of trying to identify the extent of the problem in their particular clinical context, and of trying out ways

of reducing it. No body of theory has been developed. What is now needed is a set of related investigations in which theoretically justified factors are systematically varied to identify just why patients have such difficulty understanding randomisation and equipoise. This is assessed in Chapter 3.

To provide further background information, the content of written trial information offered to potential trial recruits about randomisation and equipoise was investigated.

Descriptions of randomisation and equipoise in trial information leaflets

A collection was made of patient information leaflets dating from 1993 to 2000 and used in previous randomised trials. In total, 16 examples were collected, mainly through approaching colleagues involved in running or approving randomised trials, although some information leaflets were published with the findings of the relevant trial. As shown below, collecting was interrupted by the introduction of guidelines for wording of leaflets, which should lead to consistency across leaflets and so made further collecting redundant.

Patient information leaflets used in real trial contexts

The content of the descriptions of randomisation and equipoise in the patient information leaflets is summarised in Appendix 5. Seven elements were identified in the descriptions of randomisation:

- explicitly stating that allocation would be at random
- identifying chance as the basis of allocation
- giving an analogy of randomisation (e.g. like tossing a coin)
- describing the procedure involved in treatment allocation or the method to be used (e.g. telephoning the office, where a computer will decide which treatment you will receive)
- stating the level of chance of receiving either treatment
- stating a benefit of randomisation (e.g. removes bias)
- stating a consequence of randomisation (e.g. the doctor does not choose your treatment).

The leaflets varied greatly in the number of elements used to describe randomisation. Three leaflets used only one element: one used only 'randomly chosen', another only stated the level of chance of receiving a placebo, and the third only described the procedure of allocation to treatment. Typically, the information leaflets used three elements to describe randomisation, and the three most frequently used elements were explicitly stating that allocation would be at random, stating the level of chance of receiving either treatment, and describing the procedure or method involved in treatment allocation.

Justifications for randomisation (scientific or ethical) were rare: nine of the leaflets did not justify the use of randomisation in any way. Of the seven that included a justification for randomisation, four asserted a methodological benefit of randomisation and one stated that randomisation was necessary in order to compare groups. Two leaflets presented the current uncertainty over the effectiveness or benefits of treatments as the reason for randomisation, although it is interesting to note the infrequency of any link between equipoise and randomisation.

Two leaflets made no statements relating to equipoise at all and none stated explicitly that there was no evidence that one treatment is better than the other. When it was alluded to, equipoise was most often put in terms of possible benefits of a new treatment which were not as yet certain (seven leaflets). Others stated that it was not known which is the best treatment (five leaflets), that the treatments were currently used but have not been fully tested or have not been compared (three leaflets), or that there was conflicting evidence about which treatment was best (one leaflet).

Guidelines for writing patient information leaflets

Guidelines to help researchers to design information leaflets were published by Consumers for Ethics in Research (CERES),[97] although researchers were under no obligation to use them. These guidelines were informed by research carried out with women diagnosed with breast cancer[98] and produced in consultation with the CERES membership. More recent guidelines produced by the *Bulletin of Medical Ethics* in 1999 and revised in 2001,[99] were the result of a working party set up following the International Conference on Harmonisation. This working party produced guidelines for good clinical practice, recommending that certain main items should be included in patient information and consent forms. The working party consulted with relevant

experts and representatives of patient groups to produce easy-to-read recommendations to researchers that covered the required main items. There followed a consultation period when the guidelines were circulated to all ethics committees in the UK, after which they were finalised and implemented. The guidelines have now been incorporated into the Multicentre Research Ethics Committee (MREC) application process, whereby they are sent to all researchers for guidance in their applications for ethical approval. Ethics committees routinely use the guidelines to evaluate the quality of proposed patient information and consent forms, and forms that do not conform are returned to researchers for redrafting. Members of the working party are carrying out an ongoing evaluation of the impact that the guidelines have had on the readability of patient information and consent forms. The recommendations of these and other guidelines are shown in Appendix 5, alongside the contents of the trial information leaflets collected in this study.

The MREC and the *Bulletin of Medical Ethics* both use the same guidelines. They recommend that researchers use a description of randomisation with four elements: explicitly state that it is a randomised trial and then define it by identifying chance as the basis of allocation, describe the procedure involved in treatment allocation, and state the level of chance of receiving either treatment. The University of Bristol Ethics Department thought that the MREC guidelines were confusing and so produced their own, with recommended headings and phrases, along with sample information leaflets based on examples of past trials. They recommended the four elements listed in the MREC and *Bulletin of Medical Ethics* guidelines, along with the use of the analogy "as if 'by the toss of a coin'". All three of these guidelines recommend obtaining a leaflet from CERES for more information about patients' concerns in medical research. The leaflet in question, '*Medical research and you*', published in 1993, adds a little to the definition of randomisation by adding that the benefit of randomisation is "to make sure that treatments are compared in a fair way".

The guideline booklet that CERES published in 1994 for researchers or patients to purchase, entitled '*Spreading the word on research, or patient information: how can we get it better*',[97] recommends the fullest description of randomisation as follows: "What is a randomised trial? In this kind of trial, people are put into groups. They are sorted at random, as if 'by the toss of a coin', but now often by a computer. Each group has a different treatment, and these are compared. Randomised trials are the most exact and fair way to test which treatments work best. They are less likely to have, for example, people who are older or sicker in any one group. Each year, thousands of people take part in them." They then follow the description with a series of questions for research participants to ask themselves which cover other elements of randomisation: "What is each type of treatment in this trial like? Do I mind being put into any of the groups? Do I mind my treatment being decided by chance, not by choice? Do I mind having a new treatment when the older one might be safer and better? If you do not want to take part in the trial, this raises the question: Do I mind having treatment which may not have been tested in a trial, so that no one is sure how useful it is?" The only element that is missing from this description is the probability of receiving either treatment.

When it comes to describing equipoise, MREC, the *Bulletin of Medical Ethics* and the University of Bristol suggest that leaflets should state that we do not know which treatment is best and so we need to make comparisons, and then go on to describe the randomised trial. The CERES booklet considers it vital to mention in information that "… research stems from uncertainty. A question is being asked because no one knows the precise answer. Treatments are being tested or compared because no one knows which is the better one. Benefits are not certain but are unknown and hoped-for".

The CERES guidelines are the only ones whose recommended wording justifies the use of randomisation, and as mentioned above they do so using the scientific benefit (avoiding bias) and the assurance that its use is widespread. The other guidelines' recommendations include a statement of equipoise followed by a definition of a randomised trial, but they do not explicitly connect the two, so that randomisation is not justified (ethically) in terms of not knowing which treatment is best.

Although the descriptions recommended by the guidelines were developed through a thorough consultation process, they have not been tested using potential trial participants. Other CERES leaflets, such as '*Genetic research and you*', have been evaluated for ease of comprehension with patient focus groups, but resources for such evaluation were not available for the research information leaflets. As the use of such guidelines becomes a

requirement for ethical approval of patient information leaflets, the lack of formal evaluation becomes an important issue. To address this the present authors incorporated some of the recommended wording from the guidelines into the experimental procedures, using the part of the recommended description for randomisation from the MREC and *Bulletin of Medical Ethics* guidelines, and the definition of a randomised trial from the CERES booklet.

Reflections drawing on theory and evidence from experimental psychology

Overview

First, it may be suggested that patients' prior knowledge and expectations about the normal sequence of events in a consultation may make it hard for them to process an unexpected invitation to enter a trial. Second, once they have made the necessary switch, they are likely to attempt to make sense of why the trial is being conducted in a particular way, for example why treatments are allocated at random. However readable and clear the trial information, if it merely describes what will happen without offering explanations that connect with patients' existing knowledge and beliefs, then patients may come up with their own, incorrect, interpretations. Their consent or refusal to participate in the trial may not be genuinely informed. Third, and most speculatively, patients who realise that the aim of the trial is to increase medical knowledge rather than to provide them with the most suitable treatment may draw on their beliefs about the scientific process when they interpret trial information and decide whether or not to participate.

Background

The preceding review sections of this report suggest that trial participants often fail to understand that treatments are allocated at random, and that there is uncertainty about the relative effects of the treatments under comparison (equipoise). Although the problem was identified in the 1980s, recent publications report very similar findings. Little headway seems to have been made other than to identify the problem in a greater variety of clinical settings, although there are some interesting developments, which will be mentioned later. It could be time to consider a different approach. What follows are reflections that draw on relevant theory and experimental results in cognitive and social psychology. This same literature also informs us about methods of assessing understanding and provides warnings about possible overinterpretation or misinterpretation of patients' responses in tests of their understanding.

Findings from experimental cognitive and social psychology are usually not directly applicable to real clinical settings. The experimental work is commonly conducted on psychology undergraduates who are asked to remember the content of short written passages in order to fulfil course requirements. Participants in real and personally significant events may well handle information in ways that are importantly different. In addition, the statistical comparisons made in the experimental work do not necessarily focus on the areas of interest for understanding of consent information. Nevertheless, experimental results may identify variables that could be relevant to memory and understanding in real clinical settings, and theories developed in connection with this experimental work may offer useful ideas that could be tested in appropriately tailored investigations.

Handling an unexpected turn in the consultation

Assuming that the invitation to participate in a trial is first made in a medical consultation, the first task for the patient is to realise that the consultation has taken an unexpected and significant turn. Patients have an expectation about the sequence of events when they consult their doctor, and such expectations can be described as scripts. Scripts are goal-related sequences of events built up as a result of experience and used to interpret new events.[100] It is not only the patient who can be seen as approaching a consultation with scripts: Charlin and colleagues[101] have recently applied the concept of scripts to medical diagnosis by clinicians. These authors argue that construction of script-based clinical knowledge forms an important part of becoming expert at diagnosis. More generally, within cognitive and social psychology the term schema is used to refer to organised background knowledge within a particular domain, such as assumptions that the doctor will make a decision in the patient's best interests and that the doctor knows what is best. This background knowledge is seen as guiding the interpretation and the retrieval of new input. Experiments on scripts and schemas compare memory for typical events, which are consistent with prior knowledge, with memory for events that violate expectations in various ways. The findings

from experiments involving scripts and schemas are broadly consistent with each other. Scripts are considered first, then schemas are covered in the section 'The therapeutic misconception'.

An invitation to enter a trial violates the standard consultation script. How accurately the patient subsequently remembers this event may be determined by (1) the way in which the patient construes the deviation from the expected encounter with the clinician, for example as an interruption to the goal of obtaining a suitable treatment or as an irrelevant diversion, and (2) when and how memory is assessed, for example by means of a multiple-choice test or an open interview.

According to script theory, the memory trace for a particular event (such as the consultation in which the invitation to take part in a trial was made) is linked to the relevant generic script (specifying the event sequence of standard consultations), so that typical events that did not actually occur may be activated in memory. If participants are asked in a recognition test whether a particular typical event did occur, the heightened activation of typical but non-occurring events can lead them to judge wrongly that it did. To invent an example, patients' understanding of random allocation could be assessed by asking them to agree or disagree with the statement "Your doctor offered you the treatment s/he considered best for your condition". This describes what typically happens in a consultation but did not happen in the randomised trial, but script theory predicts that patients may be inclined wrongly to agree. Researchers might conclude that patients had misunderstood the information about random allocation.

In contrast, if understanding was assessed instead by open questions such as "How was your treatment selected?", there is no suggested event for participants to check against their memory. To follow on with the example above, patients asked open questions may be less likely to report that their doctor offered them the best treatment, and may appear to have more accurate understanding of what happened in the trial. More generally, when memory is assessed by a recall test of this kind, atypical items (random allocation in this example) can be remembered fairly accurately if testing takes place soon after the event. Generic scripts, it is suggested, play an increasingly important role in recall as the retention interval increases, so atypical events are less likely to be recalled. The extent to which this happens seems to depend on how 'pallid' or 'vivid' the atypical event was, and whether the atypical event was seen as irrelevant to the achievement of the goal or whether it interrupted goal achievement, the latter being better recalled. On the basis of this evidence, one might predict that the clearer it is that the goal of offering treatment is interrupted while the trial entry is discussed, the more likely patients may be to retain an accurate memory of the consent session.

In none of the experimental work on memory assessed by this team has memory been tested after months or years, as has been the case in some of the work on understanding of consent information in clinical contexts. An additional complication with long delays between consent session and interview is that other relevant events have occurred: the patient may know which treatment condition they are in, and they may even know the outcome of the trial. Participants may be reflecting explicitly on issues such as treatment allocation for the first time, constructing an account in response to the interviewer's questions. In such conditions it is impossible to infer what the patient understood at the time of consent. Patients' accounts given under this kind of condition can be treated as post hoc constructions that provide useful data, but provide no clear evidence of patients' level of understanding of consent information at the time they were invited to participate.

More generally, it is important to remember that participants' understanding is always inferred from their responses to researchers' questions, and the form and content of the questions asked determine what the participant reveals. Researchers may choose to set a weak criterion for understanding of randomisation, such as the mere recognition of the word random in a multiple-choice questionnaire (although this carries the risk of false recognition mentioned above). Alternatively, the criterion for understanding could be more severe, such as the ability to offer a coherent and non-contradictory account of how and why they were offered a particular treatment.

To return to the implications of the research on scripts and schemas: a simple conclusion may be that it would be difficult to go too far in emphasising to potential trial recruits the distinction between their standard consultation and the invitation to enter a trial. One account in the literature on patients' understanding of trial information, the therapeutic misconception, is consistent in many ways with the literatures surveyed above.

The therapeutic misconception

Appelbaum and colleagues[59] use the phrase 'therapeutic misconception' to refer to the belief that "every aspect of the research project … was designed to benefit [one] directly" (p. 20). Patients who hold this misconception assume that they are allocated to a treatment group on the basis of their particular needs. This implies a denial of both equipoise (because the patient assumes that the doctor knows which is the best treatment for them) and randomisation (because the patient assumes that the doctor is going to choose a treatment for them).

Although there are circumstances when it is in the patient's best interests to take part in a trial, Appelbaum's argument is that patients are inclined to make that assumption whether or not it is true. This could be seen as an example of a schema that interferes with understanding of consent information, however carefully the investigator thinks this has been explained. Appelbaum and colleagues draw on their own interviews with psychiatric patients to show how patients who can report accurately the details of treatment allocation in a randomised trial nevertheless fall prey to their underlying conviction that the clinicians are acting in the patient's best interests. Featherstone and Donovan[14] and Snowdon and colleagues[60] report results consistent with the suggestion that trial participants can maintain a therapeutic misconception.

Appelbaum and colleagues'[59] suggestion for minimising unwanted consequences of the therapeutic misconception is also in line with expectations from script or schema theory. Appelbaum's suggestion is to highlight for patients that they are no longer in a normal consultation. He proposed that patients be told, "Because this is a research project, we will be doing some things differently than we would if we were simply treating you for your condition. Not all the things we do are designed to tell us the best way to treat *you*, but they should help us to understand how people with your condition *in general* can best be treated" (p. 23). Appelbaum's intention was to try to shake patients' therapeutic misconception. However, taken within the context of script theory, such a statement would be expected to be useful if it results in patients' viewing the signing of a consent form (for example) as interruptive of the goal of the consultation, rather than an irrelevance that might have been ignored.

Making sense of the interruption

So far, it has been suggested that difficulties can arise because of inconsistency between the patient's script- and schema-based knowledge about consultations and the features of the atypical consultation in which he or she is invited to participate in a trial. These difficulties concern participants' understanding that something atypical is happening to them. However, difficulties could continue even if the patient overcomes those problems and recognises that he or she is being asked to take part in a research study. The patient now needs to understand just what this atypical happening is. Shaking people out of an inappropriate framework (a standard consultation script) does not necessarily mean that they can bring to bear instead an appropriate framework for understanding the research context of a trial. Patients' background assumptions can come into play as they try to make sense of trial information, and this can lead them to false conclusions about important aspects of the trial.

Results of several investigations have highlighted the fact that words that have a particular meaning when used within a research context can have a different everyday meaning to lay people. Featherstone and Donovan[14] suggest that people may interpret the word 'random' to mean something done without purpose. One patient questioned whether a routine treatment could be involved in a 'trial', as this involved things that were being tried out. Similarly, in another study, a patient rejected the idea that she was involved in an "experiment", as this would involve drugs with unknown effects. Rather, she described herself as being involved in "research" where doctors "were trying to find out more about you in depth". Although it is not known how common each of these views is, evidence of this kind suggests that merely providing clearer and more easily read descriptions of the trial procedures will not be sufficient to avoid failures to understand.

This suggestion is in line with conclusions drawn from work on lay understanding of scientific knowledge: work on 'lay theories' or 'folk theories'. The appropriateness of using the term theory is disputed by some authors, but that discussion need not concern us here, other than to raise a warning not to treat lay theories like explicit scientific theories that are deliberately subjected to test. Like a schema, a folk theory is an organised body of knowledge about a particular domain, which people are assumed to make use of implicitly in their everyday lives, but which they could also reflect on and report explicitly if asked.

Such reports are likely to contain inconsistencies, at least initially, particularly if the person is reflecting on his or her beliefs for the first time or constructing views in response to novel questions. Unlike a schema, the content of a folk theory is contrasted with the content of a formal scientific theory covering the same domain, such as biology or physics. Research focuses on ways in which folk theories mismatch the relevant formal theory, and on the ways in which the content of individuals' folk theories can interfere with their learning about formal theories. Researchers have examined the content of lay theories of illness, and indeed the Health Belief Model[102] and related models of social cognition that aim to predict people's health-related behaviours, rest on an assumption that people hold sets of views about illness and health that can be elicited. Work on lay theories of biology and physics has gone more deeply into just what happens when there is an attempt to replace lay beliefs with formal scientific knowledge.

This literature highlights how difficult it seems to be for people to replace long-held lay assumptions with accepted scientific principles that conflict with them. Even when a person can report back the scientific principle and apply it correctly to particular settings, his or her answers to probing questions can reveal that a conflicting lay view is still prominent. The evidence suggests that a 'deficit' approach to teaching science, in which there is a direct attempt to replace incorrect lay beliefs with scientifically accepted knowledge, is likely to be unsuccessful.[103] DiSessa[103] offers an educational strategy based on four principles: "count on extended, cumulative learning to achieve deep conceptual change; engage experiential knowledge; focus on explanation and description; seek to learn more about students' cognitive ecology and develop strategies to suit" (pp. 726–7). This approach could effectively be applied to the task of helping the lay public to understand key features of clinical trials.

People do not only hold 'accepted scientific' and 'lay' beliefs which are inconsistent with each other. Within lay theories themselves there often appear to be inconsistencies. In the light of the literature on lay theories of science, for example, when talking about random allocation, a person may use the scientific definition in one context or situation, but draw on lay meanings in different contexts. If this were generalised to the findings reported earlier concerning lay understanding of terms such as 'random' and 'trial', then it might be expected that merely explaining the scientific meaning to trial participants will not be sufficient to prevent them from subsequently slipping back into the lay usage, which will be embedded in a much broader set of schemas.

Public understanding of science and science communication

Misunderstandings seem to arise from patients' failure to realise what is involved in an evaluation of a treatment's effectiveness, and in particular from failure to realise why treatment is allocated at random. More broadly, understanding the reasons behind the design of the trial implies acceptance that the aim of the trial is to advance knowledge, rather than to identify the best treatment for each patient within the trial. If patients do take a scientific perspective on the trial, this opens up the possibility that they will draw on lay conceptions of the scientific process. Inconsistency could now arise between lay assumptions about the nature and process of science, and the perceptions of the trial investigators or the scientific community more broadly. Patients' attitudes to science may also be relevant. A UK Government survey found that medical science is of particular interest to the public. Several studies involving patients have reported an overwhelmingly positive attitude towards medical research, but a much less positive one to randomised trials.

It seems likely that people who express a positive attitude to medical research assume that it will provide answers to important questions concerning prevention and treatment of illness. More generally, there is evidence that the lay public tends to think of science as a set of rules or a methodology which finds answers.[104] This, it is claimed, leads to unrealistic expectations, and to loss of public confidence in science and scientists when the media report disagreements between scientists. Such disagreements might be assumed to arise from vested interests, or seen as a sign of incompetence. Several authors have emphasised how important it is that lay people understand how science progresses, and accept that disagreements and uncertainty are inherent to the scientific process.[105]

If the public comes to accept that uncertainty and disagreement are inherent to the scientific process, it is not clear how this thinking would be applied to particular clinical trials rather than to broader clinical questions. Although current uncertainty is the justification for a trial, the implicit assumption is that the trial will reduce uncertainty. One speculation is that potential trial participants who

assumed that the results of the trial would be subject to alternative interpretations, rather than provide clear and undisputed new knowledge, may think that taking part was of doubtful value.

Summary and conclusions

The literature cautions us against believing that tinkering with details of trial information leaflets will have more than borderline effects on patients' understanding. Appelbaum and colleagues' account of the therapeutic misconception[59] is more in line with the evidence from experimental psychology. They suggest that patients invited to enter trials are likely to miss information both about equipoise (because they assume that the doctor knows what treatment is best for them) and about randomisation (because they assume that the doctor is going to offer them that treatment). If this is correct, the radical change to trial information sessions advocated by Appelbaum and Grisso[106] may help patients to move out of their standard consultation schema and process new information effectively. These authors have devised a schedule for interviewing patients after they have been given consent information, which contains, for example, a check that patients can report in their own words that they are being allocated treatment at random.

However, one potentially important aspect is ignored in their MacCAT procedure, namely patients' understanding of why the trial is being conducted in a particular way. There could remain an undiagnosed gap in patients' understanding of why the treatments are allocated at random in a trial. If so, patients may try to make sense of this in their own way, and may end up with important misconceptions. This is the focus of interest in the experimental work reported in the remainder of this report. It is left for future research to examine the role of patients' conceptions of the scientific process.

Chapter 3

Investigations 1–6: identifying background assumptions

Broad aims of investigations 1–6

The published evidence suggests that trial participants commonly fail fully to understand that their treatment was allocated at random, and that there are no good grounds for preferring one treatment over others (equipoise). The implication of such evidence is that consent or refusal to participate in trials might not be adequately informed.

In the past, trial information leaflets have varied greatly in the way they informed patients about random allocation and equipoise, as illustrated in the section 'Descriptions of randomisation and equipoise in trial information leaflets' (p. 24) and Appendix 5. As explained in that section, UK guidelines aimed at improving the content and readability of trial information have now been incorporated into MREC application procedures.[99] These guidelines for good clinical practice were produced by a working party that consulted with relevant experts and representatives of patient groups. The aim is to specify the minimum amount of descriptive information to be offered to potential trial participants, and to ensure the use of accessible language. The recommended wording in these guidelines for leaflets does not include an explanation or a justification for the use of randomisation in clinical trials. At the time of writing, to the authors' knowledge there has been no formal assessment of patients' understanding resulting from trial leaflets that conform to the guidelines.

The oral accompaniment to trial leaflets will continue to vary, both within and across trials, and is not subject to the same scrutiny by ethics committees as the written information. It is therefore important that the written information provided to potential trial participants is as helpful as possible. It is also likely that the material in the written information will influence the content of the oral accompaniment. For these reasons, these investigations focus on participants' handling of written information, even though in a real trial setting the accompanying oral information can play a very important clarifying role.

Theory (see 'Reflections drawing on theory and evidence from experimental psychology', p. 26) suggests that simplifying language and increasing readability, although helpful, will not be sufficient to overcome failures to understand the two central trial features of random allocation and equipoise. As illustrated by the results of qualitative studies such as those by Snowdon and colleagues[60] and Featherstone and Donovan,[14] people are active processors of information, not passive recipients, and they try to make sense of new information in terms of their existing knowledge base. There is a need to examine the background assumptions that people are likely to bring to bear when they are invited to take part in a trial.

Investigations 1–6 aimed to identify such background assumptions relevant to understanding of randomisation and equipoise. All participants were healthy volunteers who were invited to answer questions about a variety of hypothetical scenarios, some of which involved medical treatments and clinical trials. Research involving hypothetical scenarios is sometimes dismissed as irrelevant to questions of how best to handle consent in real clinical trials. Such dismissal might sometimes be appropriate. For example, results from hypothetical studies asking whether or not people would agree to take part in a particular trial, may bear little relation to real recruitment rates. The present research questions, however, are well suited to this method, and as will become clear, many of them could not have been answered in real clinical trial situations. The participants were not expected to simulate the anxiety that may be felt by patients invited to take part in a real clinical trial, or to imagine how they would behave in a real clinical setting. Rather, the idea was for participants to reason carefully about the possibility of a doctor being in a position of equipoise, for example, or about the scientific advantages of random allocation to treatment arms over patient choice, or the ethics of suggesting allocating patients to treatments at random. The aim was to compare participants' judgements across sets of carefully controlled scenarios, to be able to manipulate the relevant variables, and to build up appropriate sample sizes

rapidly and efficiently. These aims could not have been achieved in a clinical setting; the research questions are highly relevant to real trial settings, but could not be answered effectively within them.

To link with current best practice, the trial scenarios used the MREC recommended wording for trial information leaflets (see 'Descriptions of randomisation and equipoise in trial information leaflets', p. 24): "Sometimes because we do not know which way of treating patients is best, we need to make comparisons. People will be put into groups and then compared. The groups are selected by a computer which has no information about the individual, i.e. by chance. Patients in each group then have a different treatment and these are compared".

Several implicit assumptions underlie this description of what happens in a randomised trial:

- that a computer can allocate randomly, by chance
- that doctors may not know which way of treating patients is best
- that when we do not know which treatment is best, it is ethically acceptable to randomise
- that there are scientific benefits to random allocation.

A reader of the description who does not share one or more of these assumptions may well fail to understand it as intended.

A series of six investigations, designed to find out whether or not members of the public share each of these underlying assumptions, is reported here.

Acceptance that a computer can allocate randomly, by chance

Investigation 1 examines whether members of the public share clinicians' and researchers' understanding of what chance or random allocation is, and whether they accept that a computer that has no information about the individual can achieve random allocation.

Acceptance that doctors may not know which way of treating patients is best

Investigations 2, 3 and 6 examine people's acceptance of the possibility of equipoise. In investigation 2, this is studied in the context of comparisons between new and standard treatments: do people tend to assume that new treatments are better, thereby denying equipoise? Investigations 3 and 6 look at acceptance of the possibility of equipoise in the context of comparisons between two standard treatments, both of which are in common use but which have not been directly compared. Do people accept that an individual doctor may be genuinely unsure about which of the two is better? This is examined both in a hypothetical non-research treatment context (investigations 3 and 6) and in a hypothetical clinical research context (investigation 6). In a research context the state of equipoise is officially recognised and therefore perhaps easier for members of the public to accept.

Acceptance that when we do not know which treatment is best, it is ethically acceptable to randomise

Investigations 1, 3, 4 and 6 examine the acceptability of random allocation. In investigation 1, participants judged whether each of a list of allocation methods, some random and some not, would be acceptable in the context of a randomised clinical trial. In investigations 3 and 6, participants judged whether or not it would be acceptable for a doctor who was in equipoise to suggest deciding on a treatment at random, in a non-research or a research context. In investigation 4, participants judged whether it was acceptable for a doctor to invite patients to enter into a randomised trial, given that the doctor either had no preference between treatments, or had a slight preference.

Acceptance that there are scientific benefits to random allocation

Finally, investigations 4, 5 and 6 examine people's views about the scientific benefits of random allocation. Whether or not people find random allocation acceptable, they may or may not recognise that it has scientific advantages over other allocation methods such as allowing doctors and patients to choose their treatment in a trial context.

For some of these questions, people's answers may be particular to a medical context. People may, for example, be more ready to accept that a lawyer can be completely unsure about the best course of action than to accept that a doctor can. People may more readily recognise the scientific benefits of random allocation to answer a non-medical than a medical research question. Investigations 1, 3, 4 and 5 included non-medical comparison scenarios in order to establish whether or not participants' answers differed across contexts. If they did, and if the results were in the direction just suggested, this might open up the possibility of using analogies to clarify for potential trial

TABLE 1 *Main research questions asked in investigations 1–6*

Question asked of participants (approximate)	Investigation					
	1	2	3	4	5	6
Can a computer allocate randomly?	✓					
Might doctors not know which way of treating patients is best?		✓	✓			✓
Is it ethically acceptable to randomise given uncertainty?	✓		✓	✓		✓
Are there scientific benefits to random allocation?				✓	✓	✓
Does medical treatment versus a research context affect judgements?						✓
Does a medical versus non-medical context affect judgements?	✓		✓	✓	✓	

participants the rationale underlying RCTs. *Table 1* summarises the main research questions dealt with in investigations 1–6.

Participants in investigations 1–6

The participants were adults attending access and part-time further education and leisure courses taught at 19 community sites run by five colleges in Staffordshire and south Cheshire, UK. *Table 2* gives their ages, qualifications and occupations. Each investigation achieved a sample that included adults from a range of ages, backgrounds and levels of education, although as most classes contained a higher proportion of women, this is reflected in the samples. Subgroup comparisons by gender, age or qualification were not planned owing to small expected numbers in some cells. No participant took part in more than one study.

Procedures common to investigations 1–6

All data were collected using brief leaflets describing hypothetical scenarios, details of which are given within the reports of the individual studies. The scenarios and questions used in the leaflets were approved by the Keele University Psychology Department Research Ethics Committee. For each investigation equal numbers of each leaflet version were produced. For between-subjects designs the versions of the leaflets were ordered consecutively, ensuring that in a class of participants all versions of that experiment's leaflets were used and participants would not receive the same version as their neighbour. Random number tables were used to decide which leaflet version would be given to the first participant. For within-subject designs the order in which participants received the two leaflets was counterbalanced and the order alternated. Again, random number tables were used to decide which leaflet the first participant would receive first.

Lecturers of each class were asked for their permission to approach the students. Before the leaflets were distributed, a researcher (CK) outlined the general purpose of the research, and told participants that their participation was voluntary, that they could leave the leaflet blank without identifying themselves and that they would be anonymous. The leaflets were then distributed consecutively to the students in each class as they had chosen to sit that day. Students were asked to complete the leaflets without discussion with other students. Participants were supervised throughout testing to ensure that there was no cross-contamination between conditions.

When all students who were willing had completed the leaflets, the researcher asked whether any were prepared to volunteer to talk through their answers. Volunteers individually took their completed leaflets and left the classroom with the researcher to participate in a tape-recorded discussion of their answers, for which they were given a £5 voucher. After discussions were complete, the researcher returned to the class, debriefed them as to the aims of the investigation and answered any questions.

The average class size was nine students (range 2–22) and the response rate for completing leaflets was over 95%. Not all classes were represented in the taped individual discussions, because the timing of the classes and breaks determined whether such interviews would be feasible. Such constraints also determined how many volunteers could be interviewed from any one class, but the interviews were distributed across classes as much as possible.

TABLE 2 *Characteristics of participants in all studies*

		Investigation								
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
	No. of participants	130	130	82	67	67	128	128	130	128
Age (years)	Range	18–70	18–80	21–61	21–81	20–80	19–82	19–62	19–55	18–64
	Mean	32.36	30.90	30.73	39.42	44.15	47.34	30.78	31.38	31.87
	SD	10.07	10.20	9.10	16.76	16.49	14.88	8.21	7.88	8.49
	Missing, *n* (%)	1 (0.8)	1 (0.8)	1 (1.2)	1 (1.5)	8 (11.9)	3 (2.3)	0 (0)	3 (2.3)	0 (0)
Gender, *n* (%)	Male	41 (31.5)	35 (26.9)	20 (24.4)	15 (22.4)	11 (16.4)	30 (23.5)	17 (13.3)	29 (22.3)	16 (12.5)
	Female	87 (66.9)	94 (72.3)	62 (75.6)	51 (76.1)	48 (71.6)	95 (74.2)	111 (86.7)	97 (74.6)	110 (85.9)
	Missing	2 (1.5)	1 (0.8)	0 (0)	1 (1.5)	8 (11.9)	3 (2.3)	0 (0)	4 (3.1)	2 (1.6)
Occupation, *n* (%)	Professional/ managerial/skilled non-manual	44 (33.8)	37 (28.5)	15 (18.3)	8 (11.9)	10 (14.9)	44 (34.4)	19 (14.8)	37 (28.5)	15 (11.7)
	Manual/semi-skilled/ unskilled	41 (31.5)	45 (34.6)	16 (19.5)	11 (16.4)	8 (12.0)	30 (23.4)	42 (32.8)	58 (44.6)	38 (29.7)
	Retired/homemaker/ student/no occupation	34 (26.2)	41 (31.5)	49 (59.8)	47 (70.2)	39 (58.2)	48 (37.5)	62 (48.4)	25 (19.2)	71 (55.5)
	Missing	11 (8.5)	7 (5.4)	2 (2.4)	1 (1.5)	10 (14.9)	6 (4.7)	5 (3.9)	10 (7.7)	4 (3.1)
Highest educational qualification, *n* (%)	Degree	11 (8.5)	8 (6.2)	4 (4.9)	7 (10.4)	10 (14.9)	39 (30.5)	1 (0.8)	2 (1.5)	4 (3.1)
	Advanced GCE (18 years)	25 (19.2)	22 (16.9)	19 (23.2)	15 (22.4)	7 (10.4)	14 (10.9)	20 (15.6)	37 (28.5)	36 (28.1)
	GCSE/'O' level (16 years)	55 (42.3)	70 (53.8)	42 (51.2)	34 (50.7)	19 (28.4)	37 (28.9)	68 (53.1)	69 (53.1)	58 (45.3)
	Other/no qualifications	26 (20.0)	25 (19.3)	11 (13.4)	7 (10.5)	19 (28.4)	26 (20.3)	36 (28.1)	16 (12.3)	27 (21.1)
	Missing	13 (10.0)	5 (3.8)	6 (7.3)	4 (6.0)	12 (17.9)	12 (9.4)	3 (2.3)	6 (4.6)	3 (2.3)

Investigation 1: do members of the public understand and accept randomisation?

(See Kerr and colleagues[107] for a similar account of this investigation.)

Summary

Members of the public (n = 130) judged whether or not each of five methods of allocation to two groups was random, and whether or not each method was acceptable. Judgements were made in the context of a medical or a non-medical scenario: allocating patients to one of two consultants, or allocating students to one of two class trips. Most participants judged correctly that allowing people their preference was not random, and that the following were random: using a computer with no information about the individual (the recommended wording for MREC trial leaflets), tossing a coin and drawing out of a hat. Judgements were split over allocating people in turn, which is not a random allocation method but shares features with randomisation. Judgements were no different in the medical and non-medical scenarios. In a further scenario describing a randomised clinical trial, most participants judged the random allocation methods to be unacceptable, even when a justification for randomising was included. Only allocation by computer was less unacceptable when a justification was given, although it was still unacceptable to over half the participants. In conclusion, there was no evidence that potential trial participants misunderstand what random allocation means, but they may well find it unacceptable in a clinical trial context.

Background

The evidence reviewed earlier suggests that participants in RCTs often fail to realise that their treatment was selected at random from among those under comparison, and this raises concern that their consent may not be adequately informed. Potential trial participants may bring little prior knowledge about trial design, and are likely to be taken by surprise when informed about random allocation. For example, Ellis and colleagues[67] found that 31% of a sample of outpatients who were not trial participants were unaware that treatment is allocated by chance in a randomised trial. Furthermore, 74% thought that the doctor would ensure that they received the best of the treatments offered in a randomised trial.

One possibility is that the problem arises because participants do not know what 'random' means in this context. In a survey of terms commonly used in clinical trial consent forms, Waggoner and colleagues[69] report that only 22% of a general public sample knew the meaning of the word 'randomly' and only 4% of those without higher education knew the meaning of the word, although the published report does not specify what the criterion for understanding was. The authors suggest using 'by chance' or 'by the flip of a coin' instead. Featherstone and Donovan[14] suggest that trial participants interpreted 'at random' to mean 'without purpose', although from their qualitative study it cannot be inferred how common such a misconception is.

How can we judge whether or not potential trial participants have an adequate understanding of what random allocation means? One possible criterion is that participants must demonstrate explicit understanding by giving a verbal definition. Another possible criterion is that participants must demonstrate a working understanding by identifying examples of random and non-random allocation methods. If the participants' overall pattern of responses matches the pattern given by experts whose understanding is not in doubt, then one can infer that the participants have an adequate working understanding of random allocation. A working understanding of random methods of allocation, rather than verbally explicit understanding, is needed to make an informed decision whether or not to participate in a RCT. Accordingly, investigation 1 examined participants' working understanding.

Members of the public were set a task that required them to draw on their pre-existing working understanding of random allocation. They were asked to judge whether or not each of a set of allocation methods was random. The random methods in the set included the description of randomisation recommended by the MREC guidelines, "… by a computer which has no information about the individual" (see 'Descriptions of randomisation and equipoise in trial information leaflets', p. 24). The set included alternate allocation (allocate in turn), a method that is not random and is rarely used in clinical trials, but which is a possible alternative to random allocation as it can abolish selection bias equally well if applied strictly.[108] Judgements were elicited about random and non-random methods of allocation in two different scenarios, neither involving a clinical trial, one medical (allocations to one of two consultants) and the other non-medical (allocations to one of two class outings). This allowed the investigators to explore the possibility that judgements are influenced by the belief that decisions in medical situations are generally made on therapeutic grounds.[59]

Somebody who understands what random allocation involves may or may not consider it an acceptable procedure to use in a particular context. In addition to judging whether various methods of allocation would be random, participants judged whether each method would be acceptable in a hypothetical randomised clinical trial scenario. The justification given in the CERES guidelines[97] was used with half of the participants to assess whether its inclusion increased the acceptability of the various methods of random allocation. As with random allocation, alternate allocation does not allow patients or their doctors to select a treatment. It is interesting, therefore, to assess how acceptable it might be in the context of a clinical trial.

In summary, the aims of investigation 1 were to assess:

- participants' judgements of whether or not allocation methods are random in two hypothetical, non-trial scenarios, one medical and the other non-medical
- the acceptability in a hypothetical randomised clinical trial scenario of allocation methods previously identified by participants as random
- the effect on acceptability judgements of providing the CERES justification for the use of random allocation in clinical trials.

Method

Participants

There were 130 participants (for details see *Table 2*). Twelve participants were interviewed individually.

Design and materials

Each participant read a leaflet that first described one of two brief hypothetical scenarios, either the class trip scenario:

> "Imagine that as part of a course everyone is entitled to go on a free trip either to Birmingham or Barcelona. However, there is only funding for about half to go to each place. The organisers decide to divide the class into two groups by chance, this means putting people into either the Birmingham or the Barcelona group at random."

or the consultant scenario:

> "Imagine that a doctor has many patients with back pain. He can refer these patients to one of two consultants. One consultant is based at the local hospital, the other is based at a hospital 30 miles away. He can only refer about half of his patients to each consultant, so the doctor decides to divide the patients into two groups by chance, this means putting people into either the local consultant or the distant consultant group at random."

Immediately below the scenario there followed a list of five methods of allocating people to the two groups, and participants were asked to judge each as random or not random. The methods were:

A. Select the groups by a computer which has no information about each individual.
B. For each person toss a coin, heads means Birmingham/near consultant, tails means Barcelona/far consultant.
C. Put printed slips of paper, an equal number of each, into a hat and for each person take a slip of paper out of the hat.
D. Ask each person which they prefer.
E. Allocate each person in turn as they arrive.

The methods were listed in three different orders (varied between leaflets): DBEAC, ACDBE or CDAEB. After the list of allocation methods, leaflets contained a further scenario, giving a description of a hypothetical clinical trial:

> "Imagine you are asked to take part in some medical research to compare two treatments. Imagine doctors currently know that both treatments help, but do not know which treatment is better. The research involves giving you one of the two treatments at random."

Half the participants were given only that description. The other half of the participants were told that medical research often requires participants to be allocated to treatment at random, and the justification of randomisation taken from the CERES guidelines:

> "Randomised trials are the most exact and fair way to test which treatments work best. They are less likely to have, for example, people who are older or sicker in any one group. Each year thousands of people take part in them."

The five methods of allocation were listed again and participants judged whether each would or would not be acceptable in the trial. On the basis of pilot work the authors decided to leave it unspecified as to whether acceptability was to the research, to the participant or to both. This design produced four different leaflets:

- class trip scenario, then trial scenario with no justification for randomisation
- consultant scenario, then trial scenario with no justification for randomisation
- class trip scenario, then trial scenario with CERES justification for randomisation
- consultant scenario, then trial scenario with CERES justification for randomisation.

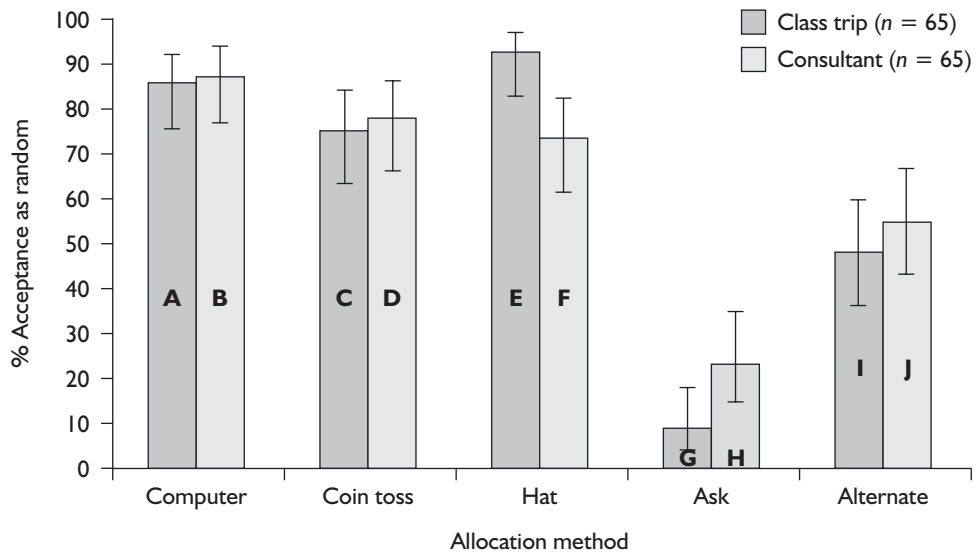
Procedure

Participants filled in their sheets in their class setting as described above, and then a few volunteers took part in audio-taped individual discussions with the researcher, explaining their judgements. These interviews were carried out to check the basis of individual participants' judgements of random allocation methods and their reasons for acceptability responses. No more than four students from any one class were interviewed, and a total of 12 individual interviews was carried out.

Results

Judgements of whether or not allocation methods were random

Figure 1 shows, separately for participants given the class trip or the consultant scenario, the percentage of people who judged each method as random. Confidence intervals at the 95% level (95% CIs) were calculated for the percentage of participants judging a certain way.[109] Where both the upper and lower limits of confidence intervals lie above 50% (e.g. the error bars for 'coin toss' in *Figure 1*) it was concluded that a significant majority of the group gave that judgement; where both limits of confidence intervals lie below 50%



A, Class trip/computer = 85.9% (95% CI 75.3 to 92.4%); B, consultant/computer = 87.3% (76.9 to 93.4%); C, class trip/coin toss = 75% (63.2 to 84%); D, consultant/coin toss = 77.4% (65.6 to 86%); E, class trip/hat = 92.1% (82.7 to 96.6%); F, consultant/hat = 73% (61 to 82.4%); G, class trip/ask = 8.1% (3.5 to 17.5%); H, consultant/ask = 22.6% (14 to 34.4%); I, class trip/alternate = 46.9% (35.2 to 58.9%); J, consultant/alternate = 54% (41.8 to 65.7%)

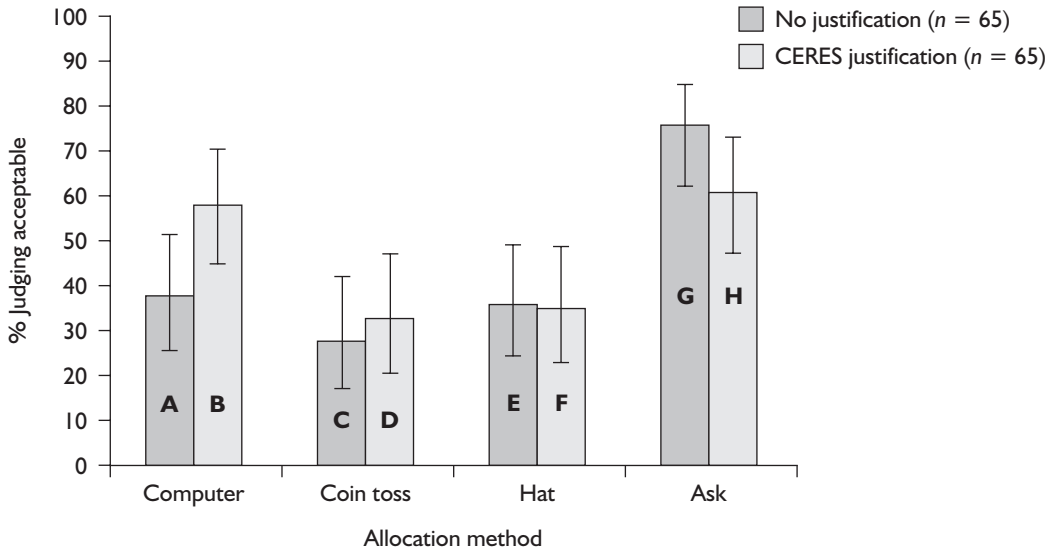
FIGURE 1 *Investigation 1: judgements of allocation methods as random*

(e.g. 'ask' in *Figure 1*) it was concluded that the majority of the group did not give that judgement. If the confidence interval spans 50% (see 'alternate' in *Figure 1*), it was concluded that neither judgement was given by the majority of the group.

The results in *Figure 1* show that most people, regardless of whether they read the consultant (medical) or class-trip (non-medical) scenario, correctly judged 'ask which they prefer' as not random, and 'computer', 'toss a coin' and 'draw out of a hat' as random. As a group, people had no consistent view (regardless of scenario considered) as to whether 'allocate in turn' (alternate) was random. As intended, the individual interviews provided a check of the basis of these judgements and supported the validity of these findings (although the number of interviews is insufficient to warrant more in-depth analysis). Participants reported that they based their judgements of random allocation on meaningful criteria such as the unpredictability of the result of the allocation ($n = 3$) (e.g. "it could be any"), the effectiveness of the method in achieving roughly half of participants in each group ($n = 5$) (e.g. "you would be able to get a balance"), avoiding bias or influence on the allocation ($n = 3$) (e.g. "nobody's got the influence to make the decision"), lack of choice ($n = 2$) (e.g. "because you wouldn't have any choice whatsoever"), not taking into account individual characteristics or circumstances ($n = 2$) (e.g. "half of them go there, half of them go there, you've got no information about them") and luck ($n = 2$) (e.g. "the luck of the draw").

Acceptability of procedures in a clinical trial context

Since the two scenarios showed similar patterns of judgements, responses in the two scenarios were combined for analysis of the judgements of acceptability. *Figure 2* shows the acceptability of the random methods ('computer', 'toss a coin', 'draw out of a hat') and the main non-random method ('ask which they prefer') in a randomised clinical trial among participants who correctly judged the random/non-random nature of the allocation method in the first scenario. The results are split by whether or not the participants were given leaflets with the CERES justification for randomisation. Confidence intervals at the 95% level are given for the percentage of participants, with or without the justification, who judged each allocation method to be acceptable. These were interpreted as before. Confidence intervals for the difference in these percentages were also calculated. The only difference CI that did not span zero (indicating that the presence or absence of the justification probably caused a differential response) was 'computer' (CI –0.373 to –0.016).



A, No justification/computer = 37.7% (25.9 to 51.2%); B, CERES justification/computer = 58.2% (45 to 70.3%);
C, no justification/coin toss = 27.7% (16.9 to 41.8%); D, CERES justification/coin toss = 32.6% (20.9 to 47%);
E, no justification/hat = 35.8% (24.3 to 49.3%); F, CERES justification/hat = 34.7% (22.9 to 48.7%);
G, no justification/ask = 75% (61.8 to 84.8%); H, CERES justification/ask = 60.4% (46.9 to 72.4%)

FIGURE 2 *Investigation 1: acceptability judgements for allocation methods in a clinical trial for participants given CERES justification or no justification*

The percentages (of those who identified the method as random) judging 'toss a coin' and 'draw out of a hat' as acceptable are very similar to each other and did not depend on whether the justification was given or not. A statistically significant majority judged each of these methods to be unacceptable. The other random allocation method, 'computer', was more likely to be judged acceptable by those receiving the justification, although still in neither case did a significant majority judge it acceptable. 'Ask which they prefer' was judged acceptable by a somewhat higher percentage of those who were not given the justification, although the confidence intervals show that this may have been due to chance.

The acceptability of 'allocate in turn' (alternate) is not included in *Figure 2* owing to its status as a non-random method, which nevertheless potentially achieves the reduction in selection bias that randomisation aims for. It is not therefore informative to consider acceptability judgements in light of whether or not they were judged random. 'Allocate in turn' was judged acceptable by 18 of those who received no justification for randomisation (28.6%, 95% CI 0.19 to 0.41, missing data $n = 3$) and by 18 of those who received the CERES justification for randomisation (29.0%, 95% CI 0.19 to 0.41, missing data $n = 2$).

The interviews contained discussion of why certain methods of allocation were acceptable and others not. Computer allocation, when found to be acceptable, was so because it has no personal information about you, it is the least open to bias and it is more removed (from the actions of the doctor) than other random methods. Some of the other random methods were considered unprofessional or not how participants would want to think their treatment had been decided. This excerpt from the fifth participant interviewed sums up many of these points: "I wouldn't want to think that my doctor had decided what I was going to have by flipping a coin, although it is a random way of doing, and the same with drawing a name out of a hat and yet I have no problem with a computer doing it … I think it's just the way it's, I don't know, a computer is a little more distant, again it's not the doctor doing it, he's allowing the computer to do it."

Discussion and conclusions

Most, but not all, participants judged correctly whether or not the allocation methods were random, irrespective of whether the setting was

medical or non-medical, and their judgements were apparently based on relevant criteria. Not surprisingly, participants as a group were divided as to whether allocating in turn was a random method: it could produce unbiased samples despite being a systematic method. It was concluded that the majority of participants shared the authors' concept of random allocation. This conclusion contrasts with that of previous authors who have suggested that the term 'random' is often not understood.[69] It may be argued that a person who cannot give an explicit definition of 'random' can nevertheless have a working understanding that is sufficient for interpreting the term in the way intended in trial information leaflets. These results support the current UK guidelines[99] in their recommended description of randomisation: "the groups are selected by a computer which has no information about the individual". The results give no great cause for concern that potential trial participants fail to understand that a computer can achieve random allocation, and this was the lone random method that was more likely to be judged acceptable when coupled with the CERES scientific justification for randomisation. No evidence was found that other analogies were more easily identified as random.

Many participants found randomisation unacceptable in the context of a medical trial. 'Allocate in turn', a non-random although scientifically appropriate method, was also judged to be unacceptable by the majority of participants. It is not clear why a large proportion of the people who correctly judged 'ask which they prefer' as not random, nevertheless saw it as an acceptable method of allocation in a randomised trial. One possibility is that these participants accepted that random allocation was to be used, but interpreted 'acceptable' as 'acceptable to patients'. Another possibility is that they rejected the idea that the trial should be randomised, and picked a different allocation method that they thought more appropriate. One reason participants might have taken this approach could be that from their perspective random allocation had no purpose within a trial context.

The results of this investigation suggest that failure to understand the meaning of random allocation is not the core reason for trial participants' difficulty in holding on to the fact of random allocation in a clinical trial context. Although some patients may not understand the meaning of the term, for many there are likely to be deeper reasons for their difficulty. They may not see any reason for random allocation in a trial context. Note, though, that somebody could fully understand the scientific reasons for randomising and yet still find random allocation unacceptable. The investigations reported below examine further the acceptability of random allocation in various contexts, and understanding of the scientific reasons for randomising.

Investigation 2: do members of the public assume that new treatments are better?

(See Kerr and colleagues.[110])

Summary

Concern has been expressed over a possible widespread belief among patients in trials that a new treatment is better than the standard, despite the lack of evidence of such superiority. Such a belief may interfere with comprehension of information about equipoise in trial information leaflets, and may render randomisation unacceptable. Members of the general public (n = 130) read a leaflet describing a hypothetical trial comparing two similar treatments for either arthritis or back pain. Half read that both treatments were standard and generally available, and the other half that one was new and available only within the trial. Participants rated any preference for one or the other treatment, gave written reasons and indicated their willingness to enter the randomised trial (used as a check on consistency, not as an indication of actual recruitment). Fifteen participants subsequently talked through their answers. Most participants expressed no preference for either treatment when both were described as standard. When one was new, more people with the arthritis, but not the back pain, scenario expressed a preference. Importantly, preference was not more likely to be for the new treatment. Rationally, those who preferred a freely available treatment were less likely to say that they would participate in the trial. In conclusion, the mere description of a trial treatment as new was insufficient to engender a preference for it over a standard treatment, although it may contribute to preference under certain additional circumstances.

Background

Investigation 1 found that many participants who apparently understood the meaning of random allocation found it unacceptable in a trial context. The unacceptability of randomisation may be tied up with failure to accept that there is genuine

uncertainty about which treatment is better. Participants may fail to understand or accept the state of clinical equipoise that justifies the trial, and assume that one treatment is already known to be better. They may fail to understand or accept that their own clinician is in a state of personal equipoise, and assume that he or she should recommend treatment based on a personal belief about effectiveness. Finally, they may have a preference for one of the treatment arms. Investigation 2 focuses on this latter possibility. The first two possibilities are assessed in investigations 3, 4 and 6.

Clearly, there are many circumstances under which potential trial participants may have a perfectly justifiable preference for one treatment arm over another, based on their own values and concerns. This investigation, however, examined whether or not members of the public tend to have an unjustified preference for new treatments. Such a preference would be understandable. Although an ethics committee will have agreed before any RCT can begin that existing evidence is consistent with a position of clinical equipoise, there is nevertheless likely to be a legitimate hope for benefits from new treatments among researchers and patients alike. For potential participants, such hope may be confused with expectation. Gallo and colleagues[85] point out the difficulty of expressing to patients the hope that a new treatment will prove to be better than the current standard treatment in some respect, alongside the current state of ignorance about the relative effectiveness of standard and new treatments. In their hypothetical trial they used a very clear statement of equipoise and its justifying role for the trial: "There is no evidence that one drug is better than the other. If we knew one was better than the other, we would not be conducting the trial".

Direct comparative evidence on whether or to what extent new treatments are found to be better than existing alternatives is rather weak; the evidence there is suggests that historically, new treatments have been as likely to be inferior as superior.[111] Furthermore, there are many examples where the new treatments not only failed to improve outcome, but actually made matters worse: high-performance oxygen therapy resulted in blindness when used to overcome breathing difficulties in babies,[112] thalidomide caused congenital abnormalities without alleviating nausea in pregnancy[113] and the use of albumin with critically ill patients may increase rather than decrease risk of death.[114]

If potential trial participants do tend to believe (not just hope) that new treatments will be better, this could interfere with their understanding and acceptance of random allocation. If the new treatment is available only within the trial, patients may consent to participate for the chance of receiving its assumed benefits. Those randomised to standard care may be disappointed because of their assumption that the new treatment is the better, possibly affecting their treatment adherence and outcome.

Concern has been expressed that trial participants may indeed hold unwarranted beliefs about the benefits of new treatments. McPherson and Chalmers[115] commented upon a "widespread and unsupported belief that new treatments are likely to be superior" (p. 78). The empirical information on this point is mixed. Snowdon and colleagues,[60] for example, interviewed parents of severely ill babies and found that the majority had a strong preference for the new treatment, but it is unclear whether this was specifically because it was new, or because of other features of the intervention. Madsen and colleagues[74] found that the wish to receive a new drug or investigation constituted a strong incentive to participate in a randomised trial but, again, the effects of newness per se were not separated. In two further studies,[85,94] using hypothetical scenarios, about half of the participants believed that new treatments were better than standard therapy and these participants were more likely to consent to participate in a hypothetical trial. However, neither of these studies specifically investigated the importance attached to a treatment being new, independent of other features of that treatment.

In contrast to the above studies, two studies suggest some preference for standard over new therapy. In one of these studies respondents thought that current treatments were generally successful and that new treatments were tested only on terminally ill patients or others with no treatment option.[66] Sheldon and colleagues[95] tested vignettes of a hypothetical cancer trial among female patients and found that many grossly overestimated the expected benefit of the standard treatment and those who did so were significantly less likely to opt for participation in the hypothetical trial. In summary, the literature does not separate the issue of mere newness of therapy from other factors that may affect willingness to be randomised, such as the success rate of the standard therapy or the nature and plausibility of the new treatment.

Investigation 2 investigated the impact of describing trial treatments as new or standard on treatment preferences and willingness to participate in a randomised trial. It would be extremely difficult to carry out a strict test of this in a real RCT as this would require varying only the way a particular treatment is described: as new or standard. The only way that this can be done ethically is in a hypothetical study.

Method

Participants

There were 130 participants (see *Table 2*). Fifteen participants were interviewed individually.

Design and procedure

Each participant read a scenario describing a randomised trial of two treatments, A and B, for either non-specific back pain or arthritis. For half of the participants in each scenario both A and B were described as usual, standard treatments; for the other half, one was described as new. The new treatment was A for half of these and B for the other half. This produced six versions in all: arthritis or back pain, standard versus standard or standard versus new, and A as new or B as new.

Each participant read a one-page leaflet describing one of two hypothetical scenarios: pulse treatments for back pain or drug treatments for arthritis. Participants were asked to imagine that they had the condition (back pain or arthritis) and that their doctor explains that there are two possible courses of treatment and asks whether they would be willing to take part in a study comparing the two treatments. The treatments were then described in a way that made them only slightly different from one another in ways that would be expected to be treated as trivial. For the back-pain scenario, treatment A was described as consisting of lots of small painless pulses and treatment B as consisting of fewer but larger painless pulses; both treatments took the same amount of time. For the arthritis scenario both treatments were drugs with no known serious side-effects; treatment A involved taking two tablets first thing in the morning and treatment B involved taking one tablet in the morning and one tablet in the evening.

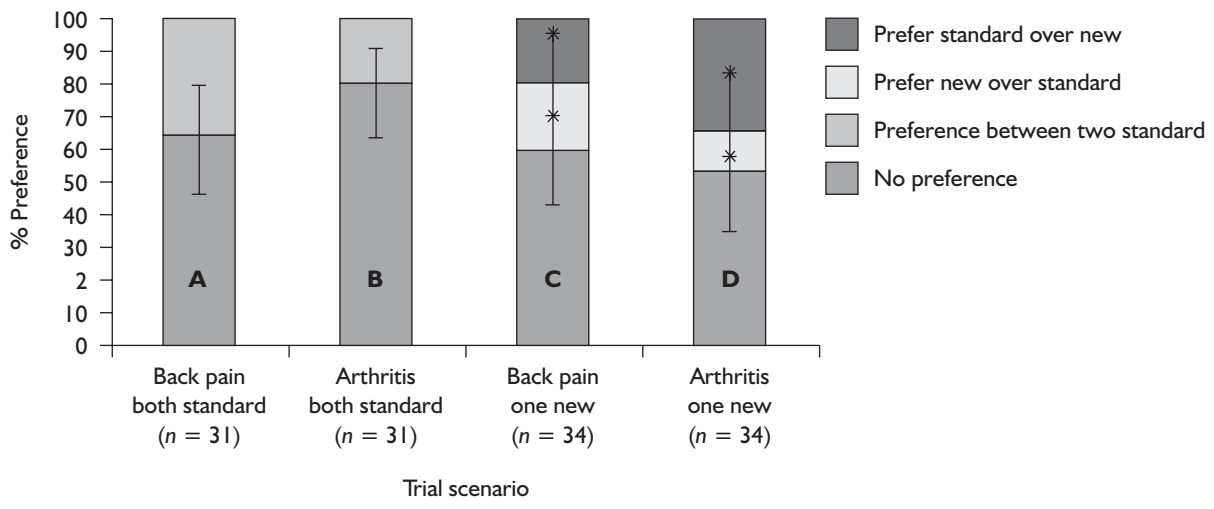
Participants were then told of the state of equipoise: "The two treatments have not yet been compared so we do not know whether one is better than the other", and that the study involved random allocation to treatments: "If you do decide to take part in the study comparing the two treatments, you will be allocated to have one of these treatments, either A or B at random. For example, the treatments would be selected by using a computer which has no information about you – i.e. by chance." They were then presented with this statement about the chance of receiving either treatment and a reminder that both treatments were standard, or which one was new, depending on the scenario: "There is an equal chance of you being assigned to have either treatment A, a standard [or *new*, depending on the scenario] treatment with many small pulses [or *that you take in the morning*], or treatment B, another standard [or *new*] treatment with few large pulses [or *that you take morning and evening*]." The scenario ended with the statement: "Neither you nor your doctor will have any control over which treatment you receive."

After reading one of the scenarios, all participants answered the same three questions:

1. "If you could choose, would you prefer one of the treatments over the other?" Participants indicated whether they were equally happy to have either treatment or had a weak or strong preference for either treatment A or treatment B.
2. "If you prefer one of the treatments what appeals to you about that treatment?" Participants who had expressed a preference gave brief, free-text answers.
3. "Would you be willing to take part in this study knowing you have an equal chance of being given either treatment?" Participants chose yes, no or don't know.

Fifteen volunteers from among the 130 participants were also interviewed individually. They were asked first to talk through their thoughts on the scenario they had been given and how they came to the answers they recorded. Any discussion of the new or standard nature of treatments that this general question elicited was encouraged by follow-up questions and probing for clarification of views. If participants did not discuss the new or standard nature of the treatments (if they had received a scenario describing trials comparing two standard treatments) they were asked to consider the difference that a new treatment might have made to their answers, or (if they had received a scenario describing trials comparing a new treatment with a standard treatment) what part the new or standard nature of the treatments had played in their answers.

The 15 interviews were transcribed verbatim and a thematic analysis was carried out on the interview



A, Both standard/back pain: no preference = 64.52% (0–64.52%), preference between two standard = 35.48% (64.52–100%) (95% CI 47 to 79%); B, both standard/arthritis: no preference = 80% (0–80%), preference between two standard = 20% (81–100%) (95% CI 63 to 90%); C, one new/back pain: no preference = 58.82% (0–58.82%) (95% CI 42 to 74%), preference new over standard = 20.59% (58.83–79.41%), preference standard over new = 20.59% (79.42–100%) [95% CI 10 (69) to 37 (96)%]; D, one new/arthritis: no preference = 51.61% (0–51.61%) (95% CI 35 to 68%), preference new over standard = 12.90% (51.62–64.51%), preference standard over new = 35.48% (64.52–100%) [95% CI 5 (57) to 29 (81)%]

FIGURE 3 *Investigation 2: expression of treatment preference when both treatments were described as standard or one was described as new*

transcripts using a grounded theory approach. Analysis was started by one author (CK) carrying out a line-by-line annotation of each interview transcript using labels to summarise the meaning of each phrase or sentence. All of the annotation labels were then collated into a list with their source interview quotes to be examined for similarity. Identical or very similar annotation labels were grouped and considered initial themes. An initial interpretation was carried out to summarise and note connections between themes. Where connections were very strong, themes were collapsed together. The analysis, including all source quotations, was passed to a second author (ER) to validate against the 15 full interview transcripts, and modified in light of comments and queries raised by this process.

Results

Treatment preferences

Figure 3 shows the percentage of participants who preferred one of the treatments when both were standard, or who preferred either the new or standard treatment when one was new. Since relatively few participants expressed a preference for one or other treatment, weak and strong preferences were combined to avoid low frequencies in the analyses. Unexpectedly, different patterns of preferences were found in the back-pain and arthritis scenarios, so the group was split by scenario for analysis. For both back pain and arthritis, when both treatments were described as standard the majority of people expressed no preference for one treatment over the other. For the back-pain scenario this was also true when one of the treatments was described as new; there was no significant difference between standard versus standard and new versus standard conditions [$\chi^2 = 0.22$, non-significant (ns)]. For arthritis, more people expressed a preference for one treatment over the other when one was described as new compared to when both were described as standard ($\chi^2 = 5.44$, $p = 0.031$, two-tailed, $w = 0.3$, a moderate effect size) (see Cohen[116]). However, for both back-pain and arthritis scenarios, preferences expressed in the new versus standard conditions were statistically no more likely to be for the new treatment than for the standard (back pain 7 new versus 7 standard, binomial test, ns; arthritis 4 new versus 11 standard, binomial test, ns).

Treatment preference in relation to willingness to participate in an RCT

Since the standard treatments were available outside the trial, participants with a preference for one of those should rationally refuse to participate in the trial to ensure that they received their preferred treatment. In line with this reasoning, participants with a preference for a standard treatment were less willing to enter the trial (15 yes, eight no) than were participants with no preference (73 yes, one no), regardless of whether they were in the standard versus standard or new versus standard conditions: ($\chi^2 = 23.30$, $p < 0.001$, two-tailed, $w = 0.5$). Participants who answered 'don't know' to whether they were willing to participate in the RCT ($n = 16$) were excluded from this analysis.

Preferences for the new treatment were too rare to analyse statistically or interpret with confidence. Six out of the 11 participants who preferred the new treatment (only available in the trial) reported being willing to participate in the RCT, the rational judgement to ensure the only chance to receive their preferred treatment. This compares with three of the 11 preferring the new treatment not willing to participate in the RCT. The other two participants with a preference for the new treatment did not know whether or not they were willing to participate in the RCT. Note that the researchers did not expect to draw any inferences from these data about absolute levels of willingness to participate in real trials. The interest was in the relationship with preference judgements, as a way of checking on the consistency of participants' judgements across questions.

Interviews

Three themes were identified that summarised the basis of interview participants' treatment preference or lack of preference:

- **New or standard nature of treatment**: whether or not a treatment was described as new was mentioned in connection with some treatment preferences, for example, "I would be quite happy to try something because it may be a better treatment, it might make you feel better" [participant 15 (P15)]. However, other participants had reservations. Two participants interpreted new to mean that a treatment had not been subjected to much previous research "it's a new thing come out and there's not been a lot of research into it and you're not sure" (P5), while two others presumed that a new treatment must have been subjected to adequate testing for it to be at a human research stage, "Once they've got to this stage, researching on people, they've got a pretty good idea" (P7). Related to this was a self-awareness of ignorance of the research process, "I have no knowledge of what tests these are required to go through before they are tested on people anyway" (P12). In general, participants were less questioning of standard treatments, for example, "has been researched into it, has been used longer, so they know whether there's side-effects or whatever" (P5). Their assumptions about standard treatments were reflected in the terms they used to refer to a standard treatment: "tried and tested" (P12), "the known one" (P13).
- **Treatment similarity or minimal difference**: participants compared the two treatments on various aspects (using the descriptive information given) to come to a conclusion about how similar they were. Participants had differing views as to what was the most important aspect of a treatment. Five participants viewed the effectiveness of treatment as the most important aspect, mainly coming to the conclusion that the treatments described in the scenarios were similar in this respect, for example, "they've got the same effects at the end of the day" (P2). However, individual participants also focused on other aspects of the treatments, including risks, "So they were equally as dangerous or not dangerous because there were no serious side-effects with either" (P7); relative benefits, "I can see two sides of it" (P1); inconvenience, "the one that would be less intrusive on my life, basically, that would allow me to carry on with my normal life" (P11); and doctors' preference, "it depends what my doctor suggests" (P3). Participants attempted to gauge the extent to which the treatments differed and decide whether this difference mattered.
- **Desperation**: in the scenarios presented several participants talked about a lack of preference in treatment due to desperation for anything that worked or might work. Arthritis in particular was perceived as a condition of severe and constant pain with little relief from current medication, "if you've got arthritis then anything's worth a try … I wouldn't be choosy" (P4). However, this view was also voiced about back pain by two participants who themselves reported suffering from chronic back pain, "I'll try anything to relieve my back pain" (P11).

Two additional themes of discussion related to potential influences on interview participants' preferences for new or standard treatments:

- **Different conditions**: four participants discussed how being diagnosed with a potentially life-threatening illness would make them more likely to risk new treatments and in some cases form a strong preference to have a new unproven medication over the standard, "I mean for instance if I was suffering from cancer and there was a new drug which hadn't gone through all the trials, but there was a possibility that it might be successful, then I would be more than willing to try it" (P15). This theme echoes thoughts expressed about desperation in the arthritis scenario and by those suffering from chronic back pain. Participants indicated that both of these conditions were considered to be serious, and so the risks of a new treatment may be acceptable. However, a preference for a new treatment was more often expressed in connection with life-threatening conditions.
- **Other treatment information**: five participants discussed how certain information, particularly about the efficacy of the standard treatment, would affect their treatment preference. An effective standard treatment would lead them to form a preference for it and not wish to try the new treatment, "the standard drug, well if that helps me with my pain I don't think I would be bothered about trying a new one" (P5). An ineffective current or previous treatment would lead them to take a chance on the new treatment being more effective, "If I'd had something before and the standard one hadn't worked then I'd want something new, if there was something new available I would want something new, that wouldn't apply, I really wouldn't want the standard one" (P14). Individual participants discussed how information on side-effects of the standard treatment would affect their treatment preference, "if like I say there is some even mild side-effects to the standard established drug that might have swayed me to have a strong preference or a weak preference either for the new one" (P12); likewise information on the effectiveness of the new treatment, "the new treatment was new and innovative, perhaps they were getting good success rates with it, perhaps I'd try it then" (P14).

Discussion and conclusions

The results provide no evidence that merely labelling a treatment as new is sufficient to engender a preference for that treatment. In both scenarios describing non-life-threatening medical conditions, the majority of participants did not express a preference for one treatment over the other when treatments were standard and differed only in minor ways. In the back-pain scenario the description of a treatment as new or standard had little impact on treatment preferences in terms of either the numbers expressing a preference or the direction of the preference. In the arthritis scenario more people expressed a treatment preference when one of the treatments was described as new, but the trend, backed up by the reasons given for individual preference, was for the standard rather than the new treatment.

The suggestion by McPherson and Chalmers,[115] which was grounded in experiences of real trials, perhaps indicates the importance of testing out such impressions in the more controlled conditions possible with hypothetical scenarios. In each scenario where both treatments were standard the majority of participants expressed no treatment preference, demonstrating that differences between treatments (necessary for the hypothetical trial to make sense) were mainly considered trivial. The separate analyses conducted for the back-pain and arthritis scenarios, due to an unexpected different pattern in results, meant a drop in the power of each. This meant that a large effect size for preference could only be confidently detected between new and standard. The fact that two independent samples were obtained to some extent compensates for the drop in power. Importantly, in both samples the small numbers that make analysis and interpretation of the direction of preferences so risky are a consequence of the large proportion of participants who expressed no preference for a new over a standard treatment or vice versa, a strong finding in itself.

It remains possible that there really is a widespread preference for new treatments that was not detected in this investigation. However, the rational connection between participants' preferences and their willingness to enter the hypothetical trial makes it likely that they were processing the information given to them appropriately. Furthermore, the comments made in the interviews suggest that participants could reflect sensibly on issues arising from the testing of new treatments, and considered these within a context of other variables that may enter their decision-making in a real-life setting, such as the severity of the medical condition and the known effectiveness or side-effects of the standard treatment.

The superficially contradictory findings from previous studies might be reconciled if patients' preferences for new or standard treatments vary

with factors such as severity of condition or believed/experienced effectiveness of the standard treatment. Indeed, it would be rational for patients who are deciding whether or not to take part in a trial to engage in a risk–benefit analysis of the treatments under comparison, taking into account their personal values as well as what is currently known.[117] Then, a preference for a treatment based on its newness may be justified in very limited circumstances, namely when the alternatives are not expected to work well. Such a preference for uncertain new treatments ahead of standard care known to offer only limited, if any, benefits could be rational and may be grounded more in hope than in expectation of a more favourable result.

Investigation 3: do members of the public accept doctors' individual equipoise and suggestions of random allocation?

(See Robinson and colleagues.[118])

Summary

In a between-groups design, this investigation compared participants' (n = 82) judgements about the possibility of a doctor or a lawyer being completely unsure about which of two treatments, or two courses of action, was best. Participants went on to judge whether it was acceptable for a doctor or lawyer who was completely unsure to suggest letting chance decide which treatment or which course of action, or to choose. Neither the medical nor the legal context involved research, since the study was interested in whether participants considered mere uncertainty to be sufficient grounds for deciding at random. Finally, participants were asked whether a doctor or lawyer with a slight personal preference for one treatment or course of action should reveal that to the patient or client. There was no difference in judgements according to context. Participants were split as to the possibility of individual equipoise. Most, even among those who accepted the possibility of equipoise, judged it unacceptable to suggest letting chance decide which treatment or course of action to select. There were no grounds for concluding that mere uncertainty was considered to be sufficient grounds for randomising. The majority of participants judged that the doctor or lawyer should reveal his or her personal preference, even though other professionals disagreed with it.

Background

The study assessed participants' acceptance of the possibility of an individual doctor being in a state of complete uncertainty between two possible treatments, and their views about the acceptability of such a doctor suggesting deciding by chance which of two treatments to offer. It may be rare for individual trialists to be in equipoise when there is a state of collective equipoise that provides ethical justification for the trial.[87,88] However, none of the patient information sheets seen by the authors makes a distinction between individual and collective equipoise. Statements such as 'doctors do not know which treatment is best' can be interpreted as implying individual as well as collective equipoise. The researchers decided therefore to find out whether participants accepted a move from individual equipoise to an offer of random allocation, instead of attempting to explain the more complicated situation of collective equipoise without individual equipoise. Note that in this investigation participants were asked about the acceptability of offering random allocation given uncertainty. There was no scientific rationale for randomising since there was no research context. Participants were also asked whether or not a doctor who had a slight preference for one or other of the treatments, which was not necessarily held by colleagues, should share that view with patients.

To find out the extent to which participants' views were particular to a medical context, a parallel legal scenario was created. This involved a lawyer who could advise a client either to go to court or to settle out of court and in particular circumstances might be in equipoise about which was the better course of action. In both the medical and the legal scenarios a lay person consulted an expert professional about a matter of personal importance, and could reasonably expect that professional to act in their client's best interests. When health and illness are involved, people may be particularly inclined to seek or assume certainty rather than uncertainty. If so, the possibility of uncertainty, and of allocating on the basis of chance, may be better tolerated in the legal than in the medical context.

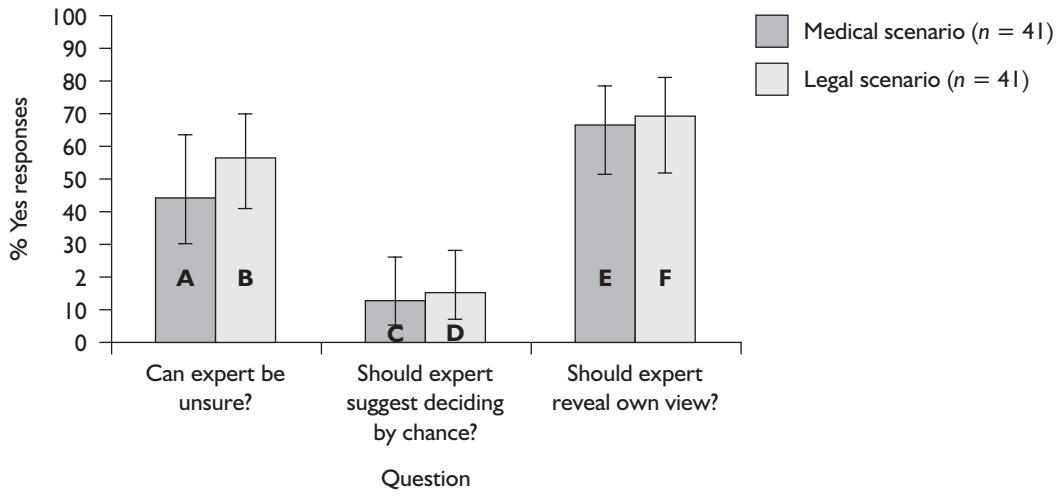
Method

Participants

There were 82 participants (see *Table 2*). Nine participants were interviewed individually.

Design

Participants received either a medical or a legal scenario.



A, Medical scenario/can expert be unsure = 43.9% (95% CI 30 to 59%); B, legal scenario/can expert be unsure = 56.09% (95% CI 41 to 70%); C, medical scenario/should expert suggest … = 12.20% (95% CI 5 to 26%); D, legal scenario/should expert suggest … = 14.63% (95% CI 7 to 28%); E, medical scenario/should expert reveal own view = 65.85% (95% CI 51 to 78%); F, legal scenario/should expert reveal own view = 68.29% (95% CI 51 to 80%)

FIGURE 4 *Investigation 3: yes responses to questions*

Procedure

Participants read one of two scenarios that provided either a medical or a legal context for professional uncertainty. The medical context was the back-pain scenario used in investigation 2, assessing two usual treatments, A and B, one involving lots of small painless pulses within a treatment session and the other involving fewer but larger painless pulses. The two treatments had not been compared so the doctor did not know whether one was better, and only one could be used on any one patient. The legal scenario described a similar situation of uncertainty: participants were asked to imagine that they had been injured in an accident and had consulted a lawyer about making a claim for compensation. The lawyer explained they could either settle out of court or go to court. The lawyer was sure that it was better to go to court if the offer was low, and better to settle if it was high, but the lawyer was unsure which was better if the offer was of a medium amount. After participants had read either the medical or the legal scenario, they read and gave yes or no answers to two questions:

- "Do you think the doctor/lawyer could ever be completely unsure about which of two treatments is better/what's best, and truly not prefer one treatment/course of action over the other?"
- "If the doctor/lawyer really was completely unsure, and did not prefer one over the other, would it be acceptable for the doctor/lawyer to suggest deciding at random? This would mean, for example, selecting a treatment/course of action by using a computer which has no information about the individual, i.e. by chance."

This final sentence was taken from the guidelines for trial information leaflets produced for UK MREC.[99]

Finally participants were asked, "Now suppose the doctor/lawyer has a hunch that one treatment/course of action is better than the other, even though he or she is pretty unsure and knows that other doctors/lawyers might disagree. Should the doctor/lawyer reveal his or her view to you the patient/client?"

Results

The results are summarised in *Figure 4*, which shows that for both the medical and legal scenarios around half of the participants thought that the doctor or lawyer could be unsure, a minority thought that it was acceptable to suggest deciding by chance, and a majority thought that doctors or lawyers should reveal their own hunches.

Medical versus legal scenarios

None of the comparisons that follow revealed differences between the legal and medical scenarios: 95% confidence intervals of the

unpaired difference between scenarios spanned zero in all cases.

- **Acceptance of the possibility of uncertainty**: for both the medical and the legal scenarios, participants were split as to whether or not the doctor/lawyer could be completely unsure. In both cases confidence intervals spanned 0.5: medical scenario proportion 'yes' = 0.44, 95% CI 0.30 to 0.59; legal scenario proportion 'yes' = 0.56, 95% CI 0.41 to 0.70.
- **Suggesting deciding by chance**: for both scenarios, significantly fewer than half of the participants judged that it would be acceptable for the doctor/lawyer to suggest deciding by chance when he or she was completely unsure: medical scenario proportion 'yes' = 0.12, 95% CI 0.05 to 0.26; legal scenario proportion 'yes' = 0.15, 95% CI 0.07 to 0.28. A problem with interpreting this result is participants' unwillingness to accept that the doctor or lawyer could be completely uncertain; some 'no' responders may have been denying the possibility of uncertainty rather than the acceptability of suggesting deciding by chance. However, in the subset of participants who accepted the possibility of uncertainty, only two out of 18 judged that it would be acceptable for the doctor to suggest deciding by chance, and five out of 23 judged that it would be acceptable for the lawyer to do so.
- **Revealing own view under uncertainty**: the majority of participants judged that a doctor or lawyer should reveal his or her own view even if it was not shared by other professionals, although for the medical scenario the proportion was barely above chance (medical scenario 95% CI 0.51 to 0.78, binomial test, ns; legal scenario 95% CI 0.64 to 0.80, binomial test $p = 0.029$).
- **Qualitative data from interviews**: the interviews suggested that participants understood the scenario and questions as intended. Comments about the legal and medical scenarios were remarkably similar. *Table 3* contains quotes from interview participants illustrating the following themes. Some participants acknowledged individuals' uncertainty, while others assumed that even if an individual did not know which course of action to take, somebody else was likely to know. Others assumed that a competent professional would or should know. Only one of the nine interviewees thought that it was acceptable to suggest deciding by chance; the others found it unacceptable. Both sides of whether a doctor should reveal a hunch about which treatment was better were represented in the interviews: "No because it's only a hunch, it's not proven or anything, is it? The hunch could be wrong"; "It's all about proof and what he says is going to have an impact, isn't it?"; "I'd welcome that"; "Their advice is what I've gone for … whatever they say I think I always expect to be right". Our interviewees thought that the lawyer should reveal a hunch: "They should be honest with you particularly if they (lawyer) are acting for you"; "They could say well I'm not sure, it's up to you, don't let me sway your decision".

TABLE 3 *Investigation 3: illustrative quotes from interviews (n = 9)*

Uncertainty (equipoise)	Acknowledging uncertainty: "He'll get results but he won't necessarily get all the feedback to him, will he, of the broader picture" (doctor) "Lawyers will never know everything, they will never know the entire story" (lawyer) Uncertainty as ignorance: "If they don't know they should send us to a specialist … who should provide that information" (doctor) "I'd have thought if he was totally unsure why not refer to somebody who was sure about what would be best for you?" (doctor) Professionals should be certain: "They must know quite a bit about each one … they should know which one would be best in your circumstances" (doctor) "I wouldn't think he would really be unsure about what's best, that's why you would go to them, wouldn't you?" (lawyer)
Deciding by chance (randomisation)	Acceptable to decide by chance: "I think it'll be all right to select at random seeing as they are both roughly the same sort of treatment" (doctor) Unacceptable to decide by chance: "I don't think chance decisions should be made with your health" (doctor) "I think it would be pretty unprofessional, I mean he's got other lawyers in his company that can advise … I mean taking a chance is probably too much" (lawyer)

Discussion and conclusions

None of the results suggested that participants thought about uncertainty any differently in the medical and legal contexts, and in both cases around half denied the possibility of individual equipoise. Given the suggestion above that trialists may often have a preference for one of the treatments, it could be argued that the participants' views were accurate. However, the interviews provided no sign that participants accepted collective equipoise and assumed that individuals would have different views within that. Rather, the comments suggested that at least some participants assumed that the required knowledge would or should be available, and the individual professional need only seek advice from others to reduce his or her uncertainty. Although the medical scenario stated that the two treatments had not been compared, participants apparently often failed to realise or accept the implications of the absence of comparison.

Even more striking than the lack of acceptance of individuals' uncertainty was the view that it was not acceptable for the uncertain doctor to suggest deciding by chance. These results indicate that potential trial participants are unlikely to accept that mere uncertainty, without any scientific context, provides sufficient grounds for randomising. In investigation 6 this was checked in a slightly different way, by stating that the imaginary patient was equally willing to receive either treatment.

Finally, a small majority of participants preferred the doctor or lawyer to reveal his or her hunch about what was best. This may suggest that participants valued the individual relationship with the professional, rather than viewing him or her merely as the means of access to agreed-upon knowledge.[117]

Investigation 4: do members of the public believe that random allocation has scientific benefits?

(See Robinson and colleagues.[118])

Summary

In a repeated measures design, participants (n = 67) read two scenarios that described research contexts. One context involved a group comparison between two medical treatments, and the other a group comparison between two methods of treating sheep for infection. Participants judged how sure experts would be about which treatment or method was better if patients or farmers were allocated to treatment groups at random, and how sure if allocation was by choice. In the medical scenario they were also asked whether it was acceptable for a doctor with no personal preference, or with a slight preference for one of the treatments, to invite patients to take part in a randomised trial. In the medical context there was no sign that participants saw any scientific benefit to random allocation over doctor/patient choice: certainty ratings were no different in the two conditions. In the sheep scenario participants judged that knowledge would be more certain with random allocation than with farmer choice, but comments made in interviews suggested that participants unexpectedly assumed that farmers given free choice would avoid one of the treatment methods. There was no sign of genuine understanding of the scientific reasons for randomising. Participants judged that it was more acceptable for a doctor with no personal preference to invite patients to enter the trial than for one with a preference, although in both cases the majority of participants judged it acceptable to offer the invitation.

Background

There is clear evidence from investigations 1 and 3 that participants found random allocation unacceptable. In those investigations, participants were expected to take the perspective of a patient, in a trial context in investigation 1 and in a non-research treatment context in investigation 3. In investigations 4 and 5 participants were encouraged to take the scientific perspective of trying to advance knowledge. Given that the recommended MREC wording for trial information leaflets includes no scientific justification for randomising, this study examined whether, in the absence of any explanation or justification for randomising, participants recognised that random allocation has scientific benefits over allowing patients and doctors to choose which treatment to have.

Again, context effects were assessed. In investigation 4 the comparison scenario involved two ways of applying chemical treatment to sheep. Farmers could be allocated one of the two methods at random, or could be allowed to choose the method for their flock of sheep. The scientific benefits of random allocation may be less easily recognised in the medical scenario, owing to interference from the knowledge that doctors and patients normally choose the treatment that they think is most suitable.

Finally, findings from investigation 3 were followed up. There, around half the participants did not accept that a doctor could be without a preference between treatments, and most judged that a doctor should reveal his or her preference to patients even when it was not shared by other doctors. In investigation 4 related questions were asked, but in a research context. The medical scenario described two doctors with differing treatment preferences and asked participants to consider the acceptability of these doctors inviting their patients to participate in the randomised trial. If, as the previous results indicate, participants tend to assume that doctors will have a treatment preference, how acceptable do they find it for such a doctor effectively to suggest deciding treatment by randomising?

Method

Participants

There were 67 participants (see *Table 2*). Eight participants were interviewed individually.

Design

Participants read both a clinical trial scenario and a sheep-dip scenario, with order of presentation alternated between subjects.

Procedure

For the clinical trial scenario, participants read: "Doctors sometimes have to make careful comparisons between two treatments in order to increase our knowledge about which is the best one. Below is an imaginary account of a typical comparison. We would like your views about how this should be carried out." There followed the description of treatments A and B for back pain, used in investigations 2 and 3. The proposed study was then described: "Doctors want to compare the two treatments in a scientific study. 500 patients with back pain have agreed to take part. Half will be given treatment A and half will be given treatment B. This will be decided randomly, for example the treatments would be selected by using a computer which has no information about the individual, i.e. by chance." Participants were then asked "Once the study is done, how sure do you think doctors would be about which is the better treatment? Remember that treatments were allocated at random and neither doctor nor patient could choose which treatment a patient had." Participants judged whether they thought doctors would be very sure (4), fairly sure (3), fairly unsure (2) or very unsure (1), or indicated that they did not know. Next, participants were asked, "If instead, the doctor and patient had chosen which treatment each patient was given, how sure do you think doctors would be about which is the better treatment?" Participants judged on the same scale as before.

In the final section of the trial scenario, participants were asked to imagine that one doctor involved in the study (Dr Smith for half of the participants and Dr Jones for the other half, just in case name had any effect) thinks that one of the treatments (treatment A for half of the participants and treatment B for the other half) might be the better, even though "as yet there is no firm evidence for this and other doctors think that treatment B/A is better. If Dr Smith's patients agree to take part, then this would mean that some of them would be randomly assigned to have treatment B, the one Dr Smith doesn't think is as good. Do you think it would be right for Dr Smith/Jones to invite his patient to enter the study?" Participants judged on a five-point scale from 'definitely wrong' (1) through 'don't know' (3) to 'definitely right' (5). Participants then made the same judgements about another doctor, Dr Jones/Smith, who "thinks both treatments are useful but is unsure as to which one is better". Half of the participants made this latter judgement before the one about the doctor who had a preference, and half made it afterwards.

The other scenario described scientists' comparison between two ways of preventing sheep from developing infections. One involved dipping the sheep in a trough of chemicals, and the other involved spraying the sheep with the chemicals as they passed through a plastic tunnel. Random allocation was described as in the trial scenario and participants judged how sure scientists would be at the end of the study about which treatment was the better, using the same scales as for the trial scenario. Finally, participants judged how sure the scientists would be if farmers had chosen which treatment to use on their farms.

Results

Certainty judgements

The results suggest that participants as a group did not think that randomisation offered any advantage in the clinical context, though they may have done so in the context of sheep: the mean certainty score (SD) for the clinical trial scenario with random allocation was 2.74 (0.70), and with patient choice was 2.74 (0.83). For the sheep-dip scenario the corresponding figures were 3.00 (0.63) and 2.62 (0.86). The certainty scores (1–4) were analysed using analysis of variance (ANOVA) with scenario (clinical trial or sheep dip) and allocation method (random or choice) as repeated

TABLE 4 *Investigations 4 and 5: illustrative quotes from interviews (n = 8, n = 8)*

Randomisation or deciding by chance	Randomisation no better than patient choice: [with randomisation or choice] "We don't know if they are all suffering from the same sort of back pain, there's too many uncertainties … I just think that the findings would be unreliable" (investigation 4, medical) [with randomisation or choice] "They are not all being kept in identical conditions so there's too many other variants that could affect the outcome of the test … I think you need some control in there for the results to have any real bearing" (investigation 4, sheep treatment)
	Randomisation can reduce bias: "You would get a good mixture", [but with choice] "That would be unsure because you would get so many patients want to do it one way and so many patients do it the other way, you wouldn't get a good mixture of the treatments" (investigation 4, medical) "You're going to be very honest as to whether it's worked or not", [but with choice] "Some people have expectations, great the doctor says I'm going to feel better so I feel better now" (investigation 4, medical)
	Randomisation results in equal groups: "they are going to like have been tested themselves each in equal amounts", [but with choice] "maybe one washing powder would have been chosen more than the other" (investigation 5, washing powder)
Choice	More information taken into account with choice than randomisation: "Because the Dr would know the patients' situation, so he would be able to distinguish which one of the two treatments would probably work better in that situation so he would be able to clarify a bit more" (investigation 5, medical) "They might have an understanding of what's best for them …" (investigation 4, sheep treatment) "they know the situations don't they so … they'd know which one would probably be better for them" (investigation 5, washing powder)
	In light of no benefit from randomisation choice is better: "at least you have the choice. It's better to have a choice than to have no choice at all" (investigation 5, washing powder)
Differences between contexts	Lack of variation or influence of sheep (investigation 4) "Sheep are sheep at the end of the day …. I think because it is totally fifty–fifty on the treatment they would be very sure what the outcome would be"
	Strong farmer preferences (investigation 4) "I'm looking at sort of financial reasons … to do things they have done in the past …. They might want to stick with the dip"

measures, and order of scenarios (trial or sheep dip first) as a between-group factor. Participants who indicated that they did not know were omitted ($n = 4$). There were no significant main effects, but the interaction between scenario and method was significant: $F_{1,59} = 9.86$, $p = 0.003$, partial $\eta^2 = 0.143$. This was due to participants' judging that with sheep treatments, scientists would be more sure with randomisation than farmers' choice, $t_{60} = 2.646$, unadjusted $p = 0.01$, $d = 0.51$, but with medical treatments there was no difference between judgements of how sure doctors would be with randomisation or choice.

Qualitative data from interviews

Interviewees' comments gave some indication of what they thought about the consequences of random allocation in comparison to letting patients and doctors choose their treatment.

Table 4 contains illustrative quotes from this (and the next) investigation. A recurring theme was the idea that more information is taken into account with patient choice and so the outcome is likely to be better than with random allocation. One participant took the view that randomisation was no better than patient choice at controlling important variables. Some participants, however, seemed to judge that allocation or response bias could be avoided with random allocation.

Some comments about the sheep treatment scenario were very similar to those given in connection with the medical scenario: with choice, farmers could draw on their knowledge to achieve a better result, although as with the medical scenario, finding out which treatment was better was confused with achieving a better result for the individual sheep. With random allocation,

although again there were concerns over lack of control, some interviewees seemed to think that this was less of a problem with sheep than with people. Comments about the sheep treatment scenario helped in interpretation of the finding reported above, that randomisation was judged to lead to greater certainty than allowing farmers to choose. Unexpectedly, some interviewees assumed that randomisation was the better method because if farmers could choose, they would all choose the sheep dip rather than the tunnel since they would then not have to invest in new equipment (although there was no information in the scenario to suggest this). There was no indication that participants appreciated the scientific reasons for randomising in the context of the sheep dip.

Implicit in two interviewees' discussions about controlling important variables was the idea of taking into account key characteristics such as age, gender, severity and type of illness in assigning patients to treatment. The acceptability of such a form of assignment is explored further in investigation 6.

Acceptability of inviting patients to enter the trial: effect of doctor's preference

The mean (SD) rating of how right it would be for a doctor with a preference for one of the treatments to invite patients to enter the trial was 3.21 (1.27), and for a doctor with no preference the mean rating was 3.94 (1.04) (1 = definitely wrong, 5 = definitely right).

An ANOVA was conducted on the right/wrong scores (1–5), preference versus no preference as a repeated measure, and order of scenarios as a between-group factor. For this analysis, 'don't know' judgements (rated 3) were included. There was a significant main effect of doctor preference ($F_{1,64} = 17.69$, $p < 0.001$, partial $\eta^2 = 0.217$). Participants revealed a clear view that it was more acceptable for a doctor in a state of individual equipoise to invite patients to enter a randomised trial, than for a doctor who had a slight preference for one of the treatments. Despite this difference, the majority of participants judged that it was right for the doctor to invite patients to enter the trial (48 out of 54 when the doctor had no preference; 34 out of 54 when the doctor had a slight preference), whether or not the doctor had a preference.

Discussion

The results give no indication that participants appreciated the scientific benefits of random allocation of treatments in a clinical trial over patient choice. The most common response was to judge that doctors would be fairly sure which treatment was better with either method (50% of participants judged in this way for patient choice, and 46% did so for random allocation). Although the statistical analysis suggested that the benefits of random allocation were more likely to be appreciated for the sheep treatment scenario, the data from the interviews did not reveal understanding that random allocation avoids bias. On the contrary, they raised the possibility that the result was due to participants making unforeseen assumptions about farmers' choices; this possibility was followed up in investigation 5.

As expected, participants considered it less acceptable for a doctor to invite patients to enter a randomised trial when he or she had a personal preference for one of the treatments. What was surprising was the finding that just over half of the participants judged it acceptable for the doctor with a preference to offer the invitation. Given the low acceptability in investigations 1 and 3 of a doctor suggesting letting chance decide on treatment in conditions of uncertainty, and given that inviting patients to enter a randomised trial is effectively the same as suggesting random allocation of treatments, this raises the possibility that the presence of a research context is highly relevant to participants' acceptability judgements. Yet there was no sign that participants recognised the scientific reasons for randomising. This issue is explored further in investigations 6 and 7.

Investigation 5: do members of the public believe that random allocation has scientific benefits? A follow-up to investigation 4

(See Robinson and colleagues.[118])

Summary

In a repeated measures design, participants ($n = 67$) read two scenarios that described research contexts. One context involved a group comparison between two medical treatments, and the other a group comparison between two washing powders. Participants judged how sure experts would be about which treatment or washing powder was better if patients or householders were allocated to groups at random, and how sure if allocation was by choice. In neither context was there any indication that participants saw any scientific benefit to random allocation over free choice: certainty ratings were

no different in the two conditions. There was no sign of genuine understanding of the scientific reasons for randomising.

Background

Given the authors' suspicions that the results with the sheep treatment condition in investigation 4 were due to participants assuming that free choice would lead to unequal numbers in the comparison groups, rather than to understanding of the scientific benefits of randomising, this study checked whether participants recognised such benefits, and whether or not there were context effects.

Method

Participants

There were 67 participants (see *Table 2*). Eight participants were interviewed individually.

Design and procedure

The design and procedure were the same as for investigation 4, except that the sheep treatment scenario was replaced with one involving a comparison of two washing powders, and acceptability judgements were not elicited.

Results

The results suggest that participants saw no advantage of randomisation in either context: for the clinical trial scenario the mean certainty score (SD) with random allocation was 2.95 (0.71) and with patient choice it was 3.10 (0.85). For the washing-powder scenario the corresponding figures were 2.97 (0.72) and 2.90 (0.83). The certainty scores (1–4) were analysed using ANOVA with scenario (clinical trial or washing powder) and allocation method (random or choice) as repeated measures, and order of scenarios (trial or washing powder first) as a between-group factor. Participants who indicated that they did not know were omitted ($n = 5$). There were no significant main effects. The interaction between scenario and method approached significance: ($F_{1,56} = 3.54$, $p = 0.065$, partial $\eta^2 = 0.059$). If anything, this reflected a different pattern from the significant interaction found in investigation 4: there was a non-significant tendency for participants to give higher certainty scores with patient choice in the clinical scenario than in any of the other conditions.

Qualitative interview data

See *Table 4* for examples of comments. As in investigation 4, the view that more information is taken into account with patient choice was voiced, although more interviewees in this group felt that the methods were equivalent (either just as sure or just as unsure with each). One participant concluded that choice was more desirable. Two participants saw an advantage of randomising in that it ensured equal-sized groups, whereas choice might not, but they saw no other benefit. Two other participants raised the concern of response bias if patients/householders chose and believed their choice to be better, but no interviewees in this group considered randomisation to be advantageous in reducing allocation bias. Most participants' comments indicated that they thought no differently in the clinical and non-clinical scenarios.

Discussion

For the clinical trial scenario, the results confirm those of investigation 4: there was no sign that participants as a group thought that a more certain result would be achieved by allocating treatments at random rather than by patient choice. The authors had wondered if participants would find it particularly hard to adopt a scientific perspective in a clinical context, and might acknowledge the scientific benefits of random allocation in a non-clinical context. This proved not to be the case with the washing-powder scenario, in line with the suspicion that the quantitative result from the sheep treatment scenario was not due to understanding of the scientific benefits of randomisation.

Investigation 6: do members of the public accept clinicians' individual equipoise? Do they accept random allocation in a research context? Do they recognise the scientific benefits of random allocation?

(See Robinson and colleagues.[118])

Summary

Participants ($n = 128$) read a scenario involving either a treatment or a medical research context. Participants judged whether an individual doctor could be completely unsure about which treatment was better and whether it was acceptable to suggest letting chance decide which treatment the patient was to receive. Participants who received the research context also judged how certain doctors would be about which treatment was better with random allocation, and how certain with a design in which matched groups were deliberately set up. In this latter design patients and doctors

had no control over which treatment the patient would receive, but participants might envisage scientific benefits and might find it more acceptable in comparison with random allocation. If so, this might give an indication of how to explain the benefits of random allocation. Results indicated that around half of the participants denied the possibility of individual equipoise, and a majority thought that suggesting randomisation was unacceptable. Research rather than treatment context had no effect on the former, but possibly rendered randomisation less unacceptable. There was no sign of appreciation of scientific benefits of random allocation over matched groups. Participants tended to misinterpret the matched design as involving doctor/patient choice.

Background

This investigation attempted to bring together and clarify the previous results. First, the study looked again at acceptance that a doctor might be in equipoise. In investigation 3 around half of the participants were unwilling to accept that an individual doctor could be completely unsure about which of two treatments was better. Comments made in interviews suggested that they sometimes assumed that a more expert colleague would know which treatment was better (even though it was stated that the treatments had not been compared), so in investigation 6 that possibility was excluded by making explicit that there was no agreement among experts. A new condition was included in which the question about which treatment was better was the subject of a research study. Participants might more readily accept the possibility of equipoise in a research context that makes it legitimate, compared with a treatment context in which uncertainty is perhaps an anomaly.

Next, the study looked again at the acceptability of a doctor suggesting letting chance decide which of two treatments a patient was to receive. This time it was stated that the patient was willing to receive either treatment. This wording avoided participants having to assume that the doctor was completely unsure. The results of investigation 4 (in which participants judged whether it was acceptable for a doctor to invite patients to enter a randomised trial) raised the possibility that participants might judge random allocation to be more acceptable in a research context; to find out, a research context was compared with a treatment context.

Finally, the results of investigations 4 and 5 were built on by examining again participants' recognition of the scientific benefits of random allocation. This time the study compared their judgements of how sure experts would be with random allocation, with judgements of how sure they would be if matched groups were created. Comments made in the interviews of investigations 4 and 5 prompted the creation of this new condition. Some interviewees saw the need to take into account patient characteristics that might influence outcome. The researchers wondered whether participants would recognise the scientific benefits of a design in which groups were deliberately matched on certain characteristics. If so, would allocation to such groups be judged acceptable even though, just as with random allocation, doctor and patient would have no control over the group to which a particular patient was allocated? If it were found that deliberate matching was judged both scientifically beneficial and acceptable, this might indicate a way of explaining the reasons for random allocation in trials.

Method

Participants

There were 128 participants (see *Table 2*). Nineteen participants were interviewed individually.

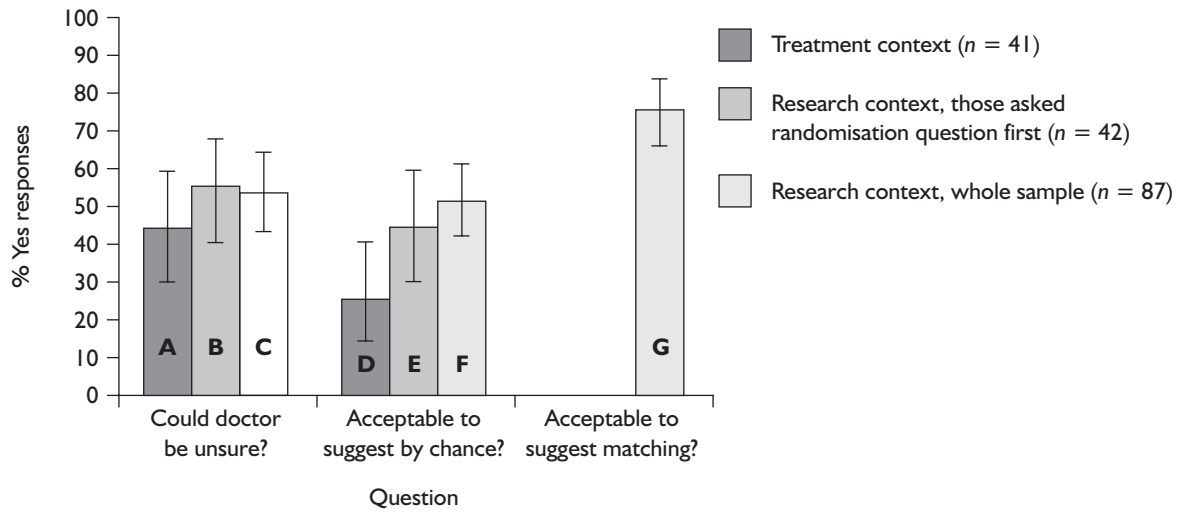
Design

There were eight groups: participants received either a back-pain or an arthritis scenario, with either a treatment or a research context, and with questions about the knowledge gained with random allocation either preceding or following questions about the knowledge gained with matching.

Procedure

Half of the participants read a scenario focused on two possible standard treatments for back pain as used in investigations 2–5, and the other half read a scenario focused on two possible standard treatments for arthritis as used in investigation 2. For both the back-pain and the arthritis treatments participants were told, "The two treatments have not yet been compared and there is no agreement amongst the experts as to which one is better." This was intended to indicate a state of collective equipoise.

For the participants in the treatment context conditions, the subsequent procedure was as follows. Participants answered yes or no to the uncertainty question, "Do you think the doctor could ever be completely unsure about which of the two treatments is better, and truly not prefer



A, Treatment context/could doctor be unsure? = 43.90% (95% CI 30 to 59%); B, research context/where randomisation question asked first. Could doctor be unsure? = 54.76% (95% CI 40 to 68%); C, research context/whole sample. Could doctor be unsure? = 53% (95% CI 43 to 64%); D, treatment context/acceptable to suggest by chance? = 25% (95% CI 14 to 40%); E, research context/where randomisation question asked first. Acceptable to suggest by chance? = 43.90% (95% CI 30 to 59%); F, research context/whole sample. Acceptable to suggest by chance? = 51% (95% CI 40 to 61%); G, research context/whole sample. Acceptable to suggest matching? = 75% (95% CI 65 to 83%)

FIGURE 5 *Investigation 6: yes responses to questions*

one treatment over the other?" This was followed by the acceptability question, "Suppose you and your doctor agree that you would be equally willing to receive either of the treatments, would it be acceptable for the doctor to suggest deciding at random?" (followed by clarification about allocating by computer as in investigation 3).

For participants in the research context conditions these two questions were preceded by the statement, "Your doctor asks if you would be willing to take part in a study comparing the two treatments. 500 people with arthritis/back pain will participate." The uncertainty question followed: "Do you think the doctor could ever be completely unsure … ?" The acceptability question was put within the context of the research study: "There are two ways of carrying out a study like this. In the first way you will be allocated to have one treatment, either A or B, at random …."

Following the acceptability question, participants given the research context answered an additional question about the knowledge gained from the study: "If they allocate 250 patients to each of the treatments at random, once the study is done how sure do you think the experts would be about which is the better treatment?" As in investigations 4 and 5, participants gave a rating from 'very sure' (4) to 'very unsure' (1), or indicated that they did not know.

Participants given the research context also made acceptability and knowledge judgements about a second way of allocating treatments, by matching: "In the second way your details will be given to the research team who will ensure that the group of people receiving treatment A and the group of people receiving treatment B are well matched. They will allocate one treatment, either A or B, to you. Neither you nor your doctor will have any control over which treatment you receive. Would it be acceptable for the doctor to suggest deciding by matching?" Participants also judged how sure experts would be at the end of the study, as for random allocation. Half of the research context participants made their judgements about acceptability of and knowledge gained from random allocation before their judgements about the matched design, and half had the reverse order.

Results

Figure 5 shows the percentage of participants answering 'yes' to the questions about the doctor's uncertainty and acceptability of random allocation or matching. The figure suggests that many participants in both the research and the

treatment contexts thought that the doctor could not be unsure, and many found it unacceptable for the doctor to suggest deciding by chance. There is a hint that randomisation may be less unacceptable in the research context. These effects were checked statistically.

Acceptance of possibility of uncertainty in research and treatment contexts

To compare views about participants' acceptance of the possibility of uncertainty in treatment and research contexts, only research context participants who were asked about the random method first (before matching) were included, since random allocation was the only method in the treatment context. In both the treatment and the research scenarios, participants were split as to whether or not the doctor could be completely unsure, in both cases confidence intervals spanned 0.5 (treatment scenario proportion 'yes' = 0.44, 95% CI 0.30 to 0.59; research scenario, randomisation first, proportion 'yes' = 0.55, 95% CI 0.40 to 0.68). Participants found it no easier to accept an individual doctor's uncertainty in a research than in a treatment context: confidence intervals for unpaired differences spanned zero in the arthritis and back-pain scenarios considered separately, and for the two combined.

Acceptability of suggesting deciding by chance in research and treatment contexts

Again, the treatment context was compared with the randomisation-first research context. In the treatment context significantly fewer than half of the participants judged it acceptable for the doctor to suggest deciding by chance (proportion 'yes' = 0.25, 95% CI 0.14 to 0.40). For the research context, participants were more split (proportion 'yes' = 0.44, 95% CI 0.30 to 0.59). However, confidence intervals for unpaired differences between treatment and research contexts spanned zero in the arthritis and back-pain scenarios considered separately, and for the two combined, providing no clear evidence that the two contexts differed in the acceptability of random allocation. Post hoc, participants who had the matched design first (labelled 'research context, whole sample' in *Figure 5*) were included, and comparing this larger sample of 83 for the research context with the treatment context, randomisation was found to be more acceptable in the research context (overall unpaired difference = 0.26, 95% CI 0.07 to 0.41).

Acceptability of matching

Participants in the research context made judgements about the acceptability of a matched design as well as of randomisation. Thirty-four participants found both allocation methods acceptable, 14 found neither acceptable, 26 found only matching acceptable and seven found only randomisation acceptable (missing data $n = 6$). Matching was judged more acceptable than randomisation (paired difference = 0.23, 95% CI 0.10 to 0.36).

Qualitative data about matching

Comments made in the interviews indicate why participants judged matching to be more acceptable than randomising. Thirteen interviewees received the research context and so had the opportunity to talk through their views about the matched groups design. Only four of these appeared to have interpreted the design as intended, that is that two matched groups would be created and neither doctor nor patient would have control over the group to which an individual patient was allocated. In contrast, seven interviewees appeared to have interpreted the design as matching treatments to patients, and three of these judged matching to be more acceptable than random allocation for that reason: "I think you'd have a better success with this one, you and the doctor actually getting together and deciding together if it could work for you" (note also the focus on individual treatment success rather than gain in scientific knowledge); "Yes that's taking into account their medical history, their age, weight whatever, everything you know as a doctor about your patient and saying yes this probably would be the best one." These participants appeared to be drawing on a schema for standard allocation of treatment, rather than taking on board the research context. For the remaining two of the 13, it was unclear how they had interpreted matching.

Knowledge gained with randomising and matching

Participants given the research context made judgements about the knowledge gained with random allocation and with matching. The mean certainty score (SD) with random allocation was 2.64 (0.74), and with matching it was 2.77 (0.64). Certainty ratings (1–4) were analysed by ANOVA, with design (random allocation versus matching) as a repeated measure and order (random or matching first) as a between-subjects variable. Participants who judged that they did not know ($n = 15$) were excluded from this analysis. The ANOVA showed no significant main effects or interactions. The results give no indication that participants discriminated between random allocation and matching in terms of the

knowledge derived from the study. For both methods, the majority of participants judged that experts would be fairly sure: 46 out of 85 (54.1%) with randomisation and 54 out of 86 (62.8%) with matching. Note, however, that the knowledge judgments need to be interpreted taking into account the information mentioned above, that some participants apparently treated the matching design as equivalent to patient choice.

Discussion and conclusions

The previous finding was confirmed, that around half of the participants did not accept that a doctor might genuinely not know what treatment is better. In this study it was made explicit that there was a state of collective equipoise, and participants again remained split as to whether or not an individual doctor could be in equipoise. It made no difference when the state of uncertainty was within a research context.

As in investigation 3, more than half of the participants thought it unacceptable for the doctor to suggest deciding by chance in a treatment context. There was a hint that randomisation might be less unacceptable in a research context, although even then only around half of the participants judged it to be acceptable.

As in investigations 4 and 5, participants seemed to be insensitive to the advantages and disadvantages of different allocation methods for achieving an advance in knowledge. In investigations 4 and 5 they did not judge that more knowledge would be derived from a study involving random allocation than from one in which patients chose their treatment. In investigation 6 they judged random allocation to be no more informative than matching. At least some participants, though, appear to have interpreted matching as involving patient choice, so judgements about knowledge gained need to be interpreted within that context.

The same proviso applies to the finding that participants judged allocation to matched groups to be significantly more acceptable than random allocation. Although only a small subsample of the participants talked through their answers, the high incidence of clear misunderstanding of the matched design argues against accepting the quantitative result at face value. There is a strong suspicion that the higher acceptability ratings difference can be accounted for by participants wrongly assuming that treatments would be matched to patients' needs.

This unexpected interpretation of the matched groups design is of interest. It is in line with Appelbaum and colleagues'[59] argument that trial participants are inclined to fall back on their assumption that treatments are selected in accordance with patients' needs. Even though the scenario stated "Neither you nor your doctor will have any control over which treatment you receive", some (but not all) participants seemed to overlook this. The very problem that prompted this research intruded even when participants were encouraged to take a scientific perspective on the trial, rather than the perspective of a patient receiving treatment within the trial.

Investigations 1–6: general discussion and conclusions

This research arose from the considerable body of evidence that despite efforts to simplify language and otherwise clarify trial information, participants in RCTs seem still to be at risk of failing to grasp, or of losing sight of, information that allocation to treatment arms is at random, and about the initial state of equipoise.

At the beginning of this section four implicit assumptions were identified that underlie the recommended MREC description of what happens in a randomised trial:

- that a computer can allocate randomly, by chance
- that doctors might not know which way of treating patients is best
- that when it is not known which treatment is best, it is ethically acceptable to randomise
- that there are scientific benefits to random allocation.

Two additional questions were asked:

- Does medical treatment versus research context affect judgements?
- Does medical versus non-medical context affect judgements?

The results of investigations 1–6 suggest that many participants shared only the first of these four assumptions. There was no sign of different judgements between medical and non-medical contexts, although within a medical context there was weak evidence that random allocation is more acceptable in a research than in a treatment context. The following text considers the evidence in relation to the first, third, second and fourth assumptions (in this order), and its implications.

Do participants believe that a computer can allocate randomly?

A prevalent view in the published literature is that patients in trials simply fail to understand the concept of random allocation, and their explicit definitions of 'random' may support this view. When looking at participants' working understanding, however, a different picture emerges. The results of investigation 1 suggest that this is not the main reason for patients' reported failures to understand that treatments were allocated randomly in trials. Most, although not all, participants appeared to share the authors' views about which allocation methods were random and which were non-random. In particular, there was little sign of difficulty with the MREC recommended statement that a computer with no information about the individual allocates at random. There was no sign of different judgements in medical and non-medical contexts.

Do participants consider it ethically acceptable to randomise given uncertainty?

Rather than a failure to understand what random allocation is, the results highlight the unacceptability of random allocation, a finding that has also been reported in the published literature summarised in Chapter 2 ('Extracted studies on attitudes towards randomisation in the context of clinical trials', p. 19). Many participants in investigation 1 judged the random methods to be unacceptable in a medical context, even when a brief justification for randomisation was included. Participants in investigations 3 and 6 also often found it unacceptable for a clinician to suggest allocating treatments at random in a treatment context. In investigation 6, when the patient was described as equally willing to receive either treatment, there was weak evidence that a research context rendered randomisation less unacceptable. Participants may have accepted that when current knowledge gives no grounds for choosing between treatments, and the patient has no preference, nothing is lost if chance decides which one the patient has. This view was certainly not prevalent.

In investigation 4, participants tended to judge that it was acceptable for a doctor to invite patients to enter a randomised trial, even when that doctor had a preference for one of the treatments. This result appears to contradict the suggestion that randomisation is often unacceptable even in a trial context. In investigation 7 this issue was examined by making a direct comparison between the acceptability of suggesting allocating treatments at random in a trial context, and of inviting patients to enter a randomised trial. The two are effectively the same, but the precise wording used and their different emphases may lead to different judgements.

Why might it be unacceptable to suggest allocating treatments at random? One relevant factor is likely to be treatment preferences. The initial exploration of this built on the published literature by examining experimentally whether participants tended to assume that a treatment described as new will be better than a standard. If they do, they might justifiably expect that the better treatment should be available on demand or according to need, rather than by random allocation. However, the results of investigation 2 suggested that merely describing a treatment as new was not sufficient to engender a preference for it. The contrary view expressed in the literature was based on clinical impression or the necessarily confounded comparisons that can be made ethically in a real trial setting. Had the investigations found that participants tended to assume that new treatments are better, they could have explored ways of highlighting the distinction between the hope that motivates a trial of a new treatment, and the current state of equipoise which justifies random allocation. Given that this seemed not to be a fruitful line to pursue, the subsequent experiments used scenarios in which both treatments under comparison were already in standard use.

Do participants accept that doctors may not know which way of treating patients is best?

Next, instead of focusing on participants' own treatment preferences, we examined participants' beliefs about doctors' treatment preferences. Randomisation may be considered unacceptable if participants assume that doctors judge one treatment to be better than the other (although recall the finding mentioned above that just over half of participants in investigation 4 judged it acceptable for a doctor with a preference to invite patients to enter a randomised trial). In investigation 3, and again in investigation 6, around half of the participants were reluctant to accept that an individual clinician could be completely unsure about which of two treatments was better. This was the case in both treatment contexts (investigations 3 and 6) and research contexts (investigation 6). Furthermore, in investigation 3 a small majority of participants judged that clinicians should reveal their hunches to patients.

The belief that doctors cannot be in individual equipoise may well be accurate. Perhaps many trialists do hold weak (or even strong) treatment preferences within the context of collective equipoise. However, so far as can be ascertained, statements of equipoise in trial information leaflets make no distinction between collective and individual equipoise. Participants who are given the information that "doctors do not know which treatment is best" are unlikely to work out for themselves that although individual doctors may have preferences there is no consensus view that one treatment is better than the other. In investigations 8 and 9 an attempt was made to explain equipoise in this way, and to explain that random allocation offers a way of avoiding the bias that may arise if doctors suggested treatment on the basis of their individual preferences.

Do participants perceive scientific benefits to random allocation?

An explanation for the scientific reasons for random allocation appears to be necessary. The participants assumed that just as much knowledge would be gained about which treatment is better if patients and doctors chose their treatment as would be gained if treatments were allocated at random. This was found in investigations 4 and 5. In investigation 6 participants did not discriminate between random allocation and a matched design in terms of the knowledge gained, although the matched design was sometimes misinterpreted as involving patient choice.

Taken together, the results of investigations 1–6 render it unsurprising that many recruits to RCTs apparently fail to make sense of descriptive trial information about equipoise and randomisation. Importantly, even if potential recruits fully understood the initial state of collective equipoise and the scientific rationale for randomising, they may still have their own preferences for one treatment and for this or other valid reasons choose not to enter the trial. Furthermore, they may still think it wrong to offer random allocation: understanding the perspective of the trialists does not require accepting it as valid. Even among clinicians whose understanding is certainly not in doubt, different views are held about the relative value of knowledge gained from randomised and non-randomised trials (e.g. Abel and Koch,[119] Herman[120] and Pullman and Wang[121]). The present results suggest that clear, descriptive trial information may not permit potential trial recruits to hold such an informed view.

A next step is to ascertain the consequences of providing potential recruits with an accessible explanation of the scientific benefits of random allocation given collective equipoise, and this step is taken in investigations 7–9.

Chapter 4

Investigations 7–9: interventions

The main argument so far is that trial participants fail to take in or remember information about random allocation and equipoise because it makes little sense to them: they commonly do not accept that doctors may not know which treatment is best, they see no scientific reasons for randomising and they find random allocation unacceptable. In general, to draw on the discussion of scripts and schemas in Chapter 2 ('Reflections drawing on theory and evidence from experimental psychology', p. 26), potential participants appear to have no relevant 'research' schema to draw upon, even when (as in investigations 4–6) the scenario emphasises a research rather than a treatment perspective. In the final three investigations the aim was to identify a way of helping participants to recognise the scientific benefits of random allocation over doctor/patient choice, on the assumption that if they understood the reason for random allocation they would be more likely to take in and remember the fact of random allocation. This may be seen as helping participants to construct a relevant research schema on which to hook trial information.

It may be that appreciation of the scientific benefits of randomisation was associated with finding randomisation more acceptable, and this was checked in investigation 7. One publicly available justification for random allocation is the one provided in the CERES guidelines (see 'Descriptions of randomisation and equipoise in trial information leaflets', p. 24),[97] which was used in investigation 1. There, it was found inclusion of this justification did render random allocation by computer less unacceptable compared with no justification. Investigation 7 checked whether or not the CERES justification helped participants to recognise the scientific benefits of random allocation over doctor/patient choice. This was assessed with the measure used in investigations 4–6, in which participants judge how sure experts will be about which is the better of two treatments with random allocation, and with doctor/patient choice. Greater certainty scores for random allocation are taken to indicate appreciation of its scientific benefits.

In investigations 8 and 9 the researchers compared the CERES justification with their own extended explanation of the reasons for randomising, which drew on the findings from investigations 1–6. For example, given participants' unwillingness to accept that doctors may not know which treatment was best, equipoise was described in terms of doctors having different hunches with no overall agreement among them.

Investigation 7: does the CERES brief justification for randomisation help people to understand the scientific benefits?

Summary

In a between-groups design, participants (n = 128) read a scenario that described a comparison of two treatments and included either the CERES brief justification for randomisation or a control description that was intended to make random allocation just as salient but with no justification. Participants judged how sure doctors would be about which treatment was better with random allocation and with doctor/patient choice. In addition, participants judged the acceptability either of the doctor suggesting selecting patients' treatment at random, or of the doctor inviting patients to enter the randomised trial. There was no difference between groups in certainty judgements, and certainty judgements were no higher for random allocation than for doctor/patient choice. The CERES justification appeared not to be effective in helping participants to understand the scientific benefits of random allocation. Acceptability judgements were higher for inviting patients to enter the randomised trial than for suggesting selection of treatment at random, perhaps because participants did not reflect on the implications of entering a trial for allocation of treatment.

Background

The first aim of this investigation was to find out whether the CERES brief justification for randomisation helped participants to appreciate

TABLE 5 *Investigation 7: certainty judgements for random allocation and doctor/patient choice (1 = very unsure, 4 = very sure)*

	Condition			
	CERES		Description only	
	Random allocation (n = 62)[a]	Doctor/patient choice (n = 60)[a]	Random allocation (n = 61)[a]	Doctor/patient choice (n = 59)[a]
Mean certainty score (SD)	2.84 (0.66)	2.75 (0.84)	2.80 (0.69)	2.80 (0.78)

[a] 'Don't know' responses excluded.

that doctors would be more certain about which of two treatments was the better, than they would be if doctors and patients chose their treatment. The comparison condition included a bland description of random allocation which, the authors judged, made the fact of randomisation just as salient as did the CERES justification, but without providing any scientific justification.

The second aim was to examine the apparently contradictory judgements made in investigation 4, where 89% of participants judged it acceptable for a doctor with no treatment preference to invite patients to take part in a randomised trial, and in investigation 6, where only 51% judged it acceptable for a doctor to suggest allocating treatments at random as part of a research study. Here, the two questions were compared within a single investigation to find out whether the slightly more oblique reference to random allocation really does result in greater acceptability.

Method

Participants

There were 128 participants (see *Table 2*). Fifteen participants were interviewed individually.

Procedure

This was based closely on the procedure used in investigations 4–6. Participants read a brief description of a research study comparing two potential treatments for back pain. For half of the participants this included the CERES brief justification for randomisation: "Randomised studies are the most exact and fair way to test which treatments work best. They are less likely to have, for example, people who are older or sicker in any one group. Every year thousands of people take part in them." The other half were given a description of randomisation of approximately the same length, which highlighted the fact of randomisation without giving a rationale: "In randomised studies, the treatment each patient gets is decided in a completely different way than usual. This is an important part of study design and every year thousands of people take part in such studies." After reading the description, participants rated how certain (1 = very unsure, 4 = very sure) experts would be about the best treatment if allocation to the experimental groups occurred (1) randomly or (2) on the basis of doctor/patient choice.

Finally, imagining themselves as suffering from severe back pain, and in the context of the randomised research study, half of the participants answered yes or no to "Would it be acceptable for your doctor to invite you to take part in the randomised research study?" and the other half answered "Would it be acceptable for your doctor to suggest your treatment (A or B) be selected at random as part of the research study?"

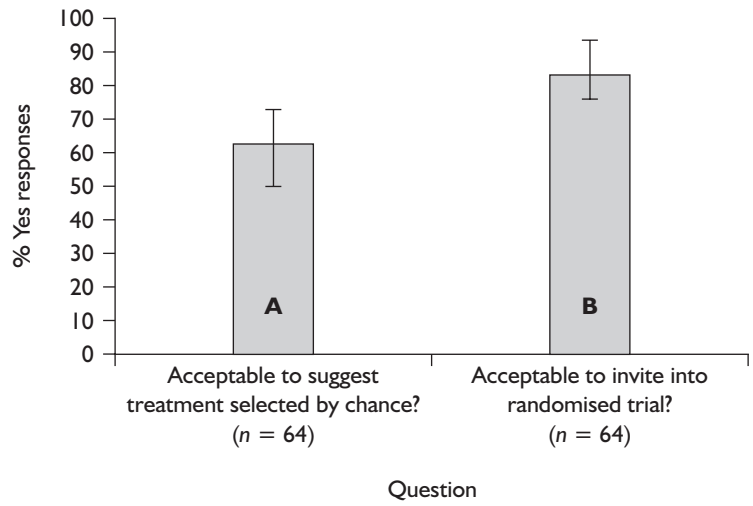
Results and discussion

Certainty judgements with randomisation and doctor/patient choice

The results appear in *Table 5*. There appears to be no discrimination between the two allocation methods for either the group given the CERES explanation or the control group given a description only. This impression was confirmed using ANOVA with allocation method (random versus doctor choice) as the repeated measure and condition (CERES versus description only) as a between-subjects factor. This analysis found no significant main effect of condition ($F_{1,115} = 0.023$, $p = 0.880$, partial $\eta^2 = <0.001$) or allocation method ($F_{1,115} = 0.026$, $p = 0.873$, partial $\eta^2 = <0.001$) and no significant interaction between the two ($F_{1,115} = 0.437$, $p = 0.510$, partial $\eta^2 = <0.004$). As a means of raising awareness of the scientific benefits of randomisation, the CERES justification appears to be ineffective.

Acceptability of randomisation

The percentage of participants saying that randomisation is acceptable is shown in *Figure 6*.



A, Acceptable to suggest treatment = 62.5% (95% CI 50 to 73%); B, acceptable to invite into trial = 82.81% (95% CI 76 to 93%)

FIGURE 6 *Investigation 7: acceptability judgements (doctor suggesting random selection of treatment or doctor inviting into randomised trial)*

To analyse acceptability judgements, 'not acceptable' and 'don't know' responses were combined. Participants were more likely to say that it was acceptable for the doctor to invite them into randomised research trials than to suggest their treatment be selected at random (2×2 $\chi^2 = 6.646$, df = 1, $p = 0.01$, $w = 0.228$). Why? The two questions amount to exactly the same thing. Possibly the more acceptable wording is a less blatant invitation to be randomised (in line with Corbett[82]): participants may fail to make the connection between entering a randomised trial and having treatment allocated at random. Comments from the interviews, reported below, are in line with this.

From *Figure 6* the acceptability of randomisation seems markedly higher than was found before. In investigation 3, when asked in the context of a medical treatment scenario, only five out of 41 participants (12.2%) thought it acceptable for the doctor to suggest selecting treatment at random. In investigation 6, in a treatment context ten out of 40 (25%) thought randomisation acceptable, compared with 42 out of 83 (50.6%) in a research context. Here, 40 out of 64 (62.5%) judged it acceptable for the doctor to suggest selecting their treatment at random. What causes this variation in responses? There are various possible explanations, which are not mutually exclusive:

- There are significant differences between the samples, but these are unlikely to account for the results. Participants in investigation 7 were younger than those in investigation 6, and less well academically qualified ($p < 0.001$ in both cases). However, post hoc comparisons within samples offer no hint that participants aged less than 40 years gave higher certainty ratings for random allocation than those aged 40 or over, and if anything the findings go the other way. Similarly, within samples there was no hint that participants with 'A' levels or above judged differently from those with lower educational qualifications.
- In investigations 3, 4 and 6, but not investigation 1, judgements of the acceptability of random allocation were preceded by judgements of the possibility of a doctor being in equipoise. There was no equipoise question in investigation 7. Perhaps participants who answer the equipoise question in the negative, having become aware of their view that doctors already know which treatment is best (or at least have some idea), then view random allocation as particularly unacceptable. The high unacceptability of random allocation in investigation 1, with no equipoise question, goes against this suggestion, but it could easily be tested in a follow-up investigation.
- The authors consider the most plausible explanation to be the salience of a research context. The results of investigation 6 provided weak evidence that participants found random allocation less unacceptable in a research than in a treatment context. In investigation 7 for

the first time participants were asked to judge the acceptability of randomisation after they had judged how sure experts would be about which treatment was better with random allocation and with doctor/patient choice. This could have made the research context even more salient, and could have encouraged participants to maintain a scientific perspective when they made their acceptability judgements. Again, this possibility could easily be tested.

Comments from interviews

The interviews are consistent with the idea that the less obvious it is that treatment is going to be selected at random, the more acceptable randomisation becomes. Six out of 15 interviewees were asked the suggestion question. Two found randomisation acceptable because, "… the doctor's just suggesting it … you might go along with it or you might not" and "(I) didn't foresee there being any reason why it was unacceptable". Three participants thought suggesting randomising unacceptable because it contravened their expectations of the consultation process: "You don't walk into the doctors and say, 'Right, today it's heads or tails'" and "Judging from this there's no tests been done and how can the doctor make an assumption about what would be the correct treatment for you?" The sixth person had said they did not know whether it was acceptable for the doctor to suggest their treatment be selected at random. Of the nine interviewees who had been asked whether it was acceptable for the doctor to invite them into the randomised trial, most of the eight people who said this was acceptable referred to research, for example saying, "I think it's absolutely essential that you get people to volunteer for all kinds of research"; "How else would we learn everything?"; "research is always needed"; "they could find better ways or, y'know, from research …".

Acceptability of suggesting randomisation in relation to certainty judgements

Finally, the study examined whether participants who appear to understand the scientific benefits of random allocation also find it more acceptable. The acceptability judgements of those who rated certainty higher with randomisation (15 judged randomisation acceptable; two unacceptable) were compared with the combined judgements of those who rated certainty higher for doctor/patient choice or saw no difference between the two (22 judged randomisation acceptable; 16 unacceptable). Those who rated certainty higher with randomisation were more likely to find it acceptable for the doctor to suggest that their treatment be selected at random (2×2 $\chi^2 = 4.911$, df = 1, $p = 0.027$; $w = 0.299$).

This is an important result for the overall account. It has shown that most people see no good reason for randomising, and this may be why they fail to take in or hold on to the information that they will be randomised. There is an argument for the importance of providing an accessible explanation of the scientific reasons for randomising, rather than just clear descriptions of what will happen in the trial. Now, an association between recognising the scientific merits of randomising and the acceptability of randomising has also been shown, although a causal relationship between the two has not been demonstrated.

Conclusions

There was no evidence that the CERES justification for random allocation helped participants to understand the scientific benefits. In investigations 8 and 9 the CERES justification was used as a control against which to compare the authors' own explanation, devised on the basis of the findings from investigations 1–6.

The findings that participants who apparently recognised the scientific benefits of random allocation over doctor/patient choice also judged random allocation more acceptable is potentially important. It is consistent with the possibility that many trial participants find randomisation unacceptable partly because they see no good reason for it. Previous investigations have shown that mere uncertainty is not considered sufficient justification for randomising. The new result from investigation 7 suggests a further empirical question: does helping participants to understand the scientific reasons for random allocation also tend to render randomisation more acceptable? The proviso made before, that it is perfectly legitimate to find random allocation unacceptable despite fully understanding the scientific reasons for it, needs to be added again.

Investigation 8: comparison of the benefits of the CERES justification for randomising and an extended explanation

Summary

In a between-groups design, participants ($n = 130$) read a hypothetical trial information leaflet that had embedded within it either the CERES brief justification for randomisation or an extended

explanation devised on the basis of results of the previous investigations. Immediately after reading the leaflet participants completed tests of understanding: (1) a task in which they filled in gaps in a passage of text related but not identical to the information leaflet; (2) a brief questionnaire to assess knowledge of randomisation and equipoise; and (3) the certainty ratings used in investigations 4–7 to assess understanding of the scientific benefits of random allocation over doctor/patient choice. Overall performance in all three tests was good, although in the gap-filling task the items about randomisation were relatively difficult. For the first time in these investigations, participants rated that doctors would be more certain of the best treatment with random allocation than with doctor/patient choice. The extended explanation was no more effective than the brief CERES justification.

Background

Investigation 7 found no evidence that participants who read the CERES brief justification understood the scientific benefits of random allocation over doctor/patient choice. In investigation 8 the authors aimed to improve on the CERES justification with their own extended explanation devised in the light of the results of investigations 1–6. The CERES wording justifies the use of random allocation, but does not attempt to explain how random allocation achieves its scientific benefits, and makes no explicit connection between randomisation and equipoise. It may be taken to imply that mere uncertainty provides sufficient grounds for randomising. The results of these investigations suggest that participants are very unlikely to consider mere uncertainty sufficient to justify random allocation, that they are loathe to accept the possibility of individual equipoise and that they see no scientific benefits of random allocation. In the extended explanation these points were addressed by referring to collective rather than individual equipoise, by making clearer the connection between randomisation and equipoise (which makes random allocation ethically justifiable, but is not in itself the reason for randomising) and by trying to make clear the scientific benefits of randomisation over doctor/patient choice.

It is important to be clear that the aim was not to persuade participants that randomisation is acceptable, but rather to explain why random allocation is considered to have scientific advantages over doctor/patient choice of treatment when the aim is to compare treatments. As mentioned previously, participants who fully understood why random allocation is currently considered preferable to doctor/patient choice on scientific grounds may still find it unacceptable.

The justifications and explanations for randomisation were embedded within a hypothetical trial information sheet, for two reasons. First, this made the overall information load more similar to that which would be experienced by real trial participants, and so positive results would be potentially generalisable to real trial information sheets. Second, it disguised from participants the fact that the study was investigating their understanding of the scientific benefits of randomisation and so minimised the risk that their responses would be influenced by this.

The certainty judgements previously used in investigations 4–7 were used as outcome measures, and two additional tests were introduced to gather a broader range of data from which to infer participants' level of understanding.

Method

Participants

There were 130 participants (see *Table 2*). There were no individual interviews.

Materials

Two versions of an information leaflet about a fictional clinical trial of two similar treatments for low back pain were created. The information was presented in five sections, which covered the purpose of the research study, the voluntary nature of participation and right to withdraw, treatment and assessment procedures, equipoise and random allocation of treatments, and risks and benefits. The full versions appear in Appendix 6. One version, 'CERES justification' included wording taken directly from the CERES guidelines[97] (p. 12), preceded by the MREC description of random allocation that was used in the previous investigations. The other version, 'Extended explanation', attempted to improve on the CERES wording by drawing on the results of the investigations. The final wording was arrived at following pilot studies and discussion with users and practitioners. This discussion took place at a specially convened workshop attended by all who were then members of the research team (ER, CK, AS, RL, DB and SE), other researchers, authors of guidelines for patients' information sheets, medical ethicists and lay representatives.

The two versions of the leaflet contained identical information and wording except for a paragraph

describing and justifying random allocation under the heading 'What will happen to me if I take part?' The CERES wording of this paragraph was:

> "Sometimes because we do not know which way of treating patients is best, we need to make comparisons. People will be put into groups and then compared. The groups are selected by using a computer which has no information about the individual – i.e. by chance, at random. One group will be given Short Pulse Electrotherapy and the other group will be given Long Pulse Electrotherapy. Allocating patients to treatment groups at random is the most exact and fair way to test which treatments work best. They are less likely to have, for example, people who are older or sicker in any one group. Each year thousands of people take part in them."

The extended explanation was longer and more complicated, but there was a rationale for including each part:

- The explanation avoided implying a state of individual equipoise, which many of the participants in previous investigations were loathe to accept, and instead introduced the idea of collective equipoise by means of doctors having different hunches about which treatment was best. Acting on the basis of hunches could create bias, but that could be avoided by randomisation.
- The explanation retained the term 'fair', but avoided the possible misconception that this means fairness to patients ('everybody has a fair and equal chance of receiving the better treatment') rather than a fair comparison between the treatments.
- The explanation emphasised that relevant information would be collected from each patient, since comments from interviews in previous investigations suggested that some participants assumed that since the computer allocating treatment had no information about the individual, the researchers would lack such information for their analyses. This seemed to be one reason why some participants thought more certain knowledge would be gained with doctor/patient choice of treatment.

The wording of our extended explanation was:

> "This study is being carried out because nobody really knows whether one treatment is better than the other. Doctors have different hunches about which is better, but they don't agree. We need to compare the two treatments on patients with similar low back pain. Half the patients have Short Pulse Electrotherapy and the other half have Long Pulse Electrotherapy. Each patient will be followed up and we will record how well they are doing. If doctors suggested each patient's treatment on the basis of their hunches, then the two groups might be different. For example, more of the sickest patients might end up being given Short Pulse Electrotherapy. Then Short Pulse Electrotherapy is not being given a fair chance. But we can prevent this bias by using a computer to allocate patients to receive either Short Pulse Electrotherapy or Long Pulse Electrotherapy. The computer does not use information about individual patients to do this, it uses chance. So long as we include a large number of patients, this random allocation makes sure the results will tell us whether patients do better with one treatment than they do with the other."

There were three outcome measures, two of them new, always presented in the same order. Full versions of the two new tests appear in Appendix 6. The first required participants to fill in missing words in a text that covered material presented in the information sheet. This is known as the cloze technique[122] and allows the assessment of comprehension without using either forced-choice questions, which can prompt falsely correct answers purely through recognition, or open-ended questions, which can be linguistically too challenging for this kind of material. Pilot data confirmed that the level of difficulty was appropriate.

The second new test was a brief questionnaire that included two contradictory statements about randomisation and two contradictory statements about equipoise, each of which the participants judged to be true or false. This questionnaire was based on a longer one used by Ellis and colleagues.[67] A pilot study showed that participants not provided with any information about randomised trials performed poorly (n = 32, 34.4% answered both randomisation questions correctly and 37.5% answered both equipoise questions correctly, 25% expected to be correct by chance).

Finally, participants gave judgements of how sure doctors would be with random allocation and with doctor/patient choice, as in investigations 4–7. In this investigation participants were also asked to choose which was the 'best way'. A similar question was used by Ellis and colleagues.[67]

Design and procedure

The two versions of the information sheet were randomly allocated to participant number and handed to participants in that order in which they sat in class. As in the previous investigations, the experimenter gave a brief introduction to the

TABLE 6 *Investigation 8: cloze test of understanding*

Section of text	CERES explanation Mean score (SD)	Extended explanation Mean score (SD)
Equipoise (two gaps; max. score = 2)	1.74 (0.51)	1.74 (0.59)
Random allocation (seven gaps; max. score = 7)	3.29 (1.94)	3.62 (2.16)
Other: purpose, procedure, risks, voluntary participation (ten gaps; max. score = 10)	8.55 (1.12)	8.40 (1.59)

TABLE 7 *Investigation 8: knowledge of randomisation and equipoise, frequency (%) of correct judgements on both items for equipoise and random allocation*

Knowledge item	CERES explanation (*n* = 65)	Extended explanation (*n* = 65)
Equipoise	44 (67.7%)	39 (60.9%) (missing data *n* = 1)
Random allocation	49 (75.4%)	42 (65.6%) (missing data *n* = 1)

study, then participants read the information sheet before handing it back to the researcher, and immediately afterwards they completed the cloze (gap-filling) test and multiple-choice knowledge of trials questionnaire, and gave their certainty and best way judgements.

Results

Cloze test of understanding

The test had three sections, on equipoise, randomisation and other information about the trial. Participants were given credit for filling a gap correctly if they inserted the same word as had appeared in the trial information leaflet, or one closely related in meaning in that sentence context. Judgements about acceptability of words were made independently by four judges (CK, ER, and two postgraduate psychology students, PL and TE). Responses were judged acceptable when at least three of the judges rated them as having sufficiently similar meaning in the sentence context. The mean scores for each section are shown in *Table 6*. Reassuringly, participants performed near ceiling on the section of the test that dealt with the purpose of the study, the procedures and risks involved, and the voluntary nature of participation. There was no reason to expect any difference between groups (CERES versus extended explanation) on this general section of the test, but better performance was predicted on the equipoise and randomisation sections for those given the extended explanation. The near-ceiling performance suggests that the basic task was well within participants' grasp. It also suggests they were sufficiently engaged with the trial information leaflet to take in this information, although since there was no control group who completed the Cloze test with no prior reading of the information leaflet, there remains the unlikely possibility that participants were drawing on prior knowledge.

Overall, participants performed more poorly on the random allocation section (mean score per item = 0.47 for CERES, 0.52 for extended explanation) than on any of the other sections (mean score per item ≥ 0.84). There were no significant differences between the two groups: a one-way multivariate analysis of variance (MANOVA) on correct scores for equipoise (out of 2), randomisation (out of 7) and other (out of 10), with version (CERES versus extended explanation) entered as a between-subjects factor, found no significant difference between the version groups across the correct scores (Wilks' $\Lambda = 0.982$, $F_{3,126} = 0.775$, $p = 0.51$, partial $\eta^2 = 0.018$).

Questionnaire on knowledge of randomisation and equipoise

As shown in *Table 7*, performance on this test was quite good among participants in both groups. As mentioned above, in the pilot study only around one-third of participants given no prior information answered both questions within each pair correctly, whereas in this investigation around two-thirds did so. It is not possible to make a

TABLE 8 *Investigation 8: certainty judgements*

Allocation method	CERES explanation Mean certainty rating (SD) 1 (very unsure) – 4 (very sure)	Extended explanation Mean certainty rating (SD) 1 (very unsure) – 4 (very sure)
Random allocation	2.95 (0.56)	3.05 (0.48)
Doctor/patient choice	2.59 (0.82)	2.79 (0.82)

formal comparison across samples, but given that the pilot participants did not differ from the investigation 8 participants in age or gender, while the pilot sample had significantly higher educational qualifications, it seems likely that the written information in the trial leaflets is responsible for this good performance. The main interest was in a difference between groups within investigation 8, with the prediction that those who received the extended explanation would more commonly answer correctly than those given the CERES justification.

This was not the case: 2×2 χ^2 tests for knowledge of equipoise and knowledge of random allocation show no significant difference in knowledge between the two groups ($\chi^2 = 0.64$, $p = 0.465$, $w = 0.07$; and $\chi^2 = 1.48$, $p = 0.251$, $w = 0.11$, respectively).

Certainty scores: appreciation of the scientific benefits of random allocation

The prediction was that participants given the extended explanation would judge experts as more certain following random allocation than doctor/patient choice, and would be more likely to identify random allocation as scientifically the best way, than participants given the CERES explanation. The results are summarised in *Table 8*.

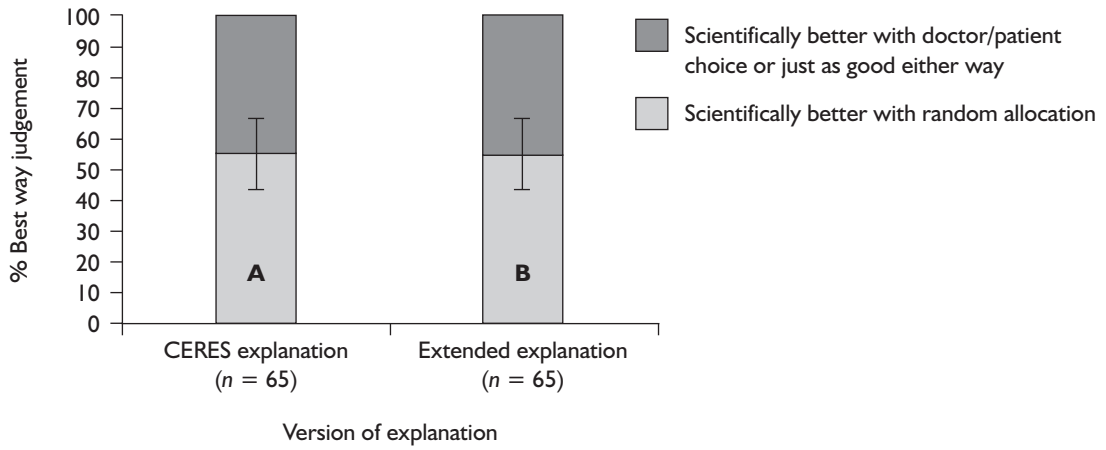
To analyse the certainty ratings, participants who responded '5, don't know' on either of the certainty ratings were excluded from calculating the means and ANOVA (CERES $n = 4$, extended explanation $n = 9$). A repeated measures ANOVA with allocation method (random versus doctor/patient choice) as the repeated measure and version (CERES explanation versus extended explanation) as a between-subjects factor found no significant difference in certainty ratings between the version groups. There was a significant effect of allocation method (Wilks' $\Lambda = 0.904$, $F_{1,115} = 12.163$, $p = 0.001$, partial $\eta^2 = 0.096$): in all groups participants rated doctors as more certain with random allocation than with doctor/patient choice. For the first time in the investigations using this measure, participants rated doctors as significantly more certain with random allocation than with doctor/patient choice, although the extended explanation appeared to have no benefits over the CERES justification (which did not perform well in investigation 7; this is discussed later).

Participants' judgements about which was scientifically the best way appear in *Figure 7*. To analyse the 'best way' responses, because of one small cell frequency, frequencies for 'at random' were compared with combined frequencies for 'doctor/patient choice' and 'just as good either way'. Frequencies were analysed using a 2×2 χ^2 test, which showed no significant difference between CERES and extended explanation groups ($\chi^2 = 0.006$, $p = 1.000$, $w = 0.002$). The higher certainty ratings for random allocation did not extend to judgements of random allocation as scientifically the best way, and there was no sign of benefit of the extended explanation over the CERES justification.

Conclusions

Overall performance in both groups was good, with the exception of the randomisation section of the cloze test. There is some evidence that a justification of random allocation (whichever one) increases appreciation of the scientific benefits of random allocation. This is surprising given the results of investigation 7, which showed no benefits of the CERES explanation compared with a control description, and no sign that either group discriminated between random allocation and doctor/patient choice in terms of certainty about which treatment was the better. This is discussed after reporting investigation 9. The results provide no evidence of benefit of the extended explanation over the CERES explanation.

There was still plenty of room for improvement in the random allocation section of the cloze test and also in the best way judgements. In the final investigation an attempt was made to achieve such improvements and also to evaluate the explanations in circumstances more similar to real trial consent sessions.



A, CERES explanation: better with random allocation = 55.38% (0–55.38%), better with doctor/patient choice/no difference = 44.62% (44.63–100%) (95% CI 43 to 67%); B, extended explanation: better with random allocation = 54.69% (0–54.69%), better with doctor/patient choice/no difference = 45.31% (54.70–100%) (95% CI 43 to 66%)

FIGURE 7 *Investigation 8: judgements of scientifically the best way following the CERES or extended explanation*

Investigation 9: comparison of CERES and extended explanations under individual testing, with passive and active methods of presentation

Summary

Participants (n = 128) entered one of four conditions at random: they received either the CERES brief justification for randomisation or the extended explanation (both embedded within a trial information leaflet exactly as in investigation 8) and they were required to process the information presented either passively or actively. In the passive condition, the experimenter gave the information orally while the participant had the leaflet in front of him or her, invited questions, then asked the participant to read the leaflet. In the active condition, which followed closely the MacCAT method of presentation, the oral presentation was given in short subsections, after each of which the participant summarised what had been said, asked any questions and heard a repeat of information missed. All participants underwent an immediate test of understanding immediately after the presentation, identical to that used in investigation 8. Thirty-two participants were also telephoned a week later and retested for their knowledge of randomisation and equipoise. Participants in all four conditions performed well in all of the tests. In particular, they judged that more certain knowledge would arise with random allocation than with doctor/patient choice, and that random allocation was scientifically the best way. There were no significant differences according to either CERES or the extended explanation, or method of presentation. The results offer no justification for using the more time-consuming active presentation method in this context, nor do they justify using the more lengthy explanation of randomisation over the CERES justification. Both versions appear to aid understanding of the scientific benefits of randomisation when used in this setting, although there were signs that information about equipoise could be missed in the CERES brief justification.

Background

The final investigation again compared the extended explanation for random allocation with the CERES justification, but this time participants were seen in individual sessions with the experimenter rather than in groups, as in all the previous investigations. This had three purposes. First, it was judged that individual sessions gave the best chance of revealing any benefits of the extended explanation over the CERES justification. Second, the researchers would have access to individuals' questions and comments as the information was presented and this might give useful information about how they interpreted each of the explanations. Third, with individual rather than group sessions the results could be generalised more readily to information given to potential trial participants, although since the participants were simulating illness there were still

very important differences from a real trial situation. The individual sessions took one of two forms. For the first (passive presentation), the experimenter gave the information on the sheet orally while the participant had the written version in front of him or her, and then the participant was asked to read the sheet and invited to ask any questions. This was intended to be similar to the procedure typically used in a researcher-led (as opposed to clinician-led) consent session in a real trial.

The second method of presentation (active presentation) was modelled on Appelbaum and Grisso's approach,[106] designed to assess patients' competence to consent to participation in a trial. This procedure was discussed in Chapter 2 ('Reflections drawing on theory and evidence from experimental psychology', p. 26). Participants are asked to summarise their understanding of each section of the consent information, and any omissions or misunderstandings are dealt with before moving on to the next session. The strength of Appelbaum and Grisso's approach is that it is based on the assumption that participants are likely to approach an invitation to take part in a trial with a script or schema based on standard doctor–patient consultations, in which doctors attempt to offer the most effective treatment for each particular patient. The weakness of the approach is that it also assumes that merely encouraging patients to abandon such misleading assumptions will be sufficient. It may be insufficient unless they have an appropriate alternative schema to fall back on. The present results suggest that many people have no such appropriate schema. In the active presentation method in investigation 9 the authors aimed to use the strengths of Appelbaum and Grisso's[106] approach while remedying what they took to be its weaknesses by providing participants with an accessible explanation. Our expectation was that the active presentation method would lead to better understanding than the standard method because of participants' engagement with the material.

Method

Participants

There were 128 participants (see *Table 2*). All were tested individually.

Design and procedure

Participants entered one of four conditions: they were given either the CERES or the extended explanation for randomisation, and they had either the passive or the active presentation. Conditions were randomly allocated to participant numbers, which were allocated consecutively when appointments were made. The trial leaflets used were the same as in investigation 8, and the outcome measures were also the same: cloze test, questionnaire for knowledge of randomisation and equipoise, and the certainty judgements and best way judgements for random allocation and doctor/patient choice. The tests were always presented in this order.

For participants in the passive group the experimenter gave the information on the sheet orally while the participant had the written version in front of him or her, and then the participant was asked to read the sheet and invited to ask any questions. For both presentation methods participants' questions were dealt with whenever possible by repeating the relevant section from the information sheet.

For participants in the active group, the experimenter again first presented the information orally, but this time after each of five sections on the sheet (the purpose of the research study, the voluntary nature of participation and right to withdraw, treatment and assessment procedures, equipoise and random allocation of treatments, and risks and benefits) participants were asked whether they had any questions about that section of information. After addressing any questions, the participant was asked to summarise his or her understanding of the section of information. Apparent misunderstandings were dealt with by repeating the correct information and omissions were addressed by using a series of predesigned probe questions. If the participant was unable to answer the probe question then the omitted information was repeated. This procedure was repeated for all five sections, after which the participant was asked to read the written information carefully. Finally, participants were given an opportunity to ask any further questions.

The final 32 participants were contacted by telephone with their agreement 1–2 weeks after their first session, and were asked again the four questions from the questionnaire to assess knowledge of randomisation and equipoise. The telephone interviewers were blind as to condition.

Results and discussion

Cloze test of understanding

Mean scores appear in *Table 9*. As in investigation 8, participants performed more poorly on the random allocation section (mean score per item 0.50 for passive CERES to 0.65 for active CERES) than on the other sections (average >0.8).

TABLE 9 *Investigation 9: cloze test of understanding*

Section of text	Mean score (SD) Passive		Mean score (SD) Active	
	CERES	Extended explanation	CERES	Extended explanation
Equipoise (two gaps; max. score = 2)	1.59 (0.71)	1.63 (0.71)	1.84 (0.45)	1.88 (0.49)
Random allocation (seven gaps; max. score = 7)	3.53 (4.65)	3.91 (2.01)	4.56 (2.06)	4.50 (1.98)
Other: purpose, procedure, risks, voluntary participation (ten gaps; max. score = 10)	8.56 (1.13)	8.06 (1.90)	8.72 (1.35)	8.78 (1.68)

TABLE 10 *Investigation 9: knowledge of randomisation and equipoise, numbers of participants who answered both items correctly for equipoise and for random allocation*

Knowledge item	Method of presentation			
	Passive		Active	
	Version of explanation		Version of explanation	
	CERES (n = 32)	Extended (n = 32)	CERES (n = 32)	Extended (n = 32)
Equipoise	25 Missing n = 1	23	28	27
Random allocation	28	26	28	29

A two-way MANOVA on correct scores for equipoise (out of 2), randomisation (out of 7) and other (out of 10), with version (CERES versus extended explanation) and presentation (passive versus active) entered as between-subjects factors, found no significant effect of version (Wilks' $\Lambda = 0.982$, $F_{3,122} = 0.746$, $p = 0.527$, partial $\eta^2 = 0.018$), a marginally significant effect of presentation (Wilks' $\Lambda = 0.942$, $F_{3,122} = 2.527$, $p = 0.061$, partial $\eta^2 = 0.058$) and no significant interaction between the two (Wilks' $\Lambda = 0.973$, $F_{3,122} = 1.137$, $p = 0.337$, partial $\eta^2 = 0.027$). As in investigation 8, the extended explanation of random allocation did not seem to have any benefit over the CERES justification. The marginally significant effect of method of presentation suggests that there may be small benefits of active presentation, but these are unlikely to be cost-effective.

Questionnaire on knowledge of randomisation and equipoise

Frequencies of correct responses appear in *Table 10*. As in investigation 8, performance overall was good. There was no sign of benefit of the extended explanation over CERES, and at most a very marginal benefit of the active method of presentation over passive: χ^2 tests carried out on version of explanation and method of presentation on whole sample, and again at different levels of other factor (e.g. effect of version of explanation among those with passive presentation only), found no significant differences between groups on knowledge of random allocation or knowledge of equipoise.

Follow-up after 1–2 weeks

The majority of participants who had answered correctly at first test performed as well after 1–2 weeks. For randomisation 24 answered both questions correctly at time 1, of whom 19 did so again at time 2. For equipoise the corresponding figures were 28 and 21. For randomisation questions, the five who made errors at time 2 only were balanced by five who made errors at time 1 only. For equipoise, in contrast, seven participants made errors at time 2 only but none made errors at time 1 only (binomial test $p = 0.02$). Despite this decline in performance on the equipoise questions, performance at time 2 still looks

TABLE 11 *Investigation 9: certainty judgements*

Allocation method	Mean certainty rating (SD) 1 (very unsure) – 4 (very sure)		Mean certainty rating (SD) 1 (very unsure) – 4 (very sure)	
	Passive		Active	
	CERES	Extended explanation	CERES	Extended explanation
Random allocation	2.96 (0.64)	3.13 (0.35)	3.06 (0.63)	3.17 (0.38)
Doctor/patient choice	2.25 (0.93)	2.43 (0.97)	2.06 (0.96)	2.45 (0.95)

substantially better than that of the uninformed pilot sample mentioned in the Method section of investigation 8, although it is not possible to make a formal comparison across samples. In investigation 9, 21 out of 32 (65.6%) were correct on both equipoise items at time 2, compared with ten out of 32 (31.2%) correct on both items in the pilot sample.

Appreciation of scientific benefits of random allocation

Mean certainty ratings appear in *Table 11*. In each of the four conditions, participants appear to give higher certainty ratings with random allocation than with doctor/patient choice. To analyse the results statistically, those who responded '5, don't know' on either of the certainty ratings were excluded (passive + CERES $n = 3$, passive + extended explanation $n = 2$, active + CERES $n = 1$, active + extended explanation $n = 3$).

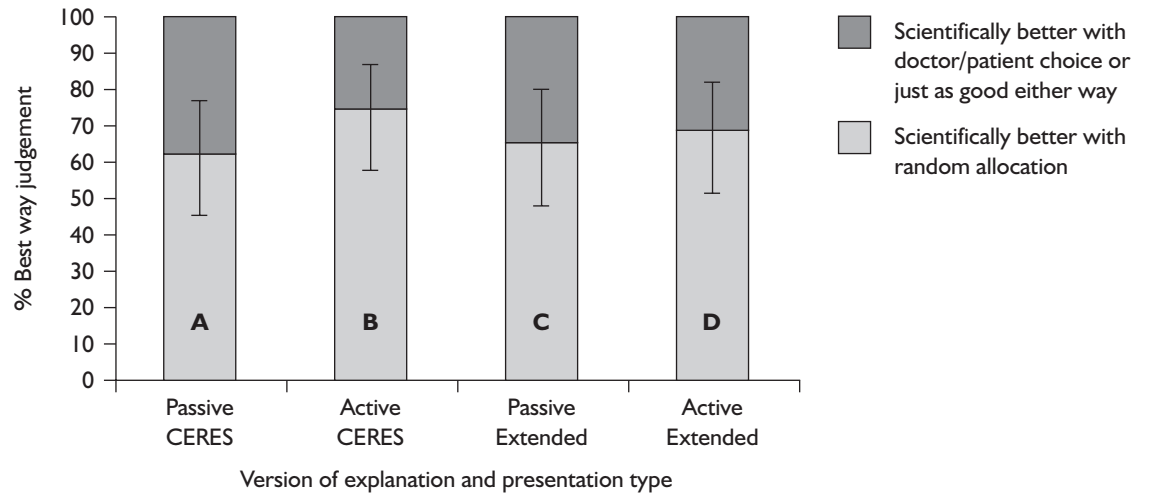
A repeated measures ANOVA with allocation method (random versus doctor/patient choice) as a repeated measure and two between-subjects factors of version (CERES versus extended explanation) and method of presentation (passive versus active) found a significant effect of allocation method (Wilks' $\Lambda = 0.642$, $F_{1,114} = 63.704$, $p < 0.001$, partial $\eta^2 = 0.358$). Participants rated doctors as more certain with random allocation than with doctor/patient choice. There was also a significant effect of version of explanation ($F_{1,114} = 4.322$, $p = 0.04$, partial $\eta^2 = 0.037$): unexpectedly and inexplicably, participants gave higher certainty ratings for both randomisation and doctor/patient choice with extended explanation than with CERES. There were no other significant effects.

Results presented in *Figure 8* suggest that unlike in investigation 8, randomisation was chosen as scientifically the best way by participants in all four groups.

Owing to low frequencies causing expected values below 5 in more than 20% of cells, for χ^2 tests 'doctor/patient choice' and 'just as good either way' were combined. The 2×2 χ^2 tests for the sample overall and calculated separately for version by different presentation groups and presentation by different version groups were non-significant. Binomial tests comparing random allocation with doctor/patient choice/just as good either way, were significant for CERES version ($p = 0.004$), extended explanation version ($p = 0.008$), passive presentation ($p = 0.033$) and active presentation ($p = 0.001$).

Active method of presentation: evidence of understanding

Participants given the active method of presentation were asked to summarise their understanding of each section of the information sheet. Transcripts were available for 56 of the 64 participants. For the sections on equipoise and random allocation, participants' summaries of the information and responses to follow-up prompt questions were scored as to whether they revealed awareness of random allocation (yes = 1, no = 0), whether they gave an adequate explanation of why random allocation was being used (i.e. referred to reducing allocation bias and aim of equality of patient characteristics between the two treatment groups, yes = 1, no = 0) and whether they reported equipoise (yes = 1, no = 0). The reliability of coding into these categories was checked by a second coder (ER), who independently scored 15 (27%) of the transcripts. Agreement was 100% for reporting of random allocation, 100% for reporting of equipoise and 73% (11/15) on whether an explanation of random allocation was adequate. The first coder (CK) agreed with the second without discussion on all four disagreements, and coded the remaining transcripts subsequently.



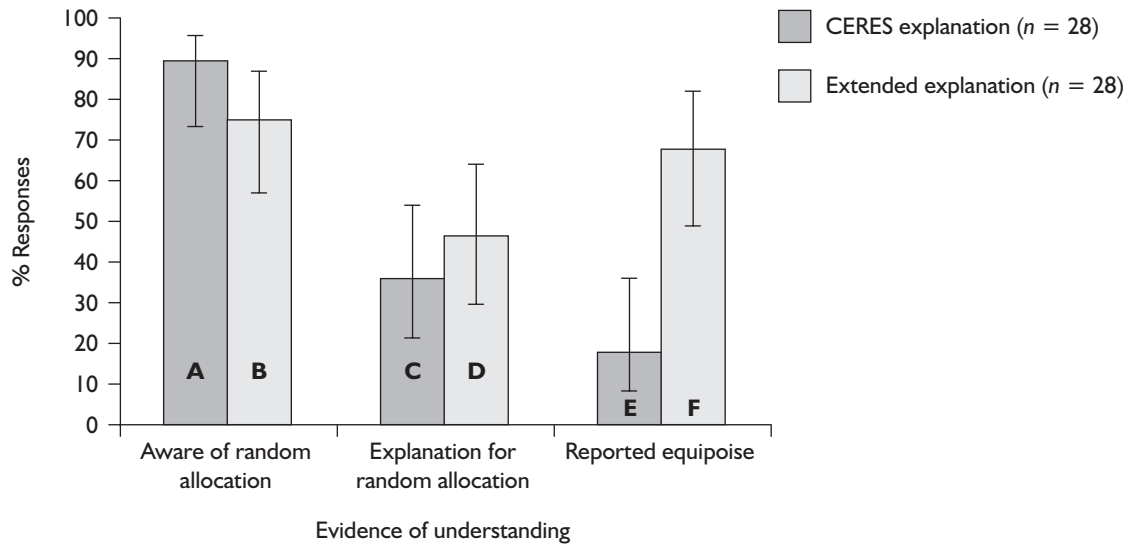
A, CERES/passive: better with random allocation = 62.5% (0–62.5%), better with doctor/patient choice/no difference = 37.5% (62.6–100%) (95% CI 45 to 77%); B, CERES/active: better with random allocation = 75% (0–75%), better with doctor/patient choice/no difference = 25% (76–100%) (95% CI 58 to 87%); C, extended/passive: better with random allocation = 65.625% (0–65.625%), better with doctor/patient choice/no difference = 34.375% (65.626–100%) (95% CI 48 to 80%); D, extended/active: better with random allocation = 68.75% (0–68.75%), better with doctor/patient choice/no difference = 31.25% (68.76–100%) (95% CI 51 to 82%)

FIGURE 8 *Investigation 9: judgements of scientifically the best way following the CERES and extended explanations with passive and active presentation (n = 32 in each group)*

The three scores were summed to give a measure of the completeness of participants' understanding of equipoise and random allocation. Reassuringly, this completeness of understanding score was significantly and positively correlated with participants' correct cloze score for the randomisation section ($r = 0.399$, $p = 0.002$) and whether participants selected random allocation as scientifically the best method over doctor/patient choice/just as good either way ($r = 0.494$, $p < 0.001$). The results for the CERES and extended explanation groups are summarised in *Figure 9*.

Participants receiving the extended explanation appeared to have the more complete level of understanding of equipoise and random allocation of treatments during information presentation, although the overall difference only nears significance [mean score (SD) for CERES group = 1.43 (0.84); extended explanation group = 1.89 (1.13), $t_{54} = 1.745$, $p = 0.087$, $d = 0.27$]. The difference is mainly due to very low levels of awareness of equipoise in the CERES group (five out of 28 CERES participants showed awareness, compared with 19 out of 28 with the extended explanation).

While these scores hint that those with the extended explanation may have fared a little better with understanding randomisation and equipoise at the time when it was explained to them, the benefits are modest at best. One of the main differences between the two explanations was that the extended explanation used doctors' hunches to explain both collective equipoise and why random allocation would be beneficial. Participants in this group who referred to doctors' views or hunches in their explanation ($n = 7$) generally provided a coherent account. Participant 111, for example (a 42-year-old female student with educational qualifications below GCSE/'O' level) said, "they will be picked at random by a computer because doctors have different views and their hunches are that one lot could be getting short term and one could be getting long term but it might not give us the right results so that's why you're gonna split them into two halves and give, pick them at random so that it was a range of different people and not certain ones getting one type and certain ones getting another type." In contrast, three participants seemed to struggle with this aspect of the explanation. For example, participant 76 (a 38-year-old women with no qualifications) said "that's slightly confusing isn't



A, CERES/aware of random allocation = 89.29% (95% CI 73 to 96%); B, extended explanation/aware of random allocation = 75% (95% CI 57 to 87%); C, CERES/explanation for random allocation = 35.71% (95% CI 21 to 54%); D, extended explanation/explanation for random allocation = 46.43% (95% CI 30 to 64%); E, CERES/reported equipoise = 17.86% (95% CI 8 to 36%); F, extended explanation/reported equipoise = 67.86% (95% CI 49 to 82%)

FIGURE 9 *Investigation 9: participants' understanding of equipoise and random allocation as reported during the active presentation method*

it … If doctors suggest each patient's treatment on the basis of their hunches then the two groups might be different, I don't understand that statement." This suggests that while the idea of doctors having hunches may be useful to some people, and avoids implying that individual doctors are in equipoise, it may not connect with widely held lay beliefs.

When asked to summarise the reasons for random allocation as part of the active presentation method, 49 of the 56 participants attempted to give one, and 23 of these were coded as adequate (41% of all 56 participants). The breakdown by CERES and extended explanation groups is shown in *Figure 9*. Many of the attempted explanations were scored as inadequate because they were statements of what random allocation achieves, rather than how or why it is important. The misconceptions and confusions that had been apparent in the interviews from investigations 4–6 were rare. In those studies, the most common explanation was that randomisation ensured that equal numbers of people tried each of the two treatments. In investigation 9 only one person (given the extended explanation) offered this as their only reason for randomising. When bias was mentioned in investigations 4–6 it was more often in relation to patients than to doctors: that patients may be more honest reporting success of a treatment not chosen by their doctor. Two participants in investigation 9 said this. In investigations 4–6 several interviewed participants confused random allocation with random selection or blinding, whereas nobody in investigation 9 made this mistake. In that respect both the CERES justification and the extended explanation appear to have achieved benefits.

Conclusions

As in investigation 8, there is no evidence that the extended explanation of randomisation has benefits over the CERES one. The active method of presentation may have small advantages over the passive method, but these are unlikely to be cost-effective given the additional amount of time involved (on average nearly twice as long). Although the discrimination between random allocation and doctor/patient choice could just be an artefact of the salience of the term 'random' in the text, the results of investigation 7 argue against that. The authors' preferred interpretation is that both the CERES justification and the extended explanation helped participants to appreciate the scientific reasons for random allocation in the context provided in investigations 8 and 9.

Why then was the CERES justification ineffective in investigation 7? There were two main differences between procedures used in investigation 7 on the one hand (when the CERES justification was ineffective), and investigations 8 and 9 on the other (when the CERES justification, like the extended explanation, was apparently successful in helping participants to understand the scientific reason for randomising).

First, in investigations 8 and 9 the justification was embedded within a trial information leaflet with a good deal of additional material about what would happen to participants in the trial. In investigation 7, in contrast, participants were given a much briefer description of the comparison between two treatments. If anything, it should be easier for participants in investigation 7 to focus on the scientific reasons for randomising, whereas participants in investigations 8 and 9 should be more likely to be diverted into thinking about patients' experience of being in a trial.

The second difference is the tests of understanding. Participants in investigation 7 made only certainty judgements of the knowledge gained with random allocation and doctor/patient choice. Participants in investigations 8 and 9, in contrast, made these judgements after they had completed the gap-filling cloze test and the questionnaire assessing knowledge of randomisation and equipoise. Perhaps these tasks encouraged participants to take a research rather than a treatment perspective, and to process actively and reflect on the information about randomisation and equipoise that they had been given in the information leaflet. In combination, these factors may have led them to understand the scientific reasons for randomising. If so, this may also explain why the summarising demanded of the active participants in investigation 9 seemed to have no worthwhile benefits: the tests given both to passive and active participants may have promoted active processing, and particularly a focus on the research design features of the trial, to a sufficient extent, and masked any benefits of active summarising. These speculations could easily be tested in further studies.

Investigations 7–9: general discussion and conclusions

There are both positive and negative aspects to the results of the intervention studies. On the negative side, the extended explanation for random allocation that was devised on the basis of Investigations 1–6 had no demonstrable benefits over the much simpler justification devised by CERES.[97] To the authors' knowledge, the CERES justification has not hitherto been evaluated to see what sense members of the public make of it. The CERES justification merely asserts the benefits of randomisation without explaining why random allocation avoids bias, or why bias may arise in the first place.

Comments from participants in investigations 4–6 suggested that at least some participants realised that two treatment groups needed to be matched in order to draw a valid conclusion about which treatment was better, but they did not see how random allocation achieved that. Other participants seemed not to understand the idea of group comparisons at all, and believed that the way to increase knowledge was to delve deeply into each individual's illness characteristics and response to the medication. In addition, the results indicated that participants had difficulty with the idea of individual equipoise.

The extended explanation for randomisation appeared to face up to these difficulties. It had the additional benefits of making clear that 'fair' comparisons are fair to treatments and not to patients, and that although a computer with no information about the individual would allocate patients to treatment groups, information about the individual would nevertheless be gathered. For all these reasons, the extended explanation was expected to be more effective than the CERES justification in helping participants to understand the scientific benefits of random allocation over doctor/patient choice. It was not, although the codings of the comments by the active group suggest that participants given the CERES justification were at risk of missing the information about equipoise.

One possibility is that had more demanding tests of understanding been used, or participants retested after a longer delay than 1–2 weeks, benefits would have been identified. It may still be that patients in real trials, who are concerned mainly with their own treatment and well-being and who may find it particularly hard to focus on the research aspects of the trial, would benefit from the more elaborate explanation rather than the brief and easily missed CERES justification.

On the positive side, within the procedures used in investigations 8 and 9, both the CERES justification and the extended explanation appear

to help participants to understand the scientific advantages of random allocation over doctor/patient choice. Since the CERES justification is shorter and simpler than the extended explanation, it may more readily be incorporated into real trial information leaflets. Even with passive presentation, intended to be similar to real researcher-led consent sessions, participants performed well in the tests of understanding that were not trivially easy.

It is important to remember, however, that the CERES justification was ineffective in investigation 7. In that study, participants as a group showed no sign of understanding the scientific benefits of random allocation. The CERES justification may be beneficial only in conjunction with active processing (which may have been promoted by the test questions in investigations 8 and 9) and a firm steer to take a research rather than a treatment perspective. Adding the CERES justification (or the extended explanation) to a trial information leaflet may well have no benefits unless there is additional encouragement to reflect on the scientific purpose of random allocation.

This tentative conclusion may be premature. In investigations 8 and 9 there was no control group like the one used in investigation 7, which had no justification for randomisation. Such a control seemed unnecessary given the poor performance with the CERES justification in investigation 7; CERES appeared to provide a suitable control for the extended explanation used in investigations 8 and 9. In the absence of such a control, it cannot be confirmed that the good performance among the CERES and extended explanation groups was due to their being given an explanation for randomisation. Performance may have been as good in a control group with no justification for randomisation, but just the description used for the control group in investigation 7. Evidence against this possibility comes from the interviews with participants from the active group, which showed that participants in investigations 8 and 9 largely avoided the misconceptions about randomisation that had been apparent in investigations 4–6. It is unlikely that this could have happened in the absence of any justification or explanation.

Chapter 5
Conclusions

Implications for healthcare

This research was not carried out in real healthcare settings. However, participants who judged random allocation unacceptable, doubted the possibility of individual equipoise and saw no scientific benefits of random allocation over doctor/patient choice in these procedures would be unlikely to reveal contrasting views if invited to enter a real clinical trial. The purpose of these investigations was to identify the background knowledge and assumptions that members of the public are likely to bring to bear if they enter a real trial setting. The results indicate that trial information leaflets that conform to current best practice may not enable potential trial participants to make an adequately informed judgement to consent or refuse to participate. Clear descriptions of what will happen may need to be supplemented with accessible explanations, along with cognitive support and encouragement to take a research rather than a treatment perspective. The results suggest that the CERES justification for randomising may be beneficial so long as it is provided in conjunction with these other supporting features. The CERES justification is currently available to people who purchase the CERES booklet,[97] but is not routinely required in trial information leaflets.

In practice, written information leaflets will often be supplemented by oral information, and this research has not examined the consequences of such supplementation. Currently, so far as the authors understand it, orally provided information is not subject to the same scrutiny by research ethics committees as are written leaflets. One possibility is that in practice, many or even most potential trial recruits are offered accessible oral explanations for randomising and that there is no need to supply explanation in the written leaflet. Research summarised in Chapter 2 ('Update of 1998 literature review') (e.g. Jenkins[51]) suggests that this is currently not the case. Even if it were, it could still be argued that it is important that patients have a written version to take away with them while they make their decision whether or not to participate, and as a reminder once the trial is underway if they do take part.

One problem with written information leaflets is that they are not tailored to the individual, and oral information is more readily adjusted in response to feedback from each patient. In practice, though, such adjustments may not always take place, or if they do they may not lead to improvements in patients' understanding.[11] Written information sheets are likely to bear the burden of responsibility for ensuring that potential trial recruits have access to the information they need, not least because what is given orally may be heavily determined by the content of the written sheet.

Although the researchers argue for the importance of explanation in written information sheets, the evidence gathered here about the background knowledge and assumptions that members of the public are likely to bring to bear when faced with such a sheet could well be helpful to researchers or clinicians who will be providing oral information. For example, knowing that patients may doubt that individual doctors can be in equipoise may prompt trialists to explain collective equipoise to potential recruits. Knowing that patients may think that doctor/patient choice of treatment will lead to just as certain knowledge as random allocation may prompt trialists to elaborate on why this is not the case. Knowing the importance (and likely difficulty) of taking a research perspective may prompt trialists to give patients the steer that they need.

Finally, and most generally, these results may provide an impetus to trialists to evaluate trial information leaflets using relevant participants, and not just to construct them using a template or readability scores. Although written information cannot be tailored to suit each individual patient, it can be piloted for its suitability for the particular patient groups who will read it. At present, the authors' understanding is that research ethics committees do not expect evidence of such evaluation to be provided, and some may be content with conformity to a given template. In an era of evidence-based medicine, the wording of trial information sheets should be based on empirical evidence that the particular group of patients for whom they are created is likely to understand them as intended.

Recommendations for research

- It is important to investigate how participants' understanding of random allocation and equipoise is influenced by oral accompaniments to written trial information. There has been some valuable work on what is actually said in recruitment sessions,[51] but further work is needed to understand the likely consequences of different patterns of oral and written information-giving, and to identify the optimal balance for maximising patients' understanding and remembering about randomisation and equipoise.
- In line with previous findings, the present results highlight participants' tendency to see a trial as aiming to identify the best treatment for each particular recruit. This tendency is likely to be even stronger among patients in real clinical settings, given that they are understandably concerned mainly with their own treatment and well-being. Yet taking this treatment perspective appears to make it harder to understand the reasons for randomising, and appears to make random allocation more unacceptable. Further research is needed to identify the most effective ways of helping potential trial participants to take a research rather than a treatment perspective.
- A disadvantage of written information leaflets is that they are not tailored to suit individual patients. They can, however, be tailored to suit the particular patient groups who will be invited to participate in a specific trial. The current emphasis on adherence to national guidelines means that this possibility may not be realised. It is important to explore the feasibility and utility of expecting trialists to provide research ethics committees with evidence that their proposed trial information leaflet has been evaluated on an appropriate sample, and not constructed merely to conform to a given template, which may not have been adequately evaluated.
- Research is needed to explore lay conceptions of the advance of medical knowledge. Comments made in these investigations suggest that some participants overestimate what is already known about the effectiveness of treatments, and doubt the need for comparisons. Some participants also appeared to have difficulty grasping the idea of comparisons between groups, rather than detailed examination of individuals. Taking part in a clinical trial is likely to be the closest encounter that many people have with science in practice, and so may provide a good opportunity for advancing science communication, but very little is known about how trial participants construe medical advances and the place that their trial may have in such advances.

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Contribution of authors

All authors approved the final report. In addition, E Robinson (Professor of Psychology) as principal investigator takes responsibility for integrity of the work as a whole. She was responsible for the overall conception and management of the project, and supervision of the design of all empirical investigations, and of the collection, analysis and interpretation of all the data, and took the lead in writing the final report. C Kerr (Research Fellow in Psychology) was principal researcher throughout the project. She conducted the literature review, collected the data for all investigations except for investigation 7, and was involved in the design, analysis and interpretation of all investigations and in drafting the final report. A Stevens (Professor of Public Health), R Lilford (Professor of Health Services Research), D Braunholtz [Senior Research Fellow in Public Health and Epidemiology (Statistician)] and S Edwards (Lecturer in Medical Ethics) attended frequent meetings with ER and CK to discuss the design, results, analysis and interpretation of each investigation. S Beck (Research Associate in Psychology) was primarily involved in the review of literature from experimental psychology, and also contributed to the main literature review. M Rowley (Research Associate in Psychology) was involved in the design, data collection, analysis and interpretation of investigation 7, and in the preparation of the final report.

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Appendix 1

Patients' understanding of consent information in the context of clinical trials

Study and Journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Agard *et al.*, 2001[23] *Heart*	Study to investigate how patients included in trials on treatment in the early phase of acute myocardial infarction experience the consent procedure Semistructured interviews were carried out with participants focusing on their knowledge of the trial in which they had participated, their experiences and feelings over being included and their attitudes towards the consent procedure. Notes made during interview were subjected to content analysis Sweden	Patients (*n* = 31) who had consented to participate in three RCTs of acute myocardial infarction between March 1998 and May 1999	1. Most participants felt that when asked to consent they either had too low a level of consciousness to understand the information given, or were in too much pain to bother 2. According to some patients their knowledge about the trial was almost non-existent and two did not know that they had been included in the trial 3. Participants felt that they had little choice in the circumstances	100% of patients who were approached and were in a stable condition participated Qualitative study *Authors did not state how long after consent participants were interviewed* *Authors described using content analysis on notes taken in interviews (coding of qualitative to give quantitative representation), yet presented results in the form of a thematic analysis with verbatim quotes* *Qualitative analysis was carried out by two of the authors although no validity checks of analysis were reported*

continued

Study and Journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Appelbaum *et al.*, 1999[7] *American Journal of Psychiatry*	Study using a new instrument to assess depressed patients' capacities to consent to research Participants were approached immediately after their first psychotherapy session, 1 week after consenting to participate in a study of maintenance psychotherapy in recurrent depression. They were given the MacCAT-CR, a semistructured interview format instrument which assessed understanding of disclosed information about the nature of the research project and its procedures; appreciation of the effects of research participation on subjects' own situations, reasoning about participation and ability to communicate choice. Subjects were administered the MacCAT-CR a second time 8–10 weeks later USA	Participants were outpatients diagnosed with depression, and the first women to enrol in the psychotherapy trial ($n = 26$)	1. The mean score on the understanding scale was 23.33 out of a maximum of 26, with no subject scoring below 20 and more than 90% of participants obtaining full credit on most items 2. The mean score on the appreciation scale was 4.89 out of a maximum of 6. The mean reasoning score was 6.50 out of a maximum of 8. 65–75% of the participants received full credit on most of the appreciation and reasoning items 3. Performance on understanding and reasoning were correlated ($p = 0.05$), while neither was correlated with appreciation scores 4. Test-retest correlations for understanding and appreciation were at or near significance ($p = 0.08$, $p = 0.01$), but not very strong. The test–retest correlation for the reasoning scale showed no relation between the first and second administration See also *Appendices 2* and *3*	Response rate was 100% Research staff members conducting the interviews received feedback on their performance; two raters scored the first five interviews independently and then met to resolve differences, they carried on rating independently until there were minimal differences. Thereafter one research assistant carried out the rating. The MacCAT-CR manual is available elsewhere *No acceptable score was given to indicate what proportion of the sample could be judged to have had the capacity to give informed consent* The authors evaluated the weak test–retest correlations as to be expected when ratings are clustered within a small range. They identified a change in participant response style as responsible for the lack of test–retest relationship on the reasoning scale

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Study and Journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Baskin *et al.*, 1998[38] *Journal of the American Geriatrics Society*	Study to identify barriers to informed consent in research involving subjects with advanced dementia Patients over the age of 65 years admitted to a teaching hospital with a diagnosis of dementia were eligible for inclusion in a randomised controlled clinical trial of palliative approaches, compared with usual care. Primary care physicians were contacted for approval and, if obtained, attempts were made to identify and contact the appropriate surrogate to give informed consent on the patient's behalf USA	For all eligible patients ($n = 146$) surrogates were sought	1. For 3% of patients their surrogate understood the study but refused to allow the patient to participate (informed refusal) 2. For 19% of patients their surrogate was unable to understand the research protocol and therefore could not give informed consent on the patient's behalf	In 47% of cases researchers were unable to engage a surrogate in the consent process *No indication is given as to how researchers assessed the understanding of surrogates*
Bjorn *et al.*, 1999[39] *Journal of Medical Ethics*	Study to investigate whether linguistic analysis and changes in information leaflets can improve readability and understanding Two information leaflets from trials of drugs for commonly known conditions/diseases (hypertension and sterilisation) were simplified by rearranging and breaking up text into smaller segments with subheadings, shortening sentences and replacing professional language with lay language. Participants were randomised to receive either an original or a revised trial leaflet and immediately after having read their leaflet, completed a multiple-choice questionnaire aimed at	Participants were recruited from centres and clubs for pensioners (aged ≥ 60 years) for the hypertension trial leaflet ($n = 135$) and female participants were recruited from workplaces for the sterilisation leaflet ($n = 100$)	1. In both cases the revised leaflet was perceived to be easier to read and easier to understand than the original trial leaflet. More participants perceived the revised hypertension leaflet as very easy to read ($p < 0.005$) than did the original, and likewise the revised sterilisation leaflet ($p < 0.001$). More participants perceived that they understood all the information in the revised sterilisation leaflet than did the original ($p < 0.001$); and for both trials, more participants judged there to be no words or concepts that they did not understand for the revised versions of the trial leaflets than did for the original versions ($p < 0.001$)	No response rate given Most results reported from the hypertension sample only. The authors point out that the hypertension study was of easier design and so easy to explain; however, the sterilisation study was more complicated and so making information more readable did not make it any less complex *No reported testing of validity or reliability of the questionnaire. Questionnaire was not included in published article*

continued

Study and Journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
	testing the cognitive understanding of the respondents Denmark		2. More than 90% of all respondents, irrespective of leaflet and trial, correctly answered that participation was voluntary and they could withdraw at any time. Participants with the hypertension trial leaflets found the revised leaflet gave a 'more open choice' as to whether one wishes to participate ($p < 0.005$) 3. Only 26% participants with the original hypertension trial leaflet and 42% with the revised hypertension leaflet correctly identified that chance decides which treatment they would receive. Most participants thought that it was the responsible doctor who decided. In the sterilisation study, by contrast, most participants answered this correctly 4. In the hypertension trial sample, cognitive understanding increased with both level of education and receiving the revised leaflet independently. There was no connection between cognitive understanding and any of the background variables for the sterilisation trial sample. For both versions of both leaflets there was a positive correlation between perceived comprehensibility and understanding ($p < 0.05$) See also *Appendix 2*	

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Study and Journal	Purpose of study and method of assessment	Sample population (n = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Carpenter *et al.*, 2000[40] *Archives of General Psychiatry*	Study to ascertain the decisional capacity for informed consent in research participants with schizophrenia and to address reduced capacity with an educational informed consent process Participants were asked to participate in a hypothetical randomised, double-blind trial of a novel antipsychotic medication. Information disclosure was followed by administering a version of the MacCAT-CR (see Appelbaum *et al.*, 1999[7]). Participants also completed a battery of cognitive tests. Following this a subset of poorly performing participants with schizophrenia participated in an educational process where subjects took part in two sessions of 30 minutes reviewing the study protocol. In addition, inpatients had access to a computerised interactive routine or flipchart designed to teach basic concepts such as protocol, random assignment, drug withdrawal and placebo USA	Participants were drawn from inpatient (n = 20) and outpatient (n = 10) research programs at a psychiatric research centre. The comparison normal group of subjects (n = 24) were recruited from community centres and a free medical clinic	1. The subjects with schizophrenia scored significantly lower than the comparison group on the understanding ($p = 0.001$), reasoning ($p = 0.002$) and appreciation ($p < 0.001$) scales 2. Cognitive measures were highly predictive of MacCAT-CR performance. Two of the cognitive tests predicted understanding scale performance ($p < 0.001$, $p < 0.006$), two predicted performance on the reasoning scale ($p < 0.01$, $p < 0.02$) and two predicted performance on the appreciation scale ($p < 0.02$, $p < 0.03$) 3. The 20 subjects who completed the MacCAT-CR a second time after the educational process showed significant improvement on understanding ($p = 0.001$), reasoning ($p = 0.04$) and appreciation ($p = 0.001$) scores, with 70% scoring 20 or higher on the understanding scale. This is a significantly larger proportion than in the normal group (46%, $p < 0.04$). There was no difference in the mean understanding of these two groups	Response rate among inpatients was 90.1% and for outpatients was 100%. *No response rate for the normal group was given* Reliability exercises were conducted involving ten raters and 12 patients; these reflected substantial between-rater agreement on the scoring of items, with intraclass correlations of understanding 0.98, and reasoning and appreciation 0.84 The patients with schizophrenia were considered to have performed poorly if they scored below the median normal group score of 20 on the understanding scale

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Cox and Avis, 1996[9] *Cancer Nursing*	Exploratory pilot study of patients' views as they progressed through anticancer drug trials Participants were interviewed three times, 2–3 days after offer of trial participation, during the review of treatment and 1 week after completion of the trial UK	Patients participating in Phase I ($n = 1$) or II anticancer drug trials ($n = 6$)	1. Respondents reported having had both written and verbal information about the trial, but their accounts of the initial consultation were characterised by poor recall even though it had taken place only a few days before the interview. Respondents felt overloaded with information and had very little time to digest it. The three points that respondents persistently recalled were the experimental nature of the drug (using the phrase 'guinea-pig' in their description of what participation involved), the fact that the drug might not benefit them, and their right to withdraw from the trial 2. In many cases the respondents expressed the view that they did not need to know about the trial in detail, instead they wanted information about what to expect once the trial was underway. Apparently patients saw information as falling into two categories, that which enabled them to be certain of what was going to happen to them and that which informed them about the trial 3. The desire to be advised about what was best for them meant that respondents found it difficult to be told that any decision was their responsibility. They felt that they did not have the background knowledge to make the decision and wanted to hand over control and responsibility to their doctors. They thought that doctors were experts and knew best	Convenience sample. *No response rate was given* Qualitative study Critical incident technique was used in design of part of the interview schedule to obtain examples of incidents that illustrate positive and negative aspects of the care they experienced. Example of interview schedule included in paper *Unclear as to what method of qualitative analysis was used* *Phase I and II trials unlikely to be randomised, especially as the paper states that in all cases there was no standard treatment available for the patients. It is unsurprising then that patients felt that in reality they had no choice, because not participating was equated with death*

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Study and Journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Davis *et al*., 1998[41] *Journal of the National Cancer Institute*	Study to test whether a simplified consent form would be less intimidating and more easily understood by individuals with low-to-marginal reading skills Participants were tested for reading ability before reading either the standard SWOG consent form (16th grade level) or a simplified form (seventh grade level) developed by LSU Medical Center. Participants were interviewed using a structured oral questionnaire developed by the investigators to assess their attitudes towards and comprehension of the form read. The participants were then given the alternative consent form and asked further questions about their preferences. Either the SWOG or the LSU form was presented first on alternate days USA	Participants (n = 183) were either patients attending private and university oncology clinics or residents at a low-income housing complex. A smaller number (n = 69) received the SWOG form first as the interviews took twice as long as when participants received the LSU form first (n = 114)	1. More participants thought the LSU form easy to read than did the SWOG form (97% vs 75%, $p < 0.0001$). The LSU form was rated as better ($p < 0.0001$). Participants reading at an eighth grade level and below preferred the LSU over the SWOG form (70% vs 30%, significance not reported), but less so participants reading at a ninth grade level or above (52% vs 48%, significance not reported). 2. There was no difference in total patient comprehension between the LSU and the SWOG forms (58% vs 56%) or on any of the ten individual questions used to assess comprehension 3. Participants' comprehension scores were related to their reading ability ($p = 0.038$ for the trend). Adults reading at or above ninth grade level had significantly higher comprehension of both forms than those reading at or below eighth grade level ($p < 0.0001$) See also *Appendix 2*	Response rate was 89% Structured oral questionnaire was piloted to ensure that the questions were clear and understandable to patients. *It was not tested for reliability and validity. Given that it was used in an interview context, no inter-rater reliability was tested or reported. Questionnaire was not included in the published article* *The authors reported the main finding that participants preferred the LSU to the SWOG form (62% vs 38%, p = 0.0033); however, this effect appears to be accounted for by the interaction with reading level reported here in main findings. The authors did not test the significance of this apparent interaction* *Scores on the ten comprehension questions were reported, but there was no indication of what the response options were, giving no information on what wrong answers people were choosing*

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Dresden and Levitt, 2001[43] *Academic Emergency Medicine*	Study comparing post-'consent' information retention following a standard industry consent form compared with a modified version The industry form (IF) for an asthma study was modified (MF) by focusing only on providing the minimum required information, increasing readability and in response to comments made by physicians, nurses and patients. Participants read randomly assigned IF or MF in the belief that they were reviewing consent forms for a real trial, and completed a multiple-choice post-consent test USA	Participants were patients who presented with asthma exacerbation at an emergency department (*n* = 100)	1. The IF resulted in correct scores ranging from below 45% (randomisation: "will I definitely get the drug if I enrol in the study?" and compensation for injury: "will I be reimbursed for both known and unknown problems related to the drug?") to 100% ("will my doctor answer questions?"), with most items ranging from 70 to 90%. The MF resulted in correct scores ranging from 54% (compensation for injury) to 100% (will my doctor answer questions), with most items ranging from 74 to 98% 2. The MF resulted in significantly higher scores on purpose, randomisation, length, risks/side-effects, benefits, alternative treatments, confidentiality and voluntary participation questions than the IF See also *Appendix 2*	*Response rate not given* If participants reported before the test that they had not read the entire form they were excluded from the study; however, those who subsequently reported within the test that they had not read the entire form were not excluded from the analysis *Neither version of the consent form was included in the paper* The post-consent test contained mainly questions that could only be answered by yes or no (ten out of 12), rather than multiple choice, although the response options were not included in the paper

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Dunn *et al.*, 2001[49] *American Journal of Psychiatry*	Study investigating whether a novel consent procedure improved the comprehension of consent for older patients with psychosis Participants were randomly assigned to receive routine (consent form read aloud by researcher while participant read own copy) or enhanced consent procedure (computerised presentation of consent information while researcher read it aloud). Then they had up to three attempts to complete a 20-question comprehension assessment with feedback and information on wrong answers given in the format of the original presentation between assessments USA	Participants were middle-aged or elderly patients enrolled in the Intervention Research Center for Psychosis in Older People ($n = 50$) and demographically equivalent normal comparison subjects ($n = 19$)	1. 11 out of the 26 patients (42.3%) who received the enhanced consent procedure scored 100% at trial 1, compared with two of the 24 patients who received the routine procedure (8.3%, $p = 0.003$). At trial 2, 21 of the 26 (80.8%) with enhanced consent procedure compared to 11 out of the 24 with routine consent procedure (42.3%) scored 100% 2. Normal comparison subjects' scores did not differ across conditions	*Response rate not given* *Comprehension was reported only in terms of how many achieved 100%, and as the questionnaire was not included in the paper there is no indication what areas of comprehension were tested or answered correctly*

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Featherstone and Donovan, 1998[14] *British Medical Journal*	Study to explore trial participants' understandings of randomisation In-depth semistructured interviews were carried out using a checklist of topics to encourage participants to describe their experiences UK	Patients (*n* = 20) from the ClasP RCT evaluating the effectiveness of laser therapy, standard surgery and the conservative management for men with symptoms related to benign prostatic disease	1. Almost all participants were aware of some aspects of randomisation and 14 of the 20 acknowledged the involvement of chance in the allocation of their treatment. Often this was described using lay examples of chance, such as a lottery or lucky dip. However, participants found randomisation confusing because lay beliefs and previous experience meant that they expected clinicians to assign them to treatment based on their specific symptoms, clinical findings and age. This is reinforced by the number and complexity of tests and questionnaires they completed during the trial. Two participants were unable to discuss randomisation because they did not believe that their allocation was different from normal clinical practice 2. In lay language the word trial means something that is tried out, while 'at random' relates to things being done without purpose See also *Appendix 2*	Sample was chosen to reflect a broad range of individuals and experiences. *Response rate not given* Qualitative study *It is unclear how long after patients were invited to participate in ClasP the interviews took place* Grounded theory analysis was used to identify common themes based on verbatim transcripts. Analysis was carried out concurrently with data collection by one researcher. The second author confirmed the accuracy of the data analysis, *but did not state how*

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Study and Journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Ferguson, 2000[26] *Journal of Reproductive and Infant Psychology*	Originally a study to assess patient satisfaction and understanding of consent information that they had received, and their motivations for having agreed to participate in research trials. Comparison of views of patients involved in a trial of a drug used in labour with those in other trials became main focus of the paper when analysis revealed different responses in that group Patients in the comparative sample were approached by medical staff during trial treatment. Patients in the labour trial were approached up to 12 months after their trial participation by the author. Patients' satisfaction with and understanding of consent information and their motivation for trial participation were assessed by interview using forced-choice and open-ended questions. Qualitative findings used to expand on quantitative findings UK	Patients who had participated in Phase II, III or IV pharmaceutical trials ($n = 104$). Labour trial sample ($n = 26$) compared with other trials sample ($n = 78$)	1. 95% of the comparative sample and 65% of the labour sample felt that the right amount of information had been provided ($p < 0.001$). The labour sample statistic may be misleading as women appeared to select this answer to reflect the fact that they were in pain at the time and could not have coped with any more information. Rather than feeling that the information was adequate to allow them to make an informed decision, they could not see the point of having any more detailed information in that situation 2. 99% of the comparative sample and 54% of the labour sample could recall receiving written information ($p < 0.0001$) 3. 100% of the comparative sample and 91% of the labour sample felt that they had understood all or most of the information ($p < 0.01$) 4. 1% of the comparative sample and 19% of the labour sample were unable to comment on their understanding of information ($p < 0.001$). 12% of women in the labour trial were unable to comment on motivation to participate because, while they may have been aware that they had agreed to take part in some research, they were not aware that it involved taking a new drug; they thought that it was routine. Women agreed to participate because they were given the impression that the level of care would be better; the fact that a doctor would remain present throughout	The response rate for the labour sample was 48%. *The response rate for the comparative group was not given, nor was the sampling method stated* *Very unmatched groups to compare. Demographic descriptions of the samples show them to be very different in terms of age, gender and employment status. Also, the groups were interviewed at different stages in their trial participation; while the comparative sample was still receiving treatment (no information given about how long they had been receiving treatment) the labour sample was interviewed 7–12 months after giving birth* Interview questions were included in the published paper, but the original consent information could not be identified owing to patient confidentiality *Qualitative findings were not reported for the comparative group*

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Study and Journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
			the birth may have been used as a selling point 5. 96% of the comparative sample and 58% of the labour sample felt that they had plenty of time to ask questions ($p < 0.0001$) 6. Labour samples' low level of satisfaction with informed consent may be accounted for by mistiming of request for consent; according to the trial protocol they should have been informed of the trial at antenatal classes, but most women reported being approached for the first time when they were in labour	

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Study and Journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Fleissig *et al*., 2001[10] *European Journal of Cancer*	Intervention study to improve communication during consultations about randomised clinical trials of cancer therapy Eligible trial patients completed questionnaires about information preferences (Patient Preference for Information Questionnaire) and attitudes to trials (Patients' Attitudes to Trials Questionnaire) before seeing their doctors. Half of the questionnaires (those completed by the intervention group) were shown to the doctors. Doctors were randomised into two groups, which varied the order of intervention or control group consultations. After the consultation, participants were asked to complete questionnaires about their satisfaction, the doctor–patient interaction and their reasons for accepting or declining treatment within a clinical trial. Doctors assessed the interview after the consultation UK	Self-selected doctors (*n* = 15) at district general and university teaching hospitals invited eligible patients with cancer (*n* = 265) to join one of 40 different randomised trials Same sample as Jenkins *et al.*[51] (this appendix and Appendix 2); also Jenkins and Fallowfield[46] (Appendix 3)	1. A larger proportion of those who accepted entry into the trial felt that they were given enough information (87.1% control, 83.2% intervention, compared with decliners 69.2% control, 63.6% intervention) 2. Most patients knew that they could leave the trial/study at any time and still be treated (98.9% control, 99.1% intervention, compared with decliners 88.9% control and 95.7% intervention), and most felt that the doctor told them what they needed to know about the trial (94.7% control, 98.1% intervention, compared with decliners 88.0% control, 91.3% intervention) 3. 19.5% of those in the control group and 13% of the intervention felt unclear about some of the things the doctor told them 4. There was no association between the doctors' ratings of the consultation and whether they had seen patients' questionnaires. There were no significant differences in patients' satisfaction with consultation between the control and the intervention group See also *Appendix 3*	Doctor response rate of 63%. Patient response rate of 90.8%, although 10% of participants did not return their questionnaires after the consultation *Questionnaires focused more on patient satisfaction and willingness to participate in trials rather than understanding. Differences between groups on items relating to understanding were not tested for significance*

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Study and Journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Fogas *et al.*, 2001[22] *Journal of Developmental and Behavioral Pediatrics*	Study evaluating children's perceptions of their participation as research subjects At least 8 months after venipuncture, children were interviewed over the telephone using a 14-item (six experience, eight attitude items) interview structure USA	Children aged 6–19 years who had a single venipuncture as part of an attention deficit hyperactivity disorder medication trial (*n* = 115)	1. Over 89% of children believed that they could have said 'no' when first asked to be in the study, and 73% believed that they could have said 'no' at the time of the venipuncture 2. 31.3% reported that the procedures were 'exactly' as explained, 30.4% 'a lot like it was explained', 14.8% 'a little' or 'a lot' different and 23.5% did not remember	89% of the original trial sample was located, 68% of these were interviewed Agreement of over 80% on test–retest reliability of 25 children, although the authors reported concern about the reliability of children's recollection of events 8 months earlier *Despite a wide age range of children, age was not examined in the results*

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Study and Journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Fortney, 1999[18] *Studies in Family Planning*	Study to assess understanding of consent information in a contraceptive clinical trial Participants were interviewed up to 289 days after they were admitted to the clinical trial about information that they had been given at consent USA, Latin America and Africa	Women in four clinical sites (USA, Africa, Latin America 1 and 2) who had consented to participate in a clinical trial to assess the effectiveness of a barrier contraceptive (n = 70)	1. 55% of women asked correctly understood the research purpose of the study 2. 79% recalled being offered alternative methods of contraception 3. 69% recalled being told who could look at their medical records 4. 79% remembered correctly how much they were paid for participating 5. 67% perceived that clinic staff would be fine with them if they withdrew from the study. However, in the African site 27% of women gave this answer, and overall understanding that withdrawal from the study was acceptable was better understood at the time of later interviews than from those conducted closer to the time of consent 6. 83% of those asked remembered being told about possible side-effects of this method of contraception, but when asked whether 'anything bad' might happen as a result of participation, the only fear anyone mentioned was the risk of becoming pregnant 7. 23% correctly recalled the estimated risk of becoming pregnant with this contraceptive method, 19% estimated too high and 41% too low. 27% correctly perceived this level of risk as high. Recall of the method's effectiveness was better among women interviewed closer to the time of consent	*Response rates were not given*. The authors commented that the original goal was 120 participants Different interviews were designed for interviewing within 6 weeks of admission and 6–26 weeks after admission or at the end of the trial. However, the interviews did not follow protocol as intended, so the data were combined. Some questions asked in the early interview were not asked in the later design, so for findings 1, 2, 3 and 6 are from a sample size of 29 women. The authors analysed the data by time since admission, but only two questions revealed differences (see findings 5 and 7) *The method of recording interview data was not mentioned, nor was the method of analysis or any reliability checks*

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Study and Journal	Purpose of study and method of assessment	Sample population (n = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Fureman *et al*., 1997[48] *AIDS Education and Prevention*	Study evaluating the impact of a supplementary video about preventive HIV vaccine trials Participants were randomly assigned to either a standard (written information only) or video-supplemented (written information and video) presentation. Participants completed a questionnaire designed to measure knowledge of the information, trust and willingness before information presentation, at the end of the session and 1–2 months afterwards USA	Participants were injecting drug users participating in a risk assessment project (n = 186)	1. General HIV vaccine trial knowledge increased for participants in both groups ($p < 0.005$, $p < 0.0005$) 2. At the test 1–2 months later, the knowledge level in the standard group had returned to the pretest level, whereas knowledge remained high for the video-supplemented group ($p < 0.005$) 3. At the end of the information session, both groups showed an increase in willingness to participate in a vaccine trial ($p < 0.05$), but there was no difference in willingness between the groups, and the increased willingness was no longer there 1–2 months later 4. Regardless of group assignment or evaluation point, knowledge about vaccine trials was not associated with willingness to participate in a trial. Willingness was associated with trust at all evaluation points and in both study groups	Acceptance rate was 45.1% 89% of the sample completed the questionnaire 1–2 months after the information session The composite trust and willingness scores had Cronbach's alphas of 0.63 and 0.75, respectively The participants for this project had been enrolled in a longitudinal study of risk behaviours for several years. Therefore, they may have previously received information informally about HIV vaccines, which may have contributed to their generally high levels of knowledge at baseline

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Study and Journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Glogowska *et al.*, 2001[31] *International Journal of Language and Communication Disorders*	Study of the attitudes of parents whose children took part in an RCT In-depth interviews were carried out 12 months into participants' involvement in the trial UK	Parents whose children participated in an RCT evaluating the effectiveness of community-based SLT for preschool children with speech and language delay (*n* = 20)	1. Parents perceived that the allocation to immediate therapy or 'watchful waiting' would take their circumstances into account and favour them: "If she'd [the therapist] seen something … and thought … this is something really serious well then he wouldn't have been put on that sort of waiting group" 2. One parent, in expressing the uncertainty that therapy had made any difference, proposed the idea of a trial. "It would be interesting if you could cut them in half … let them have therapy and just leave them alone and see what happens", apparently unaware that this was what had happened to her child See also *Appendices 2* and *3*	Parents were a subsample selected from 259 who participated in the RCT. Selection aimed to represent as wide a range of experiences as possible. Response rate was not given Qualitative study Data were analysed according to the framework method. *The authors did not elaborate on this and mentioned no checks on reliability* *Perceptions of allocation were assessed 12 months after it took place*
Gotay, 2001[16] *Cancer Epidemiology, Biomarkers and Prevention*	Study examining perceptions of the informed consent process in healthy men participating in a cancer prevention trial 2 years into their trial participation, participants received postal questionnaires including forced-choice and free-response items about their experience in the cancer prevention trial Hawaii	Healthy males who were participating in a 7-year cancer chemoprevention clinical trial (*n* = 69)	1. 68% could recall reading a consent form, 68% could recall someone explaining the consent form; the rest denied reading a form or receiving an explanation or could not remember 2. 46% did not remember whether the consent form was understandable, 29 out of the 37 who could remember rated it as easy or very easy to understand 3. 52% did not remember the amount of information in the consent form; 30 out of the 32 who could remember reported the information as 'just right'	Response rate was 82% The authors described the consent procedure at the institution as involving extended counselling about the study before signing a detailed consent form, of which they were provided with a copy

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Study and Journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Hayman *et al.*, 2001[36] *Journal of Paediatrics Child Health*	Study investigating the process and quality of informed consent, motivation and influence in parents who were invited to enrol their baby in a research project. Two anonymous postal questionnaires made up of quantitative and qualitative questions were sent to parents after the completion of the clinical research, one for consenting parents and one for declining New Zealand	Parents who had consented to their baby being tested as part of the sudden infant death syndrome (SIDS) research study (*n* = 65) and parents who had refused (*n* = 49)	Consenting parents: 1. 100% felt that they understood the purpose of the study, 98% felt that they understood the research process and 96% summarised the research study accurately 2. 100% felt able to ask questions before, 98.4% during and 100% after the study 3. 93.5% felt that the information given was good, 82.5% felt the researcher's verbal explanation was the most useful source of information, 10.5% the written information sheet and 7% a pamphlet 4. 100% felt free to refuse to participate, 98.4% knew that they were participating in a research study and 10% thought that taking part was part of their infant's treatment Declining parents: 1. 55.8% declined owing to inconvenience; 29.3% were concerned about the safety of the tests	Response rate was 69% for parents who consented and 47% for parents who declined Parents received the questionnaire between 2 weeks and 19 months after the end of their involvement in the trial *Questionnaires for decliners were much shorter and did not assess understanding of consent information*

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Study and Journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Heitenan *et al.*, 2000[13] *European Journal of Cancer*	Study aiming to determine the communicative needs of patients being invited to participate in a breast cancer clinical trial Postal questionnaire sent to patients who participated in a breast cancer trial approximately 11 months after consent. Questionnaire made up of 24 multiple-choice and five open questions about the adequacy of the oral and written consent information, aspects of decision-making, satisfaction with and usefulness of information, understanding of how treatment was chosen, reasons for participation and views of experience Finland	Patients (*n* = 261) who had consented to be randomised into an adjuvant trial of oral endocrine therapy conducted in five Finnish university hospitals in 1997	1. 91% of the patients regarded the provided consent information as easy or quite easy to understand 2. 76% remembered having received written information; 6% did not read it. 76% of patients who read it regarded it as easy or quite easy to understand and 55% felt that the written information had been helpful in decision-making 3. 23% of patients knew that they had been randomised; 51% thought that the doctor had chosen the treatment 4. 68% of patients thought that they had enough time for decision-making 5. Younger and better educated patients had a better understanding that they had been randomised, more frequently reported having received written information and having read it, and found it more understandable than older and less well-educated patients. Older and less well-educated patients were more likely to feel that they needed more time to decide See also *Appendix 2*	Response rate was 87% Patients were sent questionnaires between 5 and 17 months after they gave consent Questionnaire received feedback from ten patients. *Final version of questionnaire included in the paper. No reliability or validity tests reported*

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Study and Journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Jenkins *et al.*, 1999[51] *European Journal of Cancer*	Part of a larger study designed to improve doctor–patient communication in RCTs (see Fleissig *et al.*[10]) Taped interviews of clinical oncologists discussing randomisation into a treatment trial with the cancer patients were content-analysed against a grid matrix UK	Cancer patients (*n* = 82) who were eligible to take part in randomised trials and clinical oncologists (*n* = 5) in two UK hospital outpatient departments Same sample as Fleissig *et al.*[10] (this appendix and Appendix 3); also Jenkins and Fallowfield[46] (Appendix 3)	1. Doctors differed in the information that they discussed with individual patients about the RCT. In 82.9% of the discussions doctors described the treatments, in 87.8% they described treatment side-effects, in 96.3% doctors expressed uncertainty about treatment decisions, but in only 14.6% of these consultations was this personal rather than collective; 64.6% were not told they could leave the trial at any time. In 62.2% of cases doctors mentioned randomisation explicitly; in 95.1% they described randomisation implicitly, using analogies to describe the randomisation process in 34.1% of consultations 2. Trial information leaflets were only given in 67.1% of cases 3. Doctors rarely checked their patients' understanding of randomisation; in 82.9% they did not check at all and in 15.9% of consultations they checked a little 4. 8.5% of patients vocalised their concern about randomisation, 32.9% expressed uncertainty in treatment choices and 9.8% of patients were disturbed by the fact that the doctor did not choose the treatment even when the clinician had tried to explain the reasons for the trial See also *Appendix 2* and *4*	Recordings were sampled from a larger trial. *Response rate not relevant* *Findings lead to concern over patient consent, but do not in themselves give a measure of patient understanding*

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Study and Journal	Purpose of study and method of assessment	Sample population (n = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Joffe *et al*., 2001[11] *Journal of the National Cancer Institute*	Study aimed at designing and evaluating a brief questionnaire, the QuIC, to measure subjects' actual (objective) and perceived (subjective) understanding of cancer clinical trials After a stage of piloting with cancer research subjects and validation from two independent expert panels, the QuIC was sent to cancer patients, some twice to test reliability. The final version was tested with further patients for time and ease of administration USA	Content validity was assessed first by bioethicists with experience of trial methodology (n = 3), then by additional experts (n = 3) to provide criterion standards for judging subjects' responses. Piloting was with a convenience sample of patients and parents of patients enrolled in Phase I, II or III trials at a cancer institute in two stages (n = 9, n = 10). Evaluation was carried out with cancer patients who had enrolled in Phase I, II or III clinical trials at one of three sites in the previous 14 days (n = 207). The final testing was with adult trial participants (n = 9). Main sample is same as Joffe *et al*.[12] (this appendix and Appendix 4)	1. Participants scored an average of 79.7 on part A, objective (tested) understanding 2. Even after adjusting for the effect of negatively phrased questions, the average for the five questions addressing therapeutic misconception was 64.1, suggesting that therapeutic misconception existed in this sample 3. Participants scored an average of 87.8 for part B, subjective (own perception of) understanding 4. Where participants were retested approximately 2 weeks later, the average for part A was 79.8 compared with 77.7 initially, with an intraclass correlation coefficient of 0.66. The average for part B was 86.9 compared with 87.2 initially, with an intraclass correlation coefficient of 0.77 5. The final version of QuIC took on average 7.2 minutes to complete and was rated as very easy to complete by eight of the nine participants	Response rate for the main evaluation was 72% *As the study was testing the instrument for validity and reliability, the total scores were not interpreted or compared with any ideal or acceptable level of understanding. Scores on specific items were not reported* For further details see Joffe *et al*.[12]

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Study and Journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Joffe *et al.*, 2001[12] *Lancet*	Study measuring the quality of understanding among participants in clinical trials of cancer therapies QuIC questionnaire sent to participants 3–14 days after enrolment in a clinical trial. A brief questionnaire was sent to each participant's provider (who had signed the consent form) at the same time USA	Patients participating in Phase I, II or III cancer-directed treatment trials at three affiliated institutions (n = 207) and their providers Same sample as main sample in Joffe *et al.*[11] (this appendix)	1. 90.6% of participants in Phase III trials were aware that they were being randomly allocated to treatment 2. 88.3% recalled being offered alternatives to participation, 99% knew that they could decline participation and 89.7% knew that they could withdraw from the trial 3. Higher knowledge scores were associated with college education, speaking only English at home, being white, receiving an NCI template-based form, not signing consent at the initial discussion, presence of nurse at the consent discussion, and supplemental use of pamphlets, the Internet, magazines or books 4. Knowledge scores did not correlate significantly with consent form readability 5. Knowledge and self-assessment scores were significantly associated (r = 0.25, p = 0.0004), as were providers' ratings and respondents' knowledge scores (r = 0.23, p = 0.003), but providers' scores did not predict the knowledge scores of individual respondents whose consent they had obtained See also *Appendix 4*	Response rate was 72% for trial participants and 84% (of reports) from providers *Authors did not explain the contents or structure of the NCI template, only that it had been mandated for use by the IRB as of March 1999* For development of the QuIC see Joffe *et al.*[11]

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Study and Journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Kass *et al*., 1996[27] *Hastings Center Report*	Study to gain further insight into outpatients' reasons for participating in medical research and their understanding of the research enterprise In-depth interviews were carried out with participants at 14 institutions across the country. Participants were asked to speak freely about a number of topics relating to their experience of medical research projects in which they had been enrolled USA	Participants (*n* = 103) were drawn from a sample (*n* = 1900) of outpatients enrolled in a nationwide project determining attitudes and experiences about research. All participants in this study had reported having personal experience in medical research Same sample as Sugarman *et al*.[29] (this appendix and Appendix 3)	1. Many participants who had tried other interventions without success felt that there were no alternatives left. They characterised the decision to participate as a matter of little choice 2. The patients were very trusting of the hospitals and the research enterprise as a whole. There seemed to be a widespread belief that checks and balances were in place, and oversight ensured that no harm could be done 3. Many participants expressed that their decision to participate had been made before they had been given the consent form to sign. They assumed that they need not pay attention to what was written in a consent form, or suggested that although it was not particularly readable, it did not matter because they knew they wanted to participate in research regardless 4. For many participants, medical research and medical treatment were closely connected. Although they were able to articulate the broad goals of research, they viewed their own participation as simply another treatment option	*The authors did not indicate how the sample had been selected from the larger study* Qualitative study *The article included very little detail on methodology and reported no interinterviewer reliability or checks on reliability of the analysis. The method of qualitative analysis was not stated*

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Study and Journal	Purpose of study and method of assessment	Sample population (n = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Kruse *et al.*, 2000[44] *Controlled Clinical Trials*	Study to improve the patient education process in clinical research by varying written materials in length, reading ability level and reader appeal Participants were randomised to: control group (no intervention); leaflet group, with the leaflet paying attention primarily to reader appeal and readability; brochure group, with the brochure focusing primarily on logical composition and presentation of condensed information; or booklet group, with the booklet based on the same principles as the brochure, but with more elaborate explanations All participants completed a 17-item multiple-choice knowledge questionnaire and a Likert attitude questionnaire before receiving (or not in the case of the control) their written material and again 2 weeks later Denmark	Participants were attending outpatient clinics in the medical gastroenterology, gynaecology, orthopaedic surgery and urology departments of a university hospital (n = 415)	1. The brochure and booklet increased knowledge scores significantly compared with control ($p < 0.001$ and $p = 0.007$) 2. At entry, 46.3% of the patients obtained an acceptable knowledge score, at follow-up the proportion of patients with an acceptable knowledge score increased by 7% in the control group, 13% in the leaflet group, 24% in the brochure group and 8% in the booklet group 3. Only the booklet increased the attitude score (high score means more positive attitude) significantly compared with the control ($p = 0.01$) 4. Changes in knowledge and attitude scores were not significantly associated	59.2% patients approached were randomised; however, 40% of those approached had been excluded owing to insufficient Danish skills or judged to lack informed consent. 3% of those randomised withdrew before finishing the first questionnaire. 11% of those completing the first set of questionnaires did not return the second knowledge questionnaire and 25% did not return the second attitude questionnaire An acceptable knowledge score was defined as more than 50% correct answers The questionnaires were developed in collaboration with a panel of experts and were tested by lay people, students and employees at the authors' institute. Internal consistency was tested for both questionnaires and reported to be high

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Study and Journal	Purpose of study and method of assessment	Sample population (n = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Leach *et al*., 1999[34] *Social Science and Medicine*	Study examining the attitudes of the Gambian people to consent to medical research, and evaluating the informed consent process used in a major efficacy trial of a *Haemophilus influenzae* vaccine Semistructured interviews were conducted with acceptors and refusers to the trial in rural and urban areas. Qualitative findings illustrated quantitative findings with relevant quotes Gambia	Participants were mothers attending mobile health clinics run by the government health services who either accepted (n = 137) or refused (n = 52) to consent to the vaccine trial. Other relatives and friends were encouraged to comment and a father's view was sought if he had made the decision that his child should not join the trial	1. 90% of acceptors knew that the purpose of vaccination was to prevent illness, compared with 39% of refusers 2. 53% of acceptors were aware of possible side-effects, compared with 22% of refusers 3. Overall, refusers knew less of the subject matter than acceptors ($p < 0.05$) 4. 10% of acceptors and 4% of refusers were aware of the placebo control group. This is of concern as the overwhelming motive for participating in the trial was to receive the vaccine. Of those who were aware of the placebo, one was quoted as giving a very negative response; when she heard that some did not receive the new medication "but only mere water", she commented that "MRC is really callous" 5. 15% of acceptors who had received the information sheet at least 1 week before requesting consent understood that there was a placebo group, compared with 4% of those who had not received a sheet ($p < 0.05$) 6. 23% of parents who refused commented that they did not trust the information presented to them. They believed instead a wide range of rumours about the vaccine, e.g. that it prevents females from bearing children in future. The process of asking for consent itself caused many families to mistrust the safety of the vaccine	100% of those asked to participate in the study agreed, but whereas all acceptors were interviewed, 25% of the refusers gave incorrect addresses and could not be traced The authors pointed out that the low awareness of placebo-controlled design may only be partially explained by lack of comprehension. Trial workers apparently modified the amount of information they gave, avoiding raising issues that were complicated or controversial. The information sheet was thought not to be explicit enough on this point All interviews were taped and interviewers wrote answers directly on the questionnaires. A 25% subset was checked by retranslation of both questions and answers by a second study worker

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Study and Journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Lovegrove *et al.*, 2000[17] *Psycho-oncology*	Study aimed to identify measurable differences between women who elect to join a placebo-controlled, double-blind randomised trial of the drug tamoxifen and women who elect not to join Participants completed a number of questionnaires, including one addressing the adequacy of medical communication UK	Participants were female patients attending a clinic for women at high risk of breast cancer. All had previously been offered the opportunity to join the tamoxifen trial, half (n = 53) had elected to join and the other half (n = 53) had elected not to join the trial	1. Women who elected not to join the trial assessed the information they had been given about tamoxifen as harder to understand than those who had joined (p = 0.01, one-tailed)	Response rate was 70.1% *The only measure of understanding in the study was participants' own perception of how hard they found information on the tamoxifen to understand. This included all information that they had been given at the clinic, not just the information they had been given at informed consent*

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Study and Journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Mason and Allmark, 2000[37] *Lancet*	Study to assess whether the process of obtaining informed consent from parents to clinical trials on neonates leads to valid consent Transcripts of semistructured interviews with parents and with neonatologists were analysed against the four components of informed consent: competence (the person giving consent is mentally competent to do so), information (sufficient information is received to make an informed choice), understanding (understanding is sufficient to make a reasoned choice), and voluntariness (consent is given voluntarily) Europe	Parents of babies who had been asked for consent to neonatal trials (*n* = 200) and neonatologists seeking consent (*n* = 107) in nine European countries	1. Analysis revealed that only 29.5% of parents had given valid consent or refusal (i.e. deemed to have 'no problem' for any of the criteria of informed consent). So few had given valid consent or refusal because 21.0% of parents had competence problems, 21.5% had information problems, 22.0% had understanding problems and 10.5% had problems of voluntariness 2. 2.8% of clinicians were deemed to have no problem with obtaining consent satisfactorily. 73.8% of clinicians expressed concern over parental competence, 19.6% of clinicians reported a problem with information, 48.6% of clinicians reported a problem with understanding and 55.1% of clinicians reported a problem with feeling that consent was given voluntarily 3. 47.0% of parents relied mainly on information provided orally by the doctor for their decision 4. 9.0% of parents said they were not given an information sheet. 90.7% of clinicians used an information sheet	Response rate was 90% in one centre, 55% in another and unknown for two centres Interviewers were trained according to a study-specific interview manual. Interviews were recorded (apart from telephone interviews), transcribed and reviewed to check quality. Each interview was analysed independently by two investigators, discrepancies were reviewed independently by a third person who decided on the accepted analysis Parents' recent experience of giving consent or refusal was the focus of their interviews. Neonatologists were talking about their experience in general. *It is unclear how their interviews were assessed, given that those who were judged to have no problem with consent may just not have reported problems* The interview schedule was not included in the published paper, but is available by contacting the authors

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Study and Journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Miller *et al.*, 1996[20] *Pharmacotherapy*	Study to assess the reliability of the DICCT, an instrument developed to assess comprehension of informed consent information At the conclusion of trial enrolment participants rated their understanding of the information presented and completed the DICCT, along with vocabulary and reading measures. The DICCT consists of 14 open-ended questions regarding eight basic elements of informed consent USA	Participants (*n* = 275) were adults entering one of four prospective, randomised, double-blind, ambulatory trials of anti-infective agents	1. 70% of participants rated their understanding as thorough; this rose to 93% when those rating their understanding as near thorough were included 2. The mean score on the DICCT was 20.4 out of a maximum of 28 (achieved by only two participants), showing a lower average level of understanding than the participants had perceived 3. There was a moderate positive correlation between DICCT score and education level, but no relationship with age	Participants were sequentially enrolled in the comprehension study as they enrolled in a trial. *No response rate was reported* The DICCT for the first 50 participants was scored independently by two investigators; the inter-rater correlation was 0.84 The sample was relatively young and well-educated with no serious or critical illness, causing the authors to be cautious about generalising the reliability and validity data to other samples. *Although the participants had enrolled in randomised double-blind studies, no questions in the DICCT addressed understanding of trial design*
Montgomery and Sneyd, 1998[21] *Anaesthesia*	Study to evaluate patient satisfaction with, and recollection of, the consent process in anaesthesia trials Trial participants were sent a postal questionnaire containing questions with yes/no answers and space for additional comments UK	Participants (*n* = 157) were patients who had agreed to participate in one of six clinical trials in anaesthesia within a 21-month period	1. 82% of participants remembered having an information sheet 2. Of those who remembered the information sheet, 99% thought that it was easy to read 3. 97% of participants realised that participation was voluntary 4. 90% of participants felt that they had understood everything	Response rate was 77%. The authors acknowledged that the timelag of 6 months to 2 years between the clinical trial and being sent the survey questionnaire might have resulted in failure of recall. However, they noted that the proportion of patients who recalled the information sheet was unaffected by the duration of the timelag *The questionnaire was not included in the paper; however, the authors reported that most questions had yes/no answers which would make it very hard for anyone to answer wrongly on questions about voluntariness of participation*

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Study and Journal	Purpose of study and method of assessment	Sample population (n = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Pletsch and Stevens, 2001[32] *Journal of Family Nursing*	Study comparing the informed consent experiences of mothers of children with cancer and mothers of children with diabetes in clinical trials Semistructured interviews of 1–2 hours' duration were carried out with mothers. The audio-tapes of the interviews were transcribed for narrative analysis USA	Participants for this study were mothers whose children had cancer (n = 23) or diabetes (n = 9) and had been enrolled in clinical trials Diabetes sample same as Pletsch and Stevens[33] (this appendix)	1. Although most mothers knew whether their children were in a clinical trial, the boundaries between research and treatment were unclear or irrelevant for many. Some mothers thought that research and clinical treatment were the same	The sample was drawn from a larger family study investigating the clinical research experiences of ill children, their mothers, fathers and siblings. *No response rate was given* Qualitative study Analysis was carried out individually on transcripts, then by the team as a whole when comparing transcripts. *No measures of the reliability of analysis were reported*
Pletsch and Stevens, 2001[33] *Clinical Nursing Research*	Study identifying the factors that influenced mothers to consent to have their children involved in clinical research 1–2-hour semistructured interview. Narrative analysis was carried out on interview transcripts USA	Mothers of diabetic children who had consented for them to participate in clinical research (n = 9) Same sample as Pletsch and Stevens[32] (this appendix)	1. All mothers reported that they had understood the clinical research in which their children were being asked to participate 2. Mothers were able to describe accurately, in varying detail, the purpose and nature of the trial participation, when the study began and ended, and what their rights were 3. Mothers were certain about which aspects of their children's care were part of the study and which were not, and could clearly state the differences between clinical trial and standard medical care See also *Appendix 4*	*Response rate not given*. Part of a larger study (see Pletsch and Stevens[32]) Qualitative study Some of the children had participated in more than one clinical research trial, eight had participated in a randomised trial of an injection system and two in a randomised trial of the combined effects of insulin and insulin growth factor; two had been part of a kidney registry study *No indication given as to how recent the children's trial involvement was*

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Study and Journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Sanchez *et al.*, 2001[19] *Bioethics*	Study exploring the decision-making process of women participating in contraceptive trials 20–30-minute semistructured interviews were carried out at admission to the clinic (20 interviews), at method initiation (five interviews), after deciding not to participate in the trial (three interviews), while participating in the trial (six interviews) or after discontinuation (two interviews). Transcribed interviews were coded using the ethnograph computer program and classified using previously defined and new categories. Later interpretative analysis was carried out Chile	Women attending the research clinic of the Instituto Chileno de Medicina Reproductiva, which ran clinical trials for the development or evaluation of contraceptive methods (*n* = 36)	Authors' interpretation (see reviewers' comments in next column): 1. Women processed informed consent information according to their personal needs, cultural level and cognitive abilities, as well as information previously obtained from different sources. Women selected relevant information that made sense to them, thus receiving and processing counselling in their own terms 2. Sometimes, mistaken beliefs were not modified by new information received, especially when they came from a significant source such as mother and friends 3. The least understood topics were a method's mechanism of action and the objectives of the trial. There was occasional misunderstanding of the information given, either verbally or in the consent form. Some women had misconceptions such as thinking that there was a high risk of pregnancy during the trial 4. At the time women signed the informed consent form, most of them knew the requirements to participate, the general sequence and procedures of the trial. However, some women did not handle complete information, ignoring, for example, how long the trial would last, or the precise sequence of the procedures	*Response rate not given*. Women selected themselves for the interview according to their willingness to participate and their available time Qualitative study *No details of the qualitative analysis method were given. Findings were summarised as interpretations and mainly presented without illustrative quotes to support them*

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Study and Journal	Purpose of study and method of assessment	Sample population (n = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Schaeffer *et al.*, 1996[28] *American Journal of Medicine*	Study to assess the impact of severe disease and limited treatment options on subjects' understanding of information related to research participation Within 24 hours of giving consent, participants completed a questionnaire determining retention of information provided in the consent document, among other measures. This was repeated 4–6 weeks later USA	Participants (n = 127) were recruited from four different research protocols. Group 1 were patients with proven mestatic cancer for whom all standard treatment had failed, who consented to enter a Phase I trial to determine side-effects of a drug (n = 9). Group 2 were patients with ovarian cancer consenting to a Phase II trial determining initial effectiveness of a drug (n = 36). Group 3 were symptom-free patients with HIV who consented to a Phase III trial comparing the efficacy of two drugs alone or in combination (n = 28). Group 4 were healthy volunteers enrolled in one of two investigations of brain response to tasks and stimuli (n = 54)	1. Overall, all groups retained <35% of the disclosed information. Healthy volunteers retained overall information best within 24 hours and 4–6 weeks later (study group effect, $p < 0.05$) 2. Healthy volunteers retained the most risk information at both times and Phase I participants the least ($p < 0.0001$). Phase I and II participants retained the most information about procedures 4–6 weeks after consent, and healthy volunteers retained the least ($p < 0.001$). Information about the purpose of the study and confidentiality of the data was retained best by the symptom-free Phase III participants at both times ($p < 0.05$) 3. Retention of information about alternative therapies did not differ among the three groups of ill participants. 97% of all research participants were aware that their participation was voluntary 4. Higher educational level was associated with more information being retained by symptom-free Phase III participants and healthy volunteers, but not by sicker participants (those in Phase I and II studies) 5. The more time researchers took to explain the protocol and consent document, the greater the immediate ($p < 0.01$) and long-term retention of information about the purpose of the study ($p < 0.01$) and long-term retention of risk information ($p < 0.05$)	Response rate was 99.2%, although 10.2% of the sample consented but then did not complete the first set of questionnaires and a further 22% of the sample did not complete the questionnaires 4–6 weeks later The overall percentage retained score was calculated by dividing the total number of items recalled in seven categories by the total number possible. Reliability checks of the scoring showed 100% agreement in 94% of the forms in a random sample. *The questionnaire was reported to have been pretested for the study, but details were not included* The authors acknowledged the limitation that in the absence of an immediate postdisclosure evaluation of understanding, they could not disentangle subjects' failure to understand the disclosure and an inability to recall the information 24 hours later The consent documents used in the trials varied in length from four to eight pages, although all were judged to be written at similar reading levels (11th and 12th grade). *As the patients were participating in trials, the authors had no control over the wording and content of the trial information sheets. These were unlikely to have been based on guidelines using standard wording for describing trial procedures as used in current trials. It is unclear how any difference in information may have influenced understanding*

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Study and Journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Searight and Miller, 1996[15] *Journal of the American Board of Family Practice*	Study to examine participants' interpretation of methodological dimensions of biomedical research or the distinction between medical treatment in research and personal healthcare Research interviews were carried out with participants. The tape-recordings were transcribed and coded for thematic content using an adaptation of grounded theory analysis USA	Participants (*n* = 14) were patients who had recently completed their participation in one of two drug trial studies	1. The participants all stated that they had been adequately informed about the purposes of the study and accompanying procedures 2. All of those interviewed viewed their participation as entirely voluntary and none felt coerced 3. It was extremely rare for participants to describe the informed consent form as having educational benefit. The consent form was primarily seen as a legal document designed to prevent litigation 4. All participants could provide a reasonable definition or description of a placebo and about one-third verbalised a more sophisticated rationale for using placebos in drug trial studies 5. Participants consistently demonstrated an understanding that assignment of the placebo or active drug was randomly determined 6. Approximately one-half of the participants correctly indicated that the local investigators were blinded to the assignment categories, with most of these indicating that the pharmaceutical company had information about the assignments 7. While some of the participants did acknowledge that there may be a distinction between receiving care from their personal physician and receiving care in research, none believed that they were in any way short-changed by receiving their care as part of a research protocol. Only two participants seemed to have a formal grasp of the distinction between research for generalisable knowledge and personal medical care See also *Appendix 2*	Interviews were conducted with enough participants to ensure adequate sampling. *The authors did not indicate on what basis they judged their sample to be adequate. Response rate was not given* Qualitative study Preliminary analysis was conducted during the interview phase and formal systematic analysis was conducted after all interviews were completed. After coding, the analytical categories were reviewed by the second author and presented to a group of clinical pharmacists actively engaged in drug trial studies. Categories were refined and clarified based on their feedback *This study reports an unusually high level of patient understanding of scientific methods and their rationale for use in trials, yet the authors give no thought or indication as to why this may be, even though patients did not view the informed consent document as educational*

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Study and Journal	Purpose of study and method of assessment	Sample population (n = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Stiles *et al.*, 2001[42] *Psychiatric Services*	Study to evaluate alternative procedures for improving the understanding of research consent disclosures by people who have mental illness Participants in each group (schizophrenia, depression, control) were randomly assigned to receive either: (1) a standard consent process with feedback: the participant followed written consent disclosure while the form was read aloud, then was encouraged to ask questions about material that was not understood. After completing a recall (open-ended questions requiring a paraphrased response) and a recognition (multiple-choice) questionnaire, any participant who had not scored 100% on the recognition test received feedback and a further reading of information that the participant had not understood before a retest. Two iterations of feedback and retesting were permitted; or (2) a facilitated consent process: the researcher and participant were joined by a facilitator who used several strategies to maximise participants' understanding, e.g. asking the participant after each section of consent information was read aloud to state the main points of the section. At the end of the consent disclosure, participants completed the recall and recognition tests The written consent disclosure was either a typical consent form from an actual medication trial or a graphically enhanced version USA	Three groups of adults participated in the study, those who had either schizophrenia (n = 79) or depression (n = 82) recruited from a mental health facility, and a control group (n = 80) recruited from people waiting to be selected for jury service	1. The schizophrenia group scored significantly lower than the other groups on both the recall and the recognition tests ($p < 0.001$) 2. Overall, the use of a facilitator or a graphic format was not associated with improvements in comprehension. However, participants in the control and depression groups had higher recognition scores with the facilitator than with the feedback, and the schizophrenia group had higher recognition scores with the feedback than with the facilitator ($p < 0.49$) 3. Overall, the mean recall scores were lower than the recognition scores ($p < 0.001$) 4. In the feedback groups, 66% of the depression group, 73% of the control group and 86% of the schizophrenia group received up to two iterations of feedback and retesting. The mean first recognition scores were significantly different across the three groups ($p = 0.004$); however, the mean best recognition scores did not differ significantly among groups, with only 8% of the depression group, 5% of the control group and 17% of the schizophrenia group unable to attain 100%	Participants presented themselves voluntarily in response to a public address system announcement. *Response rate was not given* Ten participants who had either schizophrenia or depression were excluded because their cognitive function scores were below the cut-off. Four participants in the control group were excluded because brief psychiatric scores indicated that they may have psychiatric conditions The study used measures of both recall and recognition to measure understanding. *However, neither the questionnaires nor the two versions of the consent information were included in the published article, so it is unclear what areas of understanding of information they are measuring*

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Study and Journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Sugarman *et al.*, 1998[29] *IRB: A Review of Human Subjects Research*	Study identifying attitudes towards research and research experience among outpatients Participants were approached while awaiting clinic appointments and interviewed using a 10-minute multiple-choice questionnaire. Participants' reports of past or current research participation were compared with their medical records USA	Patients (*n* = 1882) in the waiting rooms of medical oncology, radiation oncology and cardiology outpatient clinics at 16 institutions across the USA Same sample as Kass *et al.*[27] (this appendix)	1. For 6% of the 570 participants who reported that they were or had been participants in research, there was strong evidence that they were not participants in research but receiving standard treatment 2. For 6% of the 1223 participants who reported that they were not or never had been in medical research there was clear evidence that they had or were participating in research 3. 78% of patients who reported being in research believed that the policy for dropping out of the project was that they could withdraw at any time and for any reason. 7% believed that it was only possible to leave a study when doctors in charge of the project told them they could, and 15% reported some other policy 4. Patients thought that 'medical experiments' were riskier than 'medical research' (70% vs 10%), but that 'medical research' was riskier than 'medical studies' or 'clinical investigations'. Patients' estimation of the likelihood that they would receive unproven treatments followed the same pattern. Subjects thought that they would be better off in 'medical research' than in 'medical experiments', 'clinical trials' or 'clinical investigations' See also *Appendix 3*	Response rate was 95.7% Piloting of the areas of interest was carried out with focus groups in two institutions other than those involved in the main study. The questionnaire was developed based on the salience of issues to these patients and the terms they used. *No reliability testing of the instrument was reported* *For patients who had participated in trials, no information was given as to how long ago they were recruited into trials. Types of trial were described in terms of disease burden, risk and whether it was treatment or diagnostic, rather than phase of trials*

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Study and Journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Titus and Keane, 1996[52] *Journal of Clinical Ethics*	Study to examine how researchers describe components of their own process to gain consent from research subjects Four questions about the proposed process of gaining consent were included in the IRB application process. Researchers were unaware of the purpose of this element of their application	Participants were researchers (*n* = 167) who applied to one of four IRBs for approval over a 6-month period	1. While 52% of researchers focused on describing the study's purpose and 47% on its procedures, fewer gave a meaningful description of the purpose of the research (32%) or what they wanted subjects to do in their studies (30%). A meaningful discussion on all other areas was virtually non-existent. Researchers indicated only infrequently that they discussed benefits, risks, alternatives, costs, confidentiality, non-participation or withdrawal, or that they gave subjects time to ask questions or think about the project 2. 30% gave participants some time to consider participating. One-third of researchers were initiating studies in which more time could have been allowed for the participants to consider the request	The IRB exempted the study from review, so all applications were included without the researchers' knowledge or permission. *Response rate not relevant* Researchers' descriptions of their behaviour do not necessarily reflect what actually happened when they met the participants. *Nor do they necessarily give any indication of what other individuals obtaining consent in their studies do* The authors considered the answers on the applications as a 'dress rehearsal' for the researchers and as they did little to demonstrate knowledge of, or proficiency in, conversing with participants about informed consent, they speculated that researchers generally did not go beyond the self-reported description
van Stuijvenberg *et al.*, 1998[35] *Archives of Disease in Childhood*	Study to assess the quality of the informed consent process in a paediatric setting A questionnaire containing structured and semistructured items was posted to parents after the end of the children's trial participation, but before the trial outcome was known The Netherlands	Parents who had volunteered their child for a randomised, double-blind, placebo-controlled trial of ibuprofen to prevent febrile seizure recurrences (*n* = 181)	1. 73% of parents were aware of the major study characteristics 2. 97% of parents evaluated the verbal information that they received as easy to understand. 95% of parents evaluated the written information and consent form as easy to understand 3. 89% of parents felt positive about the informed consent procedure 4. 25% of parents felt obliged to participate See also *Appendix 2*	Response rate was 79% Although parents were unaware of the trial outcome, their awareness and self-reported understanding of consent information were being evaluated after the end of their trial participation. *The published paper did not specify how long trial participation was, although it did state that the investigator contacted parents every 3 months if no fever was reported* *The questionnaire used was not included in the published paper and no reliability or validity testing was reported*

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Study and Journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Verheggen *et al.*, 1996[30] *Patient Education and Counselling*	Study to obtain insight into how informed consent is applied in the daily practice of clinical trials by studying how patients experience and evaluate clinical trial information disclosure Patients (trial participants and refusers) were interviewed by means of a questionnaire within 4 weeks of being asked for their consent to participate in a clinical trial. Patients were asked about the informed consent procedure. Concepts were operationalised using multiple five-point Likert items Structured interviews with trial clinicians were conducted after the patient fieldwork was complete to give further insight The Netherlands	Patients (n = 172) were randomly selected from 26 clinical trials, and refusers (n = 26) were included for a more representative sample of patients approached for clinical trials in a university hospital setting. Trial clinicians (n = 32) had obtained informed consent during the enrolment procedure Same sample as Verheggen *et al.*[96] (Appendix 4)	1. 58% of patients indicated that they had received written information from the trial clinician. 44.9% of these patients could not indicate how many control visits would take place during their involvement in the clinical trial (the term 'control visits' is not defined in the paper). 42.4% of patients did not know how long they would be involved in the clinical trial. No differences were found between participants and refusers with regard to the level of understanding of written information disclosure. The higher a patient's level of education, the better a patient appears to understand the written information disclosure ($p < 0.01$) 2. 93.8% of trial clinicians perceived it as important that patients fully understand what trial participation implies 3. 84.4% of trial clinicians thought that their explanation about the clinical trial was comprehensible for patients; 12.5% were not sure about this. 78.1% thought that they could assess the extent to which patients actually understood information disclosure; 18.8% doubted their ability to do this. 84.4% said that they checked whether patients understood what was going to happen before they gave informed consent 4. Trial clinicians doubted patients' ability to comprehend nearly 15 out of 20 medicolegal aspects of information disclosure, including type of study and study objective, treatment alternatives, collection of data, privacy and confidentiality of data, and study design	Response rate among trial participants was 93%, among refusers 86% and among trial clinicians 100% The only reported measures of patient understanding (which was not the focus of the research) appear to relate to understanding of written information, which only 58% of patients reported having received The clinicians were giving views on their consent behaviour in general, rather than a particular interaction. *There were no objective measures of what information was given at consent, only self-reports* The authors presented the Informed Decision-making Checklist to be handed out to patients by trial clinicians when providing information on a clinical trial. The checklist is claimed to give a clear account of the pros and cons of a particular trial in a language that the average patient could understand, and is expected to enable patients to make an informed choice. *It is unclear how this checklist was developed and no validity or reliability testing is reported*

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Study and Journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
			of the trial, including the randomisation and selection procedure 5. Trial clinicians expected patients to comprehend more easily aspects such as involvement in a clinical trial, not having regular treatment, trial duration, name and accessibility of those responsible, voluntary participation, no negative influence on treatment of non-participation and the possibility to withdraw from the trial at any time 6. In the main, trial clinicians emphasised aspects of a trial that they expected a patient to understand easily and did not emphasise issues that they expected patients to have more difficulty in understanding See also *Appendices 2* and *4*	
Waggoner and Sherman, 1996[45] *IRB: A Review of Human Subjects Research*	Study to test the understanding of 27 words, phrases or symbols commonly used in proposed clinical research consent forms Participants were given a two-page questionnaire containing the 27 items and monitored during their completion of the form USA	Participants were adults recruited in a number of community locations (*n* = 302)	1. <10% of the lay population sample accurately knew the terms pruritus, metabolite, sequelae or concomitant 2. 10–30% accurately knew the terms Institutional Review Board (IRB), malaise, titrate or serum 3. 31–50% accurately knew the terms investigator, analgesic, transient, reproductively abstinent, replication, mean (blood pressure reading), baseline visit or concurrent 4. Educational level played a large role in understanding, with those who had experienced college education frequently understanding more terms than those who had <12 years of schooling	*No response rate was given* *No information was given as to how the list of terms was compiled* *The questionnaire was not included, so there was no indication of what inaccurate understandings participants were making* *The noted effect of educational level was only observed, rather than tested statistically*

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Study and Journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Weston *et al.*, 1997[47] *Patient Education and Counselling*	Study to evaluate the effect of a patient information video during the informed consent process of a perinatal trial Participants were randomised to receive either written information about the Term Prelabour Rupture of the Membranes (Term PROM) study and watch an information video (video group), or to receive written information only (control group). Participants completed a questionnaire testing knowledge about and attitude towards the trial immediately after watching the video (video group) or receiving the written information (control group) and again 2–4 weeks later Canada	Participants (n = 90) were women between 19 and 33 weeks of gestation and so were ineligible for the PROM study	1. No significant difference initially in the number of women in the two groups that showed adequate knowledge (i.e. answered at least nine of 11 content questions correctly) 2. 2–4 weeks later the number of correct content questions was lower in both groups, but the video group had retained more information than the control group (p = 0.01) 3. More women in the video group than in the control group said that they would definitely participate in the study (p = 0.01)	*No response rate was given* Questionnaire was aimed at testing knowledge rather than understanding. *The questionnaire was not published in the paper and so it is unclear whether it was of multiple-choice design or whether participants gave free-text answers. No validation or reliability checks on the questionnaire were reported*
Williams *et al.*, 1997[24] *New Zealand Medical Journal*	Study evaluating the suitability and comprehension of the consent procedure used in the Hirulog Early Reperfusion/Occlusion study (HERO-1) Postal questionnaires sent to consenting and declining patients New Zealand	Patients who consented (n = 48) or declined (n = 6) participation in the HERO-1 study	1. 35% (17/48) of consenters compared with 100% (6/6) of decliners comprehended the written consent (p = 0.01) 2. 69% (33/48) of consenters and 83% (5/6) of decliners understood the verbal explanation (ns) 3. Overall reported comprehension of written and verbal consent was 43% (23/54) and 70% (38/54), respectively	Response rate was 92% for those who had not died or emigrated *Content and design of the postal questionnaire were not reported, nor was the questionnaire included in the paper. Comprehension and understanding appear to have been measured by a single, self-report item for written and verbal information; however, this was not made explicit by the authors* *Content of written and verbal consent information was not reported* *Authors did not state how long after consenting or declining the questionnaires were posted*

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Study and Journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Wirshing *et al.*, 1998[8] *American Journal of Psychiatry*	Study to evaluate a structured and rigorous informed consent procedure involving subjects with schizophrenia Informed consent forms were read and explained to participants, who then answered a questionnaire (Informed Consent Survey) relating to each research protocol. Protocol procedures were reiterated until patients answered 100% of the questions correctly. One week later, participants were asked the same questions to ascertain how much of the information they had retained USA	Participants were patients with schizophrenia ($n = 49$) participating in ten ongoing double-blind clinical research trials	1. Patients' median score on the first presentation of questionnaire was 80% correct 2. 53% of patients required a second attempt to obtain 100% correct and 37% of patients required three or more attempts. 3. Scores improved between the first questionnaire and the one completed 7 days later ($p = 0.02$). 4. 96% felt that they were adequately informed	*No response rate was given* The authors gave a full description of the 'legal standards' for assessing patients' understanding of consent information, including being able to appreciate the significance of information for one's own situation and being able to manipulate the information rationally to make comparisons and weigh outcomes. The authors claim that their Informed Consent Survey incorporates these 'legal standards' for assessing patients' capacities to understand informed consent. *However, this claim is not supported by any reported tests of validity or reliability* *The questionnaire covers many aspects of trial information, but no analysis of responses to individual items was reported, so there is no indication of which aspects were better or worse understood* *The questionnaire, with correct answers, is included in the published paper, but appears to test knowledge, recall and the ability to learn correct answers to certain questions, rather than measuring understanding*

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Study and Journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Wragg *et al.*, 2000[50] *Social Science and Medicine*	Study (1) to determine the effect of framing information about HRT on the formation of preference for or against HRT; and (2) to investigate the relationship between individual differences and the decision to participate in a clinical trial Participants were divided into two groups, ambiguous and explicit. The ambiguous group watched a video and read an information leaflet, which emphasised a current state of uncertainty about the relative costs and benefits of HRT (similar to commonly used trial information). The explicit group watched a video and read an information leaflet, which contained numerical detail about currently known facts about HRT (similar to information available to doctors) Half of each group were asked to express a preference for taking/not taking HRT based on the information. The other half were asked to imagine that they had been asked to participate in a randomised trial of HRT compared with placebo, and asked to express their willingness to participate in the trial based on the information UK	Participants were women aged 25–40 years who had not already been involved in a clinical trial and who were not already on HRT ($n = 100$). Half were recruited from medical settings and the other half from non-medical settings	1. Women learned as much about HRT, regardless of framing of information 2. Women who received explicit information were more likely to hold a view about whether or not they would take HRT ($p < 0.05$) and were more likely to refuse entry to the trial ($p < 0.05$)	The response rate among those recruited from a medical setting was 98.0% and 87.7% among those recruited from non-medical settings The knowledge questionnaire covered topics included in the information sheets relating to HRT and the menopause. The knowledge test did not assess participants' understanding about randomisation or other features of clinical trials, as half of each group did not receive information about the hypothetical clinical trial

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Study and Journal	Purpose of study and method of assessment	Sample population (n = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Yuval *et al.*, 2000[25] *Archives of Internal Medicine*	Study to examine the perspective of the Israeli patient cohort who participated in the Fourth International Study of Infarct Survival (ISIS-4), a randomised trial in acute myocardial infarction Participants were sent a patient questionnaire 1–3 months after the acute event. One of the three different periods of hospitalisation to which the questionnaire related was the explanation of the study and patient comprehension at the time of consent and randomisation Israel	Participants (n = 150) were patients recruited to the ISIS-4 study in 14 centres in Israel	1. 32% recalled having had both an oral and a written explanation, 71% recalled the oral explanation and 5% recalled only the written description of the project 2. 31% of patients reported that they had full comprehension of the study, 50% partial and 19% little or no understanding 3. Reported comprehension was related to patient estimations of duration of the explanation ($p < 0.001$) and recollection that there was an opportunity to ask questions ($p < 0.001$), but not to the recalled personnel explaining the study or whether the explanation was remembered to be oral or written	Response rate was 41.7%, including some questionnaires that were only partially completed *Measures of the informed consent procedure and the patients' comprehension of information were all patients' perceptions and recollections up to 3 months after the event*

SWOG, Southwestern Oncology Group; LSU, Louisiana State University; IF, industry form; MF, modified form; SLT, speech and language therapy; NCI, National Cancer Institute; HRT, hormone replacement therapy.

Appendix 2

Understanding of randomisation in the context of clinical trials

Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Aaronson *et al.*, 1996[53] *Journal of Clinical Oncology*	Study to assess the effect of telephone-based nursing intervention on awareness and understanding of patients offered entry to a clinical trial Patients were randomised to one of two informed consent procedures: (1) standard informed consent procedure based on verbal and written information from physician; or (2) standard informed consent plus a supplementary, telephone-based contact with an oncology nurse Knowledge and understanding were assessed during an interview (a series of semistructured questions with follow-up probes based on recall of information) 1 week after completion of the consent process The Netherlands	Eligible cancer patients for Phase II or III trials at the Netherlands Cancer Institute ($n = 30$)	1. 54% of group 1 and 75% of group 2 were aware, where applicable, of the randomisation procedures used to allocate treatment ($p < 0.01$) 2. 17% of patients who had not been referred to this study, but had been successfully recruited to a trial at the institute, were aware of the use of randomisation procedures, where relevant. This was significantly lower than group 1, who were in principle exposed to the same standard informed consent procedure	64% of patients enrolled in clinical trials during the study period were referred by clinicians to participate in the informed consent study, 82% of those who were referred and could be contacted participated Ratings of levels of awareness were performed independently by two researchers using patient responses in interview compared with their medical record and the pertinent trial protocol. The level of inter-rater agreement was high, with discrepancies for less than 5% of ratings

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Appelbaum *et al.*, 1987[59] *Hastings Center Report*	Investigation to assess the prevalence of therapeutic misconception (patients' view that every aspect of a research project has been designed to benefit themselves) Consent transactions in four research studies on the treatment of psychiatric illness were observed. Subjects were interviewed immediately after consent was obtained. Two studies compared the effects of two medications on a psychiatric disorder (one used, in addition, a placebo control group). A third study examined the relative efficacy of two dosage ranges of the same medication and a fourth examined two different social interventions in chronic psychiatric illness, compared with a control group USA	Actively psychotic schizophrenic patients, non-psychotic schizophrenic patients, minimally symptomatic, borderline and depressed patients (*n* = 88)	1. 69% of subjects had no comprehension of the actual basis for their random assignment to treatment groups 2. 28% of subjects had complete understanding of the randomisation process 3. 40% of subjects stated their explicit belief that assignment would be made on the basis of therapeutic needs 4. 44% of subjects failed to recognise that some patients who desired treatment would not receive it (i.e. be assigned to control group or placebo) 5. 91% of subjects were unable to recognise a single way in which joining a protocol would restrict the treatment they would receive 6. In the two drug studies in which adjustment of medication dosage was tightly restricted, 50% of subjects said explicitly that they thought their dosage would be adjusted according to their individual needs 7. Many subjects constructed elaborate but entirely fictional means by which an assignment would be made that was in their best interests, particularly evident when information about group assignment was only covered in written consent forms	*No response rate was given* Not all issues addressed were relevant to each project, so percentages relate to a variety of sample sizes ranging from 27 to 80 *Some participants were given extra information, but it is unclear as to whether they were included in the results. Their general improvement in understanding was claimed, but no results were reported to support this* *The paper summarises findings from four studies within a wider discussion and does not give detailed information on how observations and interviews were carried out and assessed*

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Appelbaum *et al.*, 1999[7] *American Journal of Psychiatry*	Study using a new instrument to assess depressed patients' capacities to consent to research Participants were approached immediately after their first psychotherapy session, a week after consenting to participate in a study of maintenance psychotherapy in recurrent depression. They were given the MacCAT-CR, a semistructured interview format instrument which assessed understanding of disclosed information about the nature of the research project and its procedures; appreciation of the effects of research participation on subjects' own situations, reasoning about participation, and ability to communicate choice USA	Outpatients diagnosed with depression, and the first women to enrol in the psychotherapy trial (*n* = 26)	1. When performance was lower on the appreciation scale it was usually because participants had not fully appreciated that the frequency of therapy to which they would be assigned in the randomised phase of the study would not be based on their individual needs See also *Appendices 1* and *3*	Response rate was 100% Research staff members conducting the interviews received feedback on their performance; two raters scored the first five interviews independently and then met to resolve differences; they carried on rating independently until there were minimal differences. Thereafter, one research assistant carried out the rating. The MacCAT-CR manual is available elsewhere
Bjorn *et al.*, 1999[39] *Journal of Medical Ethics*	Study to investigate whether linguistic analysis and changes in information leaflets can improve readability and understanding Two information leaflets from trials of drugs for common conditions/diseases (hypertension and sterilisation) were simplified by breaking up text into smaller segments with subheadings, shortening sentences and by replacing professional language with lay language. Participants were randomised to receive either an original or a revised trial leaflet and immediately after having read their leaflet, completed a multiple-choice questionnaire aimed at testing the cognitive understanding of the respondents Denmark	Participants were recruited from centres and clubs for pensioners for the hypertension trial leaflet (*n* = 135) and female participants were recruited from workplaces for the sterilisation leaflet (*n* = 100)	1. Only 26% participants with the original hypertension trial leaflet and 42% with the revised hypertension leaflet correctly identified that chance decides which treatment they would receive. Most participants thought that it was the responsible doctor who decided. In the sterilisation study, by contrast, most participants answered this correctly See also *Appendix 1*	*No response rate given* *No reported testing of validity or reliability of the questionnaire. Questionnaire was not included in published article*

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Davis et al., 1998[41] *Journal of the National Cancer Institute*	Study to test whether a simplified consent form would be less intimidating and more easily understood by individuals with low-to-marginal reading skills Participants were tested for reading ability before reading either the standard SWOG consent form (16th grade level) or a simplified form (seventh grade level) developed by LSU Medical Center. Participants were interviewed using a structured oral questionnaire developed by the investigators to assess their attitudes towards and comprehension of the form read USA	Participants (*n* = 183) were either patients attending private and university oncology clinics or residents at a low-income housing complex. A smaller number (*n* = 69) received the SWOG form first as the interviews took twice as long as when participants received the LSU form first (*n* = 114)	1. Participants' comprehension scores were related to their reading ability. Overall, 41% of participants correctly answered the question 'what determines which treatment you get?' However, only 12% of participants reading at or below eighth grade level answered this item correctly, compared with 75% of those reading at or below ninth grade level See also *Appendix 1*	Response rate was 89% Structured oral questionnaire was piloted to ensure that the questions were clear and understandable to patients. *It was not tested for reliability and validity. Given that it was used in an interview context, no inter-rater reliability was tested or reported. Questionnaire was not included in the published article* *Scores on the ten comprehension questions were reported, but no indication of what the response options were, giving no information on what wrong answers people were choosing*
DCCT Research Group, 1989[61] *Controlled Clinical Trials*	Study to evaluate a multicomponent programme developed to educate prospective volunteers and enable them to make an informed decision about participating in the DCCT Volunteers participated in a 2–4-month educational programme run concurrently with further medical eligibility screening. The educational programme used audiovisual and written material, measures of past adherence and confidence of ability to participate. Those eligible for the trial completed a knowledge test about concepts related to trial participation. The knowledge test was repeated 1 year later USA	Volunteers identified by physicians and local advertising who attended a presentation of a detailed slide show about DCCT and consented to further eligibility testing and the educational programme (*n* = 278)	1. 97% of eligible volunteers had knowledge of the random assignment when they gave consent, and 98% had this knowledge 1 year later 2. 100% knew the meaning of random assignment when they gave consent and 99% knew this 1 year later	Response rate was 100% for the first test and 79% for the test a year later Knowledge was measured by a 14-item multiple choice questionnaire. If a participant did not score 100%, they were re-educated and asked to complete the test again. *It is unclear whether the results presented as at consent were the scores on the first or second test. No reliability or validity testing of the questionnaire was reported*

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Dresden and Levitt, 2001[43] *Academic Emergency Medicine*	Study comparing post-consent information retention following a standard industry consent form compared with a modified version The industry form (IF) for an asthma study was modified (MF) by focusing only on providing the minimum required information, increasing readability and in response to comments made by physicians, nurses and patients. Participants read randomly assigned IF or MF and completed a multiple-choice post-consent test USA	Patients who presented with asthma exacerbation at an emergency department (*n* = 100)	1. 44% of those who received the IF compared with 78% of those who received the MF correctly answered the randomisation question "will I definitely get the drug if I enrol in the study?" ($p = 0.0005$) See also *Appendix 1*	*Response rate not given* If participants reported before the test that they had not read the entire form they were excluded from the study; however, those who subsequently reported within the test that they had not read the entire form were not excluded from the analysis Neither version of the consent form was included in the paper The post-consent test contained mainly questions (ten out of 12) which could only be answered by yes or no, rather than multiple choice, although the response options were not included in the paper
Ellis and Butow, 1998[66] *Australian and New Zealand Journal of Public Health*	Study to explore knowledge of, and attitudes towards, randomised clinical trials among women in the community and breast cancer patients Focus group interviews were conducted with groups of approximately four to eight participants exploring, among other topics, women's knowledge of the clinical trial process Australia	Mothers or grandmothers of children attending a local primary school (*n* = 21) and breast cancer patients (*n* = 20)	1. Most women were aware that clinical trials involved a comparison of treatments, but were unsure how this would happen. The reason why treatment would be allocated at random was poorly understood See also *Appendices 3* and *4*	Response rate not available for the mothers and grandmothers sample; however, of those willing 70% were able to attend the focus groups. For the patient sample, 41.3% were willing to participate, but fewer than half were able to attend on the days when focus interviews were arranged Qualitative study Salient issues were noted during the discussions and compared with points identified by a second person from transcripts of audio-tapes of the discussions to identify themes. The final list of issues was discussed to ensure consistency of interpretation between the two authors

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Ellis *et al.*, 1999[67] *Health Expectations*	Study to assess the understanding of and attitudes towards randomised clinical trials among patients attending oncology outpatient clinics Participants completed a questionnaire assessing knowledge and attitudes to clinical trials Australia	Patients (*n* = 60) attending medical oncology outpatient clinics	1. 31% of participants were unaware that treatment is allocated by chance in a randomised trial 2. 74% thought that the doctor would ensure that they received the best of the treatments offered on a randomised trial See also *Appendices 3* and *4*	Response rate 100% The questionnaire was developed from the literature and focus group interviews (see Ellis and Butow[66]). *No reliability tests were reported*
Featherstone and Donovan, 1998[14] *British Medical Journal*	Study to explore trial participants' understandings of randomisation In-depth semistructured interviews were carried out using a checklist of topics to encourage participants to describe their experiences UK	Patients (*n* = 20) from the ClasP RCT evaluating the effectiveness of laser therapy, standard surgery and the conservative management for men with symptoms related to benign prostatic disease	1. Almost all participants were aware of some aspects of randomisation and 14 of the 20 acknowledged the involvement of chance in the allocation of their treatment. Often this was described using lay examples of chance, such as a lottery or lucky dip. However, participants found randomisation confusing because lay beliefs and previous experience meant that they expected clinicians to assign them to treatment based on their specific symptoms, clinical findings and age. This is reinforced by the number and complexity of tests and questionnaires they completed during the trial. Two participants were unable to discuss randomisation because they did not believe that their allocation was different from normal clinical practice 2. In lay language the word trial means something that is tried out, while 'at random' relates to things being done without purpose. Some patients found these terms difficult to incorporate into their accounts of the trial See also *Appendix 1*	Sample was chosen to reflect a broad range of individuals and experiences. *Response rate not given* Qualitative study *It is unclear how long after patients were invited to participate in ClasP the interviews took place* Grounded theory analysis was used to identify common themes based on verbatim transcripts. Analysis was carried out concurrently with data collection by one researcher. The second author confirmed the accuracy of the data analysis, *but did not state how*

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Freimuth *et al.*, 2001[70] *Social Science and Medicine*	Study investigating the barriers to participation of African–Americans in clinical and public health research Seven focus groups about medical research and knowledge or research terms and procedures were carried out before showing "*Miss Evers' boys*" a film about the Tuskegee Syphilis study. Transcripts of discussions were analysed thematically USA	African–Americans of varying income levels recruited from communities in four major regions of the USA (*n* = 60)	1. While a few participants correctly defined randomisation, many did not understand the term and two described it as "not giving any thought" or "no specific target group"	*Response rate not given* Qualitative study *No reliability checks of analysis were reported*
Gallet *et al.*, 1994[63] *Archives des Maladies du Coeur*	Study to assess comprehension of participants in a multicentre randomised trial, the Mexiletine and Placebo Antiarrhythmic Coronary Trial (IMPACT) 85-item questionnaire administered at the start of the final interview, at which participants were told the results of the trial, 5–21 months after consent had been secured France	Participants were patients with a recent myocardial infarction (*n* = 77) who had participated in IMPACT	1. 42.8% of participants correctly replied that treatment allocation had been randomised through 'drawing lots' 2. 36.4% thought that allocation had been made according to the seriousness of the infarctus 3. 16.9% thought that it was made according to the age of the patient 4. 2.6% thought that it was made according to the psychological state of the patient during the acute episode 5. 14.4% of participants were ignorant of the method in which the treatments had been distributed	94% of surviving trial participants completed the questionnaire *Comprehension based on recall at least 5 months and sometimes nearly 2 years later*

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Glogowska *et al.*, 2001[31] *International Journal of Language and Communication Disorders*	Study of the attitudes of parents whose children took part in an RCT In-depth interviews were carried out 12 months into participants' involvement in the trial UK	Parents whose children participated in an RCT evaluating the effectiveness of community-based SLT for preschool children with speech and language delay (*n* = 20)	1. Parents perceived that the allocation to immediate therapy or 'watchful waiting' would take their circumstances into account and favour them: "If she'd [the therapist] seen something … and thought … this is something really serious well then he wouldn't have been put on that sort of waiting group" 2. One parent, in expressing the uncertainty that therapy had made any difference, proposed the idea of a trial. "It would be interesting if you could cut them in half … let them have therapy and just leave them alone and see what happens", apparently unaware that this was what had happened to her child See also *Appendices 1* and *3*	Parents were a subsample selected from 259 who participated in the RCT. Selection aimed to represent as wide a range of experiences as possible. *Response rate not given* Qualitative study Data were analysed according to the framework method. *The authors did not elaborate on this and reported no checks on reliability* *Perceptions of allocation were assessed 12 months after it took place*
Heitenan *et al.*, 2000[13] *European Journal of Cancer*	Study aiming to determine the communicative needs of patients being invited to participate in a breast cancer clinical trial Postal questionnaire sent to patients who participated in a breast cancer trial approximately 11 months after consent. Questionnaire made up of 24 multiple-choice and five open questions about the adequacy of the oral and written consent information, aspects of decision-making, satisfaction with and usefulness of information, understanding of how treatment was chosen, reasons for participation and views of experience Finland	Patients (*n* = 261) who had consented to be randomised into an adjuvant trial of oral endocrine therapy conducted in five Finnish university hospitals in 1997	1. 23% of patients indicated that they had been randomised, 51% that the doctor had chosen the treatment, 7% that they had chosen the treatment and 10% indicated it had been chosen another way 2. Younger and better educated patients had a better understanding that they had been randomised See also *Appendix 1*	Response rate was 87% Patients were sent questionnaires between 5 and 17 months after they gave consent Questionnaire received feedback from ten patients. *Final version of questionnaire included in the paper. No reliability or validity tests reported*

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Howard *et al.*, 1981[65] *Controlled Clinical Trials*	Study to assess comprehension of participants in the Beta-blocker Heart Attack Trial (BHAT) In-depth home interviews in person or over the telephone to assess recalled information 2 weeks to 15 months after the participants had joined the trial. Participants stated their perceptions in their own words, which were then coded to indicate their degree of understanding USA	Random sample of participants in BHAT from 11 geographical areas (*n* = 64)	1. While 83% of participants recognised that some participants took the experimental drug and others took a placebo, only 42% knew that the allocation of treatment was based on chance	Response rate was 98% Unclear as to how responses were coded, no inter-rater reliability reported Knowledge measured 2 weeks to 15 months after consent. *There was no analysis of whether time of interview influenced recall*
Jenkins *et al.*, 1999[51] *European Journal of Cancer*	Part of a larger study designed to improve doctor–patient communication in RCTs Taped interviews of clinical oncologists discussing randomisation into a treatment trial with the cancer patients were content-analysed against a grid matrix UK	Cancer patients (*n* = 82) who were eligible to take part in randomised trials and clinical oncologists (*n* = 5) in two UK hospital outpatient departments Same sample as Fleissig *et al.*[10] (Appendices 1 and 3); Jenkins and Fallowfield[46] (Appendix 3)	1. In 62.2% of cases doctors mentioned randomisation explicitly with a rationale; in 95.1% they described randomisation implicitly, using analogies to describe the randomisation process in 34.1% of consultations 2. Doctors rarely checked their patients' understanding of randomisation; in 82.9% they did not check at all and in 15.9% of consultations they checked a little 3. 8.5% of patients vocalised their concern about randomisation and 9.8% of patients were disturbed by the fact that the doctor did not choose the treatment even when the clinician had tried to explain the reasons for the trial See also *Appendices 1* and *4*	Response rate not relevant as the recordings were sampled from a larger trial *Findings lead to concern over informed consent, but do not in themselves give a measure of patient understanding*

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Jensen *et al.*, 1993[64] *European Journal of Cancer*	Study to assess comprehension of patients offered entry in a clinical trial Structured interview 3 months after having received information. Interview included 36 questions and was tape-recorded. Recalled information was measured on a four point scale: good, reasonable, questionable and bad Denmark	Eligible women for three Danish breast cancer cooperative group trials dealing with adjuvant treatment of primary breast cancer (*n* = 34)	1. Patients' memory was rated 'good' for the randomisation aspect of the project in 73% of patients	Response rate was 94% By interviewing women 3 months after information had been received, their recall was in the light of their trial experience Interviews were carried out by two researchers, who coded their interviews. The codings were further analysed and cross-rated by researchers
Kjoergaard et al., 1998[68] *Danish Medical Bulletin*	Study to investigate knowledge about RCTs and attitudes towards clinical research, and to examine relationships between demographic variables, knowledge and attitude Participants completed questionnaires designed by the authors, including an 18-item multiple-choice test evaluating knowledge about RCTs Denmark	Outpatients (*n* = 415) attending medical gastroenterology, gynaecology, orthopaedic surgery and urology departments	1. 37.7% of participants knew what a randomised trial was 2. 47% correctly identified the reason for using randomisation	Response rate was 57.5% The questionnaires were subjected to psychometric analysis. *The methods, but not the results of this analysis were reported*
Madden, 1994[71] *Breast-cancer, randomised controlled trials and consent*, London: SSRY	Study eliciting views and experiences of breast cancer treatment and research In-depth interviews were carried out with participants UK	Women who had been treated for preliminary breast cancer (*n* = 50) and professionals in the breast cancer field (*n* = 40) Same sample as Alderson[98] (Appendix 4)	1. Many women and health professionals were not very sure about what research terms and concepts such as randomisation or equipoise meant. Some women who had been involved in RCTs were not familiar with basic concepts about the trials See also *Appendix 3*	*No response rate given* Qualitative study *Method of qualitative analysis not stated, nor were any reliability checks of analysis*

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Searight and Miller, 1996[15] *Journal of the American Board of Family Practice*	Study to examine participants' interpretation of methodological dimensions of biomedical research or the distinction between medical treatment in research and personal healthcare Research interviews were carried out with participants. The tape-recordings were transcribed and coded for thematic content using an adaptation of grounded theory analysis USA	Participants (*n* = 14) were patients who had recently completed their participation in one of two drug trial studies	1. Participants consistently demonstrated an understanding that assignment of the placebo or active drug was randomly determined 2. Perceptions of the randomisation process were sometimes very concrete, including analogies such as rolling dice or basing allocation on who walked in the door at what time 3. Approximately one-half of the participants correctly indicated that the local investigators were blinded to the assignment categories, with most of these indicating that the pharmaceutical company had information about the assignments 4. While some of the participants did acknowledge that there may be a distinction between receiving care from their personal physician and receiving care in research, none believed that they were in any way short-changed by receiving their care as part of a research protocol. Only two participants seemed to have a firm grasp of the distinction between research for generalisable knowledge and personal medical care See also *Appendix 1*	Interviews were conducted with enough participants to ensure adequate sampling. *The authors did not indicate on what basis they judged their sample to be adequate. Response rate was not given* Qualitative study Preliminary analysis was conducted during the interview phase and formal systematic analysis was conducted after all interviews were completed. After coding, the analytical categories were reviewed by the second author and presented to a group of clinical pharmacists actively engaged in drug trial studies. Categories were refined and clarified based on their feedback *This study reports an unusually high level of patient understanding of scientific methods and their rationale for use in trials, yet the authors give no consideration or indication as to why this may be, even though patients did not view the informed consent document as educational*

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Simes *et al.*, 1986[62] *British Medical Journal*	Study to assess the effect of different consent procedures on comprehension of patients offered entry to a clinical trial Respondents randomly allocated to one of two consent types: individual approach (details of the treatment left to the discretion of each consultant, after which verbal consent was obtained) and total disclosure (all information about treatments given to patients with written copy to consider overnight, written consent obtained the following day). Questionnaire completed before receiving treatment and again 3–4 weeks later, with responses recorded on a five-point scale, included questions testing patients' recall of research aspects Australia	Cancer patients eligible for any one of 16 trials (*n* = 55)	1. More patients in the total disclosure group understood that their treatment was selected by randomisation ($p = 0.004$), although more than half the patients in each group who were told about randomisation failed to understand it	42% of eligible patients participated, but only 5.3% of those not included had refused to take part The original plan was to include 100 patients, but the study ended early because of declining numbers when several of the RCTs closed The information contained in the relevant consent form and given during the consent interview was used to judge the correct responses on the questionnaire in each case. *No reliability or validity testing was reported for the questionnaire*

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Snowdon *et al.*, 1997[60] *Social Science and Medicine*	Study describing the views of parents who consented that their critically ill newborn baby should be enrolled in a neonatal trial In-depth interviews were carried out while the trial was ongoing, at variable times after recruitment (child's age 47–140 weeks, mean age 97 weeks) UK	Participants were couples who had entered their child in the ECMO trial (*n* = 21) Same sample as Snowdon *et al.*[83] (Appendix 3); also Snowdon *et al.*[76] (Appendices 3 and 4)	1. All parents used or responded to terms such as random and randomisation as if they were familiar; the interviews often revealed puzzlement and some confused interpretations of events 2. Parents held different models of the trial; most of the models only saw the new (ECMO) treatment as part of the trial, with conventional management (CM) being outside the trial as the treatment the baby was on before and would continue with if not selected for the trial. Consequently, some parents whose children had received CM believed that they had not been chosen to take part in the trial. Of those who had received ECMO some believed that they chose it over CM, and others that it was offered and they agreed 3. In 12 of the 21 interviews, at least one of the parents was aware of the random nature of allocation; eight of the 12 were parents whose child received CM. The majority of parents had a preference for ECMO at the time of consent, so randomisation was generally seen as the gateway to the desired treatment, the point at which access to the desired treatment was given or denied 4. Instead of randomised allocation some parents felt that treatment decision was made on therapeutic grounds, i.e. the baby was given a treatment appropriate to their need 5. In some interviews references to chance coexisted with accounts of a non-random process. Some parents knew that there was a computer involved, but suggested that the doctor made the decision, the computer was checking availability of beds, or checking their baby's details against other ones in the trial 6. Parents understood randomisation as a scientific method, an ethical way of making a difficult decision or a way of managing scarce resources. Even when the need for randomisation was accepted most parents found it difficult to accept that it was fair See also *Appendix 4*	The participating couples were selected out of a willing sample of 41 (response rate of 58.6%) to seek a balance of babies allocated to the two treatments, CM and ECMO Parents of deceased children were not included *Parents were giving retrospective accounts of their understanding of consent information up to over 2 years after giving consent. No objective measure of information they had been told or given was available* Qualitative study Transcribed interviews were analysed using the Atlas-ti text analysis computer package to code data and record detailed comments for each section of interview. After coding all interviews were reread, along with detailed comments

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
van Stuijvenberg *et al.*, 1998[35] *Archives of Disease in Childhood*	Study to assess the quality of the informed consent process in a paediatric setting A questionnaire containing structured and semistructured items was posted to parents after the end of the children's trial participation, but before the trial outcome was known The Netherlands	Parents who had volunteered their child for a randomised, double-blind, placebo-controlled trial of ibuprofen to prevent febrile seizure recurrences (*n* = 181)	1. 50% of parents were aware of the random allocation procedure 2. 88% were aware of the 50% chance of being assigned a placebo. See also *Appendix 1*	Response rate was 79% Although parents were unaware of the trial outcome, their understanding of consent information was being evaluated after the end of their trial participation. *The published paper did not specify how long trial participation was, although it did state that the investigator contacted parents every three months if no fever was reported*
Verheggen *et al.*, 1996[30] *Patient Education and Counselling*	Study to obtain insight into how informed consent is applied in the daily practice of clinical trials by studying how patients experience and evaluate clinical trial information disclosure Structured interviews with trial clinicians were conducted after the patient fieldwork was complete to give further insight The Netherlands	Patients (*n* = 172) were randomly selected from 26 clinical trials, and non-participants (*n* = 26) were included for a more representative sample. Trial clinicians (*n* = 32) had obtained informed consent during the enrolment procedure Same sample as Verheggen *et al.*[96] (Appendix 4)	1. 96.8% of clinicians believed that patients do not understand the study design of the trial (randomisation, placebo, control groups selection procedure) 2. 70% of clinicians did not emphasise the study design of the trial in informed consent discussions with patients See also *Appendix 1* and *4*	Response rate among trial participants was 93%, among non-participants 86% and among trial clinicians 100% *Findings lead to concern over informed consent, but do not in themselves give a measure of patient understanding (study was not designed with that aim)*
Waggoner and Mayo, 1995[69] *IRB: A Review of Human Subjects Research*	Study to assess understanding of commonly used terms in research information and consent forms Participants were asked the meaning of 25 words or phrases in an individual interview USA	Participants (*n* = 287) were adult members of the general public approached in various public settings	1. 22% overall, 28% of college-educated participants and 4% of high-school or lower educated participants knew the meaning of the word 'randomly'	Response rate was 98% *The authors gave no indication of how they selected the words or phrases to be included in the questionnaire, and reported no development or testing of the questionnaire*

DCCT, Diabetes Control and Complications Trial; ECMO, extracorporeal membrane oxygenations; CM, conventional management.

Appendix 3

Attitudes towards randomisation in the context of clinical trials

Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Albrecht *et al.*, 1999[81] *Journal of Clinical Oncology*	Study to investigate relationship between physician behaviour and patient accrual to a clinical trial Patient–physician interactions where the possibility of a clinical trial was presented to the patient were video-taped. Interactions were coded using a system [(Moffitt Accrual Analysis System, (MASS)] developed by the authors USA	Oncologists (*n* = 12), research nurses (*n* = 3) and cancer patients eligible for a Phase II or III clinical trial (*n* = 48)	1. Physician explanations of randomisation were coded in 53% of interactions where patient was accrued to the trial, compared with 40% where patients were not accrued. Likewise, random procedures were described in 89% of interactions where patient was accrued to the trial, compared with 50% where patients were not accrued	Response rate was 98% The MAAS coding system was checked for reliability (random sample of 15% of video-tapes), giving average Cohen's kappa reliability assessments of 0.67 over 73 checklist items and 0.64 over 17 global items, and divergent validity *It is unclear whether the absence of a description or explanation of randomisation means that it was not mentioned at all*
Appelbaum *et al.*, 1999[7] *American Journal of Psychiatry*	Study using a new instrument to assess depressed patients' capacities to consent to research Participants were approached immediately after their first psychotherapy session, 1 week after consenting to participate in a study of maintenance psychotherapy in recurrent depression. They were given the new MacCAT-CR instrument, and a set of questions about their perceptions of the consent procedures and their reasons for having decided to participate in the psychotherapy study. USA	Outpatients diagnosed with depression, and the first women to enrol in the psychotherapy trial (*n* = 26)	1. 25% of participants mentioned that the treatment conditions were controlled by research requirements rather than by subjects' individual needs when asked for reasons why others might not want to participate See also *Appendices 1* and *2*	Response rate was 100%

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Corbett *et al.*, 1996[82] *Journal of Medical Ethics*	Study to ascertain attitudes to different methods of obtaining informed consent for RCTs Participants were interviewed in a variety of settings. Among other tasks, participants were asked to rate seven wordings explaining randomisation as to how good an explanation they thought each was UK	Members of the public (*n* = 50), medical secretaries (*n* = 25) and medical students (*n* = 25)	1. The statement, "you will be allocated to one of two treatments, with each treatment having equal chance of being the one you will receive" was the most popular description of randomisation 2. The randomisation statements that were most disliked were those involving the tossing of a coin and names being pulled from a hat 3. Members of the public disliked "one of the two methods of treatment will be chosen by chance, and not by a decision made by the patient or doctor" more than the other groups of participants did ($p < 0.05$) 4. Medical students disliked "a computer will perform the equivalent of tossing a coin to allocate you to one of the two methods of treatment" less than did the other groups ($p = 0.0095$)	*No response rate was given* The questionnaire was checked for readability and scored 11.6 on the Gunning Fog Index, which was considered acceptable for patient information leaflets *Participants were asked to rate how good each of seven explanations of randomisation were; however, the data are reported in terms of which explanation participants preferred. It is therefore ambiguous as to whether people were rating how good they thought the explanations were at describing randomisation or how acceptable they were as a procedure to use. In order to carry out the former, people would have to have a clear understanding of what randomisation is, something that this paper does not address*
Ellis and Butow, 1998[66] *Australian and New Zealand Journal of Public Health*	Study to explore knowledge of, and attitudes towards, randomised clinical trials among women Focus group interviews were conducted with groups of approximately four to eight participants exploring, among other topics, women's perceptions of the advantages and disadvantages of receiving treatment in a clinical trial Australia	Mothers or grandmothers of children attending a local primary school (*n* = 21) and breast cancer patients (*n* = 20)	1. Random allocation of treatment and the uncertainty or experimental nature of clinical trials were perceived as major negative aspects of clinical trials by both groups of women See also *Appendices 2* and *4*	Response rate not available for the mothers and grandmothers sample; however, of those willing 70% were able to attend the focus groups. For the patient sample, 41.3% were willing to participate, but fewer than half were able to attend on the days when focus interviews were arranged Qualitative study Salient issues were noted during the discussions and compared with points identified by a second person from transcripts of audio-tapes of the discussions to identify themes. The final list of issues was discussed to ensure consistency of interpretation between the two authors

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Ellis *et al.*, 1999[67] *Health Expectations*	Study to assess the understanding of and attitudes towards randomised clinical trials among outpatients Participants completed a questionnaire assessing knowledge and attitudes to clinical trials. Participants were asked to indicate their willingness to participate in a hypothetical randomised clinical trial Australia	Patients ($n = 60$) attending medical oncology outpatient clinics	1. 51% of participants agreed that randomised trials were the best way of finding out whether one treatment was better than another 2. 88% of participants believed that patients should be asked to take part in trials testing new treatments; however, only 33% of participants would consider taking part in a trial comparing different treatments where treatment was selected at random by a computer 3. Willingness to participate in a clinical trial was most strongly influenced by patients' perception of the doctor ($p = 0.05$) and their attitudes towards experimentation and uncertainty in treatment allocation ($p = 0.05$) See also *Appendices 2* and *4*	Response rate was 100% The questionnaire was developed from the literature and focus group interviews (see Ellis and Butow[66]). *No reliability tests were reported*
Fallowfield *et al.*, 1998[72] *European Journal of Cancer*	Study to test an instrument to be used by doctors in explaining randomisation to individual patients ARTQ, a seven-item self-report questionnaire devised by the authors UK	Cancer patients attending outpatient appointments and/or chemotherapy treatment in two major cancer centres ($n = 315$)	1. 91.1% believe that patients should be asked to take part in medical research 2. 76.8% would be prepared to take part in a study comparing two treatments 3. 44.8% would agree to participate if treatment was randomised 4. 68.4% of those who initially said they would not agree to participate if treatment was randomised changed their mind when given further information about the randomisation procedure ARTQ discriminated between three categories of patients: 1. comfortable with the concept of randomisation. 2. some concerns but with fuller explanation prepared to consider randomisation 3. firmly against randomisation and participation in trials whatever information is provided	Response rate was 97.5% The ARTQ was piloted in two stages with 50 patients at a time for comprehensibility, ease of administration and acceptability to patients. The full questionnaire is published in the paper

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Fleissig *et al.*, 2001[10] *European Journal of Cancer*	Intervention study to improve communication during consultations about randomised clinical trials of cancer therapy Eligible trial patients completed questionnaires about information preferences (Patient Preference for Information Questionnaire) and attitudes to trials (Patients' Attitudes to Trials Questionnaire) before seeing their doctors for an informed consent discussion UK	Self-selected doctors (*n* = 15) at district general and university teaching hospitals invited eligible patients with cancer (*n* = 265) to join one of 40 different randomised trials Same sample as Jenkins *et al.*[51] (Appendices 1 and 2); also Jenkins and Fallowfield[46] (this appendix)	1. 92.1% of participants thought that patients should be asked to take part in medical research 2. 69.1% said that they would be prepared to take part in a study comparing different treatments 3. 34.7% said that they would be prepared to take part in a study where treatment was chosen at random 4. 56.6% of those who responded 'no' or 'don't know' to taking part when treatment was chosen at random thought that knowing that collective clinical equipoise existed would encourage them to take part, 68.8% thought that knowing they could leave the study if the treatment did not suit them would encourage them to take part, and 71.1% thought that if the doctor told them all about the two treatments before they were allocated it would encouraged them to take part 5. 70.3% of those who responded 'no' or 'don't know' to taking part when treatment was chosen at random would change their mind and be willing to participate if (1) either treatment was completely suitable, (2) they could leave the study if the treatment did not suit them, and (3) there was plenty of information before the random choice was made See also *Appendix 1*	Doctor response rate of 34.9%. Patient response rate of 90.1%, although 10% of participants did not return their questionnaires after the consultation *Unclear whether high agreement that patients should be asked to take part in research was in contrast to not being asked, or not taking part* *The Patients' Attitudes to Trials Questionnaire is reported more fully in Fallowfield* et al.[72]

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Glogowska *et al.*, 2001[31] *International Journal of Language and Communication Disorders*	Study of the attitudes of parents whose children took part in an RCT In-depth interviews were carried out 12 months into participants' involvement in the trial UK	Parents whose children participated in an RCT evaluating the effectiveness of community-based SLT for preschool children with speech and language delay (*n* = 20)	1. Some parents considered it unethical to withhold a treatment, even where its value was unproven and equipoise existed 2. Other parents saw the trial as a way of saving money, as only half the children received immediate treatment See also *Appendices 1* and *2*	Parents were a subsample selected from 259 who participated in the RCT. Selection aimed to represent as wide a range of experiences as possible. *Response rate not given* Qualitative study Data were analysed according to the framework method. *The authors did not elaborate on this, and reported no checks on reliability*
Jenkins and Fallowfield, 2000[46] *British Journal of Cancer*	Study to identify reasons why patients agreed or declined entry into randomised trials of cancer following discussions conducted by clinicians in UK hospitals Questionnaire specifying 16 possible reasons that may have influenced the decision to accept or decline treatment; answers along a five-point scale, from strongly agree to strongly disagree. Completed at home by patients after discussions with clinicians; patients asked whether they had decided to participate, decline or did not know UK	Patients with cancer who had been asked to participate in RCTs (*n* = 204) Same sample as Fleissig *et al.*[10] (Appendix 1 and this appendix); also Jenkins *et al.*[51] (Appendices 1 and 2)	1. 38.1% of those who agreed to enter, and 62.7% of those who refused, agreed with the statement, "the idea of randomisation worried me" 2. 76.5% of those who declined entry agreed with the statement, "I wanted my doctor to choose my treatment rather than be randomised", as did 51.7% of those who agreed to enter 3. 19.6% of those who declined trial entry gave their most important reason as worry about randomisation 4. 17.6% of those who declined trial entry gave their most important reason to decline trial entry as they wanted the doctor to choose their treatment rather than be randomised	Response rate was 85% The questionnaire used was similar in design to that developed for an earlier study and it was piloted on 50 patients with cancer in clinical trials. *The questionnaire was supposed to have been in Appendix 1; however, no appendices were published with the article*

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Jensen *et al.*, 1993[64] *European Journal of Cancer*	Study to assess comprehension of patients offered entry in a clinical trial Structured interview 3 months after having received information. Interview included 36 questions and was tape-recorded Denmark	Eligible women for three Danish breast cancer cooperative group trials dealing with adjuvant treatment of primary breast cancer (*n* = 34)	1. 94% of patients viewed the detailed information as positive, making it easier to cope with the disease and treatment situation. The two patients who did not feel this way instead felt that the information, especially about the trial, had increased their anxiety. They felt that the process would have been easier had the doctors chosen the treatment or, if trials were necessary, that the randomisation had been made without their knowledge	Response rate was 94% *By interviewing women 3 months after information had been received, they were comparing the received information with their own experience of the treatment* Interviews were carried out by two researchers, who coded their interviews. The codings were further analysed and cross-rated by researchers
Llewellyn-Thomas *et al.*, 1991[80] *Social Science and Medicine*	Study to examine the relationship between willingness to participate and patients' desire to take control of personal decisions One of the three tasks that each participant carried out was a randomisation task assessing willingness to participate in a trial in which a series of scenarios was presented Canada	Non-eligible colorectal cancer patients in a hypothetical decision scenario using a protocol of a chemotherapy trial for colonic adenocarcinoma (*n* = 60)	1. Randomisation task: 42% of respondents would consent to trial entry. 63% of refusers reported aversion to randomisation as the primary reason for non-participation	*No response rate given*

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Madden, 1994[71] *Breast cancer, randomised controlled trials and consent*. London: SSRY	Study eliciting views and experiences of breast cancer treatment and research In-depth interviews were carried out with participants UK	Women who had been treated for preliminary breast cancer (*n* = 50) and professionals in the breast cancer field (*n* = 40) Same sample as Alderson[98] (Appendix 4)	1. Women were positive about the idea of research, but did not want to participate personally in an RCT because they wanted to receive the best treatment at the time. They felt that people should take part in research but it is different when it comes to you, especially with something as serious as cancer 2. The health professionals reported discomfort with randomisation because it made their patients feel uncertain; they felt that if the surgeon does not know best, how could patients trust them? 3. Women perceived the risks of taking part in research as very high and only worth it if the potential benefit was of the highest kind, e.g. life-saving See also *Appendix 2*	No response rate given Qualitative study *Method of qualitative analysis not stated, nor were any reliability checks of analysis*
Madsen *et al*., 2000[74] *Journal of Internal Medicine*	Study investigating attitudes to clinical trials in patients with ulcerative colitis and inflammatory bowel disease Questionnaires completed at study entry (Trials 1 and 2), after second magnetic resonance imaging (Trial 2), after treatment termination (Trials 1 and 2) and after follow-up period (Trial 1). Questionnaires used mainly multiple-choice questions to measure attitudes towards different aspects of clinical trials Denmark	Participants in an open-label randomised study Trial 1 (*n* = 32), and participants in a consecutive diagnostic study Trial 2 (*n* = 47) compared with identical questions put to outpatients (*n* = 128) and general public (*n* = 325) samples	1. 71.9% of the Trial 1 sample had a positive view towards randomisation, compared with 44.7% of the Trial 2 sample ($p = 0.06$). 46.9% of outpatients and 55.7% of general public had a positive view towards randomisation 2. In free text almost all respondents stated that the primary reason for their attitude was that drawing lots was the most just and fair method to ensure a random distribution between groups See also *Appendix 4*	Response rate was 100% at study entry, 100% of the Trial 1 and 94% of the Trial 2 answered the second questionnaire, and 66% of the Trial 1 and 72% of the Trial 2 answered the study termination questionnaire. *Details of the recruitment, characteristics and response rates of the outpatient and general public samples were not reported* Questions and response options are reported in the paper *The authors interpret result 2 as evidence of an acknowledgement of randomisation as the most just and fair way to distribute patients between test interventions. This interpretation does not follow from the results*

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
McQuellon *et al.*, 1995[75] *Journal of Clinical Oncology*	Study eliciting preferences for the treatment of mestatic breast cancer Participants were interviewed using four hypothetical treatment scenarios varying side-effects from low to life-threatening, the scenario descriptions did not include the possibility of a cure. In scenario 4, designed to simulate a randomised trial comparing standard chemotherapy or high-dose experimental chemotherapy, participants were asked whether they would allow the flip of a coin to determine which therapy they received. USA	Female early-stage breast cancer patients (*n* = 115)	1. In scenario 4, 90% would not allow the flip of a coin to determine which treatment they received	Response rate was 95.2%, although a further 50% of all eligible participants could not participate owing to access, transport, comprehension and illness *Although scenario 4 was designed to simulate a randomised trial, it was presented as a treatment choice for the patient, with no statement of equipoise between the two treatments and giving no research context*
Purdy *et al.*, 2000[73] *Journal of General Internal Medicine*	Study to elicit the views of research among enrolees in an HMO Self-completed postal questionnaire USA	Participants were enrolees in an HMO (*n* = 207), 61% (*n* = 114) research participants and 49% (*n* = 93) general members	1. 94% supported research within the HMO 2. 20% would be willing to take part if they could not determine which treatment they would receive (i.e. random allocation)	Response rate was 57% *The term HMO is not defined anywhere in the paper, but appears to refer to managed care organisations* The split-half consistency of the main scale items of the questionnaire was satisfactory (Cronbach's alpha = 0.77)

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Slevin *et al.*, 1995[77] *British Journal of Cancer*	Study to explore patients' views about clinical trials, with the aim of devising a strategy to encourage patients to consider entering them Participants were asked to complete a multiple-choice questionnaire ascertaining what they knew about research and which aspects of research trials were considered appealing or unappealing UK	Cancer patients (*n* = 75), mainly outpatients attending oncology clinics	1. One of the two least appealing aspects of clinical trials was that the treatment was decided by the trial rather than the doctor or the individual; 25% found this slightly unappealing and 24% greatly unappealing 2. 97% of patients ranked reasons other than the treatment being decided by the trial, not the doctor, as the most important aspect of research trials 3. Of the 58% who indicated that they would not participate in research or who were unsure, 51% selected would prefer the doctor to make the decision about the treatment as the reason, and 9% would prefer to be able to choose treatment	*No response rate was given* The questionnaire was developed from a pilot containing open-ended questions tested on 34 oncology outpatients. The study questionnaire was tested with clinic nurses for validity and ease of understanding

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Snowdon *et al.*, 1998[83] *Controlled Clinical Trials*	Study about how parents whose children participated in a neonatal trial reacted to the idea of Zelen randomisation or prerandomisation Towards the end of a broader semistructured interview, interviewers read aloud the single consent method (only those randomised to experimental treatment gave consent) and clarified any parental uncertainty. Participants were asked to assess the notion of Zelen randomisation in light of their own experiences of taking part in the trial UK	Participants were parents (n = 44) of surviving infants who had participated in the ECMO trial Same sample as Snowdon *et al.*[60] (Appendices 2 and 4), also Snowdon *et al.*[76] (this appendix and Appendix 4)	1. Some argued for Zelen randomisation on the grounds that it protects those randomised to CM from knowing there is a potentially life-saving treatment that their child will not receive. It also protects them from the upsetting notion of treatment being decided at random and removes the difficult decision to participate in a trial from half of the parents 2. Others argued against Zelen randomisation as it deprived parents of information that they are part of research, which deprives them of associated benefits (commitment to the trial, involvement at follow-up, making an altruistic decision). The doctors being perceived as going behind people's backs would also have implications on how they would be seen. Also, those in the experimental group would in effect be choosing between two treatments. This may be seen positively as parents want the right to choose, but if there is no evidence about the experimental treatment, there is nothing on which to base the decision. It would be an impossible decision to make in difficult circumstances and parents would feel responsible for the decision even if later it appeared to have been the wrong one. Also, any benefits of protection from information would be lost if parents found out about the trial at a later date 3. 21 parents were for Zelen randomisation and 20 were against, the others unclear or unable to decide. Parents of infants who were allocated to CM were more likely to reject Zelen randomisation	Response rate was 61% Qualitative study Transcribed interviews were analysed using the Atlas-ti textual analysis computer package. *No reliability check of the analysis was reported* No parents of infants who died during the trial were interviewed

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Snowdon *et al.*, 1998[76] *British Medical Journal*	Study assessing views of parents whose children had participated in the ECMO neonatal trial about feedback of trial results Participants were presented with the main findings of the ECMO trial: babies randomised to ECMO were more likely to leave hospital alive than those who received conventional management. The chances of experiencing problems 1 year later were the same whether they had received CM or ECMO. Participants were interviewed about their views in light of these findings UK	Parents of surviving children (*n* = 24) who had participated in the ECMO trial and at an earlier date indicated that they wanted to be informed of the results Same sample as Snowdon *et al.*[60] (Appendices 2 and 4); also Snowdon *et al.*[83] (this appendix)	1. Randomisation seemed unfair, but parents recognised difficulties where there is uncertainty over treatment. However, it was hard to accept that babies were denied the better treatment by chance See also *Appendix 4*	Response rate was 61% Qualitative study Transcribed interviews were analysed using the Atlas-ti textual analysis computer package. *No reliability check of the analysis was reported* No parents of infants who died during the trial were interviewed
Sugarman *et al.*, 1998[29] *IRB: A Review of Human Subjects Research*	Study identifying attitudes towards research and research experience among outpatients Participants were approached while awaiting clinic appointments and interviewed using a 10-minute multiple-choice questionnaire. Participants' reports of past or current research participation were compared with their medical records USA	Patients (*n* = 1882) in the waiting rooms of medical oncology, radiation oncology and cardiology outpatient clinics at 16 institutions across the USA Same sample as Kass *et al.*[27] (Appendix 1)	1. Of the 112 who always declined to be in research, 56% said that wanting to have medical decisions made by themselves and their doctors, not by medical researchers, contributed a lot to their decision See also *Appendix 1*	Response rate was 95.7% Piloting of the areas of interest was carried out with focus groups in two institutions other than those involved in the main study. The questionnaire was developed based on the salience of issues to these patients and the terms they used. *No reliability testing of the instrument was reported*

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Tambor *et al.*, 2000[78] *Journal of Women's Health and Gender-based Medicine*	Study to assess practical and ethical barriers to conducting a randomised trial of prophylactic surgery for women at increased risk for developing breast cancer or ovarian cancer, or both Identified at-risk women were invited to attend an education and counselling session. Those who attended completed a postsession questionnaire asking about their willingness to participate in hypothetical research studies on breast and ovarian cancer risk reduction. The hypothetical research studies included a randomised trial, a non-randomised trial and a registry with three treatment options of surveillance, chemoprevention and prophylactic surgery. Physicians were asked as part of a postal survey about their likelihood of recommending RCT participation to an at-risk woman USA	Women who had been identified as at risk through relatives diagnosed with cancer for a questionnaire study assessing attitudes towards genetic testing for cancer susceptibility 1 year previously ($n = 403$). Physicians were randomly selected and from five specialities ($n = 247$)	1. 18.7% of women said that they would be willing to take part in a randomised breast cancer trial, 84.8% a non-randomised trial and 79.1% a registry 2. 16.9% of women said that they would be willing to take part in a randomised ovarian cancer trial, 75.9% a non-randomised trial and 74.7% a registry 3. The strongest predictors of willingness to enrol in RCTs were having children (breast cancer trial $p < 0.01$, ovarian cancer trial $p < 0.05$) and willingness to have a prophylactic mastectomy if found to carry a susceptibility mutation ($p < 0.05$) 4. There was a significant association by speciality ($p < 0.01$). The most willing group comprised oncologists, with 76.1% likely to recommend participation in an RCT to an at-risk woman. The least willing were family/general practice; however, 41.7% were willing to recommend participation in an RCT	Response rate was 22% for women and 49% for physicians *Women's differences in willingness to participate were not tested for statistical significance*

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Tercyak *et al.*, 1998[79] *Diabetes Care*	Study to identify the reasons why adolescents refuse to participate in a randomised trial on intensive treatment for diabetes Participants were provided with the results of the DCCT, which showed that intensive therapy could reduce a number of risks, but was associated with some negative effects such as weight gain. Participants were asked to participate in a similar trial in adolescents and those refusing the trial received a semistructured interview to describe reasons for study refusal USA	Participants were adolescents diagnosed with type 1 diabetes who refused participation in a randomised trial of intensive therapy ($n = 43$)	1. 95% of adolescents gave reasons other than randomisation for why they refused participation in the trial; issues of inconvenience were most frequently cited	Response rate was 100% Category coding of verbatim responses in interviews was conducted by two raters with 100% agreement *No mention was made as to whether the adolescents understood the concept of randomisation* Of the two nurse recruiters, one had 60% of adolescents approached refusing trial entry, compared with 27% refusal with the other nurse recruiter
Wiley *et al.*, 1999[123] *Cancer Practice*	Study to investigate parents' knowledge and perceptions about randomisation in clinical trials for children with cancer, and influences on knowledge and perceptions Clinical Investigation Randomisation Scale (CIRS) devised in an earlier feasibility study, 32 items pertaining to randomisation using a five-point Likert scale from strongly agree to strongly disagree, as well as fixed-choice and open-ended questions. Questionnaire posted to all participants within 3 months of randomisation eligibility on the child's clinical trial USA	Parents of patients with various forms of childhood cancer who either accepted or refused randomisation ($n = 192$)	Logistic regression analysis revealed three items predictive of consent to randomise in >85% of early parental decisions: 1. "Randomisation provides the best opportunity for my child to be cured of his/her cancer" predicted consent to randomise ($p < 0.0001$) 2. "I did not have enough time to make the decision about randomisation" predicted refusal to randomise ($p = 0.001$) 3. "Randomisation will help primarily in the treatment of future children more than my child" predicted refusal to randomise ($p = 0.04$)	*Response rate not stated* Factor analysis revealed two factors loading on two subscales, knowledge and perceptions. Reliability of the CIRS was assessed giving an entire scale Cronbach's alpha of 0.62, and coefficients of 0.62 and 0.82 for the knowledge and perceptions subscales, respectively *The paper's main focus is devoted to predicting consent rather than describing parents' knowledge of and perceptions of randomisation. The latter remains unclear*

Appendix 4

Equipoise in the context of clinical trials

Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Alderson, 1996[87] *Journal of Medical Ethics*	Study exploring health professionals' and breast cancer patients' views of equipoise Patients and health professionals were interviewed. Screened women completed questionnaire surveys UK	Participants were patients who had been treated for primary breast cancer (treated women, *n* = 50), doctors, nurses and radiographers working in breast cancer specialist centres or general surgery units (health professionals, *n* = 40), and women on breast screening lists (screened women, *n* = 93) Same sample as Madden[71] (Appendices 2 and 3)	1. Few of the health professionals had heard of the word 'equipoise', although most accepted the concept. 25% thought that an individual doctor could achieve equipoise, 13% thought that the whole breast care team could share equipoise and 18% thought that patients could achieve equipoise 2. 15% of health professionals thought that women generally accepted current uncertainty about the nature and treatment of breast cancer when they were informed, 25% thought that women preferred to be informed, and 15% thought that women were too distressed and preferred not to know 3. 68% of treated women would want to be informed about current uncertainty if they were asked to take part in a trial, and 4% would not 4. 14% of screened women thought most treatments have been tested, and 56% believed that current knowledge is too limited 5. 83% of health professionals, 80% of treated women and 22% of screened women believed that trials were valuable in showing which treatments are harmful or useless	Response rate was 57.8% among screened women. *Response rates for the health professionals and the treated women samples were not given* Qualitative study *Detailed methods were not reported in the published paper, so it is unclear how data were collected in the interviews. Also, the design and development and procedure for administration of the questionnaire used with the screened women were not reported, nor was the questionnaire included in the paper*

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Cassileth *et al.*, 1982[86] *Journal of the American Medical Association*	Study to document the attitudes of current and potential patients toward investigative treatment, their views of the purpose, importance and appropriateness of clinical research, and their reasons for participating in clinical trials Participants anonymously completed a multiple-choice questionnaire developed for this study USA	Patients with cancer (*n* = 104), cardiology patients (*n* = 84) and members of the general public (*n* = 107)	1. 23% of respondents thought that "doctors know privately which one of the investigated treatments is best" and 47% were uncertain about this possibility	*No response rate was given* *Although the authors state that the questionnaire was pretested, no other information on its development is given*
Ellis and Butow, 1998[66] *Australian and New Zealand Journal of Public Health*	Study to explore knowledge of, and attitudes towards, randomised clinical trials among women in the community and breast cancer patients Focus group interviews were conducted with groups of approximately four to eight participants exploring, among other topics, women's knowledge of the clinical trial process and their willingness to consider participating in a clinical trial Australia	Mothers or grandmothers of children attending a local primary school (*n* = 21) and breast cancer patients (*n* = 20)	1. A number of women believed that current treatments were generally successful, and new treatments were only tested on terminally ill patients with no other treatment options. In addition, some women felt that clinical trials were not appropriate for serious diseases such as cancer See also *Appendices 2* and *4*	Response rate not available for the mothers and grandmothers sample; however, of those willing 70% were able to attend the focus groups. For the patient sample, 41.3% were willing to participate, but fewer than half were able to attend on the days when focus interviews were arranged Qualitative study Salient issues were noted during the discussions and compared with points identified by a second person from transcripts of audio-tapes of the discussions to identify themes. The final list of issues was discussed to ensure consistency of interpretation between the two authors

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Ellis *et al.*, 1999[67] *Health Expectations*	Study to assess the understanding of and attitudes towards randomised clinical trials among patients attending oncology outpatient clinics Participants completed a questionnaire assessing knowledge and attitudes to clinical trials Australia	Patients (*n* = 60) attending medical oncology outpatient clinics	1. 24% of participants thought that the doctor would know that one of the treatments offered in a randomised trial was better than the other 2. 18% thought that clinical trials are offered only when the doctor considers the situation hopeless 3. 19% thought that clinical trials test treatments that nobody knows anything about 4. If there is no evidence to suggest that one treatment is better than another, 2% would prefer the doctor to pretend there is no uncertainty and recommend a treatment, 30% would prefer the doctor to tell them that he or she does not know which is better and invite them to take part in a clinical trial to find out, 63% would prefer the doctor to tell them that he or she does not know which is better but give their opinion, and 3% would prefer the doctor to tell them that he or she does not know which is better and let the patient choose the one they want See also *Appendices 2* and *3*	Response rate was 100% The questionnaire was developed from the literature and focus group interviews (see Ellis and Butow[66]). *No reliability tests were reported*

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Gallo *et al.*, 1995[85] *Lancet*	Study to compare informed consent and randomised consent in terms of participation rates in a clinical trial, and to assess whether the severity of prognosis affects participation rates Participants were enrolled in a hypothetical trial of experimental versus standard therapy, and randomly assigned to groups asked for conventional informed consent or prerandomisation consent Participants were presented with a consent form on a computer, tailored to the study group to which they were assigned. The severity of prognosis was varied from 20 to 80% probability of survival to 5 years with standard treatment Participants were asked whether they would consent, and about their perception of the severity of the disease and of the relative efficacy of the standard and experimental treatment Italy	Participants were healthy subjects who visited a scientific exhibition (*n* = 2035)	1. 51.7% of participants believed that the new treatment was better than the standard one 2. 38.2% correctly understood the supposed theoretical equipoise 3. Even among subjects who apparently understood the a priori equal effectiveness of the treatments, more of the group prerandomised to standard treatment than of those prerandomised to experimental treatment refused consent (52.4% versus 13.2%)	*Response rate not given* *The findings are not broken down by severity of prognosis. Although it is not reported, being told that you only have a 20% chance of survival to 5 years with the standard treatment may make it more likely that a participant will believe that the new treatment will be better than the standard one. The authors reported that the worse the prognosis the lower the refusal rate in all but group 4, where refusal means rejecting the experimental treatment in favour of the standard treatment*

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Jenkins *et al.*, 1999[51] *European Journal of Cancer*	Part of a larger study designed to improve doctor–patient communication in RCTs Taped interviews of clinical oncologists discussing randomisation into a treatment trial with the cancer patients were content-analysed against a grid matrix UK	Cancer patients (*n* = 82) who were eligible to take part in randomised trials and clinical oncologists (*n* = 5) in two UK hospital outpatient departments Same sample as Fleissig *et al.*[10] (Appendices 1 and 3); also Jenkins and Fallowfield[46] (Appendix 3)	1. In 96.3% of consultations doctors expressed uncertainty about treatment decisions, but in only 14.6% of these consultations was this personal rather than general 2. 32.9% of patients expressed uncertainty in treatment choices See also *Appendices 1* and *2*	Response rate not relevant as the recordings were sampled from a larger trial
Joffe *et al.*, 2001[12] *Lancet*	Study measuring the quality of understanding among participants in clinical trials of cancer therapies QuIC questionnaire sent to participants 3–14 days after enrolment in a clinical trial. A brief questionnaire was sent to each participant's provider (who had signed the consent form) at the same time USA	Patients participating in Phase I, II or III cancer-directed treatment trials at three affiliated institutions (*n* = 207) and their providers (*n* = 61) Same as main sample of Joffe *et al.*[11] (Appendix 1)	1. 75% of patients and 46% of providers correctly agreed that "the main reason cancer clinical trials are done is to improve the treatment of cancer patients" 2. 26% of patients and 80% of providers correctly disagreed that "all treatments and procedures in my clinical trial are standard for my type of cancer" 3. 30% of patients and 82% of providers correctly disagreed that "the treatment being researched in my clinical trial has been proven to be the best treatment for my type of cancer" 4. 37% of patients and 71% of providers correctly disagreed that "compared with standard treatments for my type of cancer, my clinical trial does not carry any additional risks or discomforts" 5. 71% of patients and 95% of providers correctly agreed that "there may not be direct medical benefit to me from my participation in the clinical trial" See also *Appendix 1*	Response rate was 72% for trial participants and 84% (of reports) from providers For development of the QuIC see Joffe *et al.*[11] The authors noted that all of the Phase III trials included compared one or more investigational groups to a standard group. Respondents in these trials would have been aware of their treatment assignment, and if assigned to standard treatment may have misinterpreted questions relating to the standard nature of trial treatments (relevant to results 3 and 4)

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Johnson *et al.*, 1991[89] *Journal of Medical Ethics*	Study to evaluate the level of collective equipoise that people think is ethical, i.e. the condition necessary for a trial to be offered to patients Subjects asked to indicate the level of collective doubt (equipoise) between two treatment modalities that would make a trial ethical. This level of doubt was presented on a series of cards showing varying numbers of experts favouring one or other treatment arm. A set of scenarios was presented in random order UK	Members of the general public hypothetically assuming the role of an ethics committee member (*n* = 93)	1. Degree of tolerated inequality of numbers favouring treatment A or B was greatest when the condition was less serious (headache analgesics) than when it was fatal (cancer or AIDS treatment) 2. The median level of equipoise was 67%, with interquartile range 60–75% 3. 97% would regard a trial as substantively unethical if equipoise was disturbed above 80:20 4. A high level of collective equipoise was demanded if the issues were highly emotive, e.g. if the trial involves infants collective equipoise must be high (close to 50:50)	Participants were a convenience sample. *Response rate not given* 20 subjects out of an original sample size of 113 were excluded either because they could not understand the concept, or because the intellectual effort required was too demanding
Madsen *et al.*, 2000[74] *Journal of Internal Medicine*	Study investigating attitudes to clinical trials in non-cancer patients Questionnaires completed at study entry (ROC and MRCRUC), after second magnetic resonance imaging (MRCRUC), after treatment termination (ROC and MCRUC) and after follow-up period (ROC). Questionnaires used mainly multiple-choice questions to measure attitudes towards different aspects of clinical trials Denmark	Participants in an open-label randomised study ROC (*n* = 32), and participants in a consecutive diagnostic study MRCRUC (*n* = 47) compared with identical questions put to outpatients (*n* = 128) and general public (*n* = 325) samples	1. 87.5% of the ROC sample and 83.0% of the MRCRUC sample rated the wish to receive the 'new' drug/investigation as either important or very important to their decision to participate in the trial 2. Compares to 75.1% of the ROC sample and 73.5% of the MRCRUC who rated the wish to help future patients by helping to test 'new' drugs/investigations as either important or very important to their decision to participate in the trial See also *Appendix 3*	Response rate was 100% at study entry, 100% of the ROC and 94% of the MRCRUC answered the second questionnaire, and 66% of the ROC and 72% of the MRCRUC answered the study termination questionnaire. *Details of the recruitment, characteristics and response rates of the outpatient and general public samples were not reported* Questions and response options are reported in the paper

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Millon-Underwood *et al.*, 1993[88] *Cancer Nursing*	Study to assess attitudes towards participation in cancer prevention and treatment trials among an African–American sample Participants completed an instrument including 21 forced-choice items, four items requiring sentence completion and/or explanation of response USA	Cancer patients and public from a population of African–Americans in a hypothetical scenario using investigational cancer prevention, diagnostic and treatment programmes and/or trials (*n* = 220)	1. 8% thought that cancer patients who participate in trials receive the best treatment. 20% thought that cancer patients who take the treatment that their physician recommends receive the best treatment; however, only 26% of these expressed a belief that the physicians knew which treatment was the most effective. 17% believed treatments to be 'the same' whether in a trial or recommended by a physician	Approximately 400 people were approached to take part and 325 people were willing to participate, a response rate of approximately 81%. The sample was randomly selected from those willing to take part The instrument was reviewed by panel of four experts, including two nurses, a psychologist and a statistician The study aimed to elicit views from a minority group that is at high risk of cancer but poorly represented in treatment trials. *The authors did not compare the findings from this minority group with other findings or a control group*
Mohanna and Tunna, 1999[93] *British Journal of Obstetrics and Gynaecology*	Study to identify factors affecting the decision of pregnant women to withhold their consent to participate in a clinical trial Semistructured interviews UK	Women who had previously been invited to participate in a clinical trial, Pre-term Labour: Affecting Neonatal Outcome by Early Testing (PLANET), but who had declined (*n* = 18)	1. The wording of the information sheet was viewed with suspicion, especially the word trial, which implied risks 2. The placebo arm added to uncertainty; the view was if the drug is good for you then it should be given to all women, and the idea that some high-risk women would not receive the drug was seen as unfair. They took the view that half of participants would be denied a new treatment	All women who had declined to take part in the PLANET trial but who went on to have a healthy birth were invited to participate by letter; response rate was 6%. Authors took the decision not to approach non-responders as the small sample was sufficient for the qualitative study Interviews were carried out up to 2 years after women were invited to participate in the PLANET trial Interviews were content-analysed. To improve the reliability and validity of the analysis, two colleagues of the authors were asked to read the transcripts and generate their own themes; these individual analyses corroborated the original interpretations

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Study and journal	Purpose of study and method of assessment	Sample population (n = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Myles *et al.*, 1999[94] *Anesthesiology*	Study to investigate the different effects of randomisation methods on recruitment rates Patients were asked to consider enrolling in a hypothetical anaesthesia trial. Patients were allocated randomly to one of five methods of randomisation and consent: one-sided standard informed consent, prerandomised consent to experimental treatment, prerandomised consent to standard treatment, one-sided physician modified informed consent (no clinical equipoise, physician believes experimental drug may be better), or one-sided patient modified informed consent (patients allowed to increase or decrease the chances of receiving the experimental drug after consenting) USA	Participants were patients who were hospitalised and due to have surgery within 24 hours (n = 770)	1. Consent rates were higher in those patients who thought that the experimental treatment was the better treatment ($p < 0.001$) 2. Overall, 44.7% of participants thought that the new treatment was better than the standard one, 2.7% thought that it was worse and 52.5% were unsure as to which was the better treatment	Response rate was 97.3% The authors included the question about which treatment was thought to be better as a check that they had not misled the patients. In the information provided it said "… there is some evidence that this new drug, Imaginon, results in less side effects …". The authors believed that this might have influenced patients' views; however, it reflected the usual rationale for conducting clinical trials

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Pletsch and Stevens, 2001[33] *Clinical Nursing Research*	Study identifying the factors that influenced mothers to consent to have their children involved in clinical research 1–2-hour semistructured interview. Narrative analysis was carried out on interview transcripts USA	Mothers of diabetic children who had consented for them to participate in clinical research (*n* = 9) Same sample as Pletsch and Stevens[32] (Appendix 1)	1. Mothers looked carefully to see how their children might personally benefit from participation in the study. Mothers generally believed that there must be some direct and immediate advantage for their children if they were expected to be in clinical research. Benefit was conceptualised as something that made daily illness-related behaviours easier, more convenient or less painful for their children, including monetary recompense 2. Participants generally agreed that trials involving their children had to be low risk; however, in the majority of cases their calculations of risk were not based on concrete evidence. They reasoned that research medicine would have been tried many times in numerous studies before being offered to their children, they associated ideals of precision, competence and honour with research, and that mothers need not worry about harm to their children as researchers would have thought of everything. They felt that no doctor in any research study would offer them something that could harm their children or something that was untried as their children were in stable health; riskier therapeutics were assumed to be tried on sicker children See also *Appendix 1*	*Response rate not given*. Part of a larger study (see Pletsch and Stevens[32]) Qualitative study Some of the children had participated in more than one clinical research trial, eight had participated in a randomised trial of an injection system, two in a randomised trial of the combined effects of insulin and insulin growth factor, and two had been part of a kidney registry study *No indication given as to how recent the children's trial involvement was*

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Sheldon *et al.*, 1993[95] *Cancer Investigation*	Study investigating the effect of cancer patients' view of the effectiveness of standard therapy on their willingness to participate in a randomised trial Participants were randomised to receive either one of two forms of a written, clinical vignette that described a hypothetical patient considering a choice between the standard treatment and a clinical trial comparing standard treatment with another treatment. One form numerically described results with standard treatment in terms of 10-year disease-free survival; the other verbally described outcomes with standard treatment in less specific, qualitative terms USA	Ambulatory, female cancer patients (*n* = 282)	1. Many patients in both groups grossly overestimated the actual benefit expected with standard treatment, and those who did were significantly less likely to choose trial participation	*Response rate not given* *Study was only reported in brief along with related work and a discussion of how doctors can attempt to address this issue within consultations. Data were only presented in a summary, without exact numerical findings*
Slevin *et al.*, 1995[77] *British Journal of Cancer*	Study to explore patients' views about clinical trials, with the aim of devising a strategy to encourage patients to consider entering them Participants were asked to complete a multiple-choice questionnaire ascertaining what they knew about research and which aspects of research trials were considered appealing or unappealing UK	Cancer patients (*n* = 75), mainly outpatients attending oncology clinics	1. One of the two least appealing aspects of clinical trials was the greater chance of obtaining 'experimental' treatments; however, 72% of respondents scored the greater chance of obtaining 'new' treatments as greatly appealing 2. 11% rated the "greater chance of obtaining new treatments" as the most important aspect of research trials, whereas 1% rated the "greater chance of obtaining experimental treatments" as the most important aspect of research trials 3. Of the 58% who indicated that they would not agree to participate in research or were uncertain, 33% selected "would worry about receiving new treatment" as their reason	*No response rate was given* The questionnaire was developed from a pilot containing open-ended questions tested on 34 oncology outpatients. The study questionnaire was tested with clinic nurses for validity and ease of understanding

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Snowdon *et al.*, 1997[60] *Social Science and Medicine*	Study describing the views of parents who consented that their critically ill newborn baby should be enrolled in a neonatal trial In-depth interviews were carried out while the trial was ongoing, at variable times after recruitment (child's age 47–97 weeks) UK	Participants were couples who had entered their child in the ECMO trial (*n* = 21) Same sample as Snowdon *et al.*[83] (Appendix 3); also Snowdon *et al.*[76] (Appendix 3 and this appendix)	1. Parents held different models of the trial; most of the models only saw the new (ECMO) treatment as part of the trial, with conventional management (CM) being outside the trial as the treatment the baby was on before and would continue with if not selected for the trial 2. The majority of parents had a preference for ECMO at the time of consent, so randomisation was generally seen as the gateway to the desired treatment, the point at which access to the desired treatment was given or denied See also *Appendix 2*	The participating couples were selected out of a willing sample of 41 (response rate of 58.6%) to seek a balance of babies allocated to the two treatments, CM and ECMO Qualitative study Transcribed interviews were analysed using the Atlas-ti text analysis computer package to code data and record detailed comments for each section of interview. After coding all interviews were reread, along with detailed comments
Snowdon *et al.*, 1998[76] *British Medical Journal*	Study assessing views of parents whose children had participated in the ECMO neonatal trial about feedback of trial results Participants were presented with the main findings of the ECMO trial: babies randomised to ECMO were more likely to leave hospital alive than those who received conventional management. The chances of experiencing problems 1 year later were the same whether they had received CM or ECMO. Participants were interviewed about their views in light of the findings UK	Participants were parents of surviving children (*n* = 24) who had participated in the ECMO trial and at an earlier date indicated that they wanted to be informed of the results Same sample as Snowdon *et al.*[60] (Appendix 2 and this appendix); also Snowdon *et al.*[83] (Appendix 3)	1. Some parents felt that researchers had been pretty sure before the start that ECMO would be likely to come out better; the trial confirmed what they already suspected See also *Appendix 3*	Response rate was 61% Qualitative study Transcribed interviews were analysed using the Atlas-ti textual analysis computer package. *No reliability check of the analysis was reported* No parents of infants who died during the trial were interviewed

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Sugarman *et al.*, 2001[92] *Journal of the American Geriatric Society*	Study examining proxy decision-making and informed consent processes of clinical research Proxies were interviewed by telephone after giving verbal informed consent (12 within 1 month, 11 between 1 month and 1 year, and 26 more than 1 year after enrolment) and 2–4 months after the initial interview. Interviews were transcribed and coded using themes that emerged in the interviews USA	Proxies of patients with dementia who were participating in clinical research into dementia (*n* = 49)	1. Proxies chose participation in clinical drug trials over standard management because they believed there was nothing else available or they hoped that the experimental medication would be better than the existing medications available at the time, either by being more effective or by having fewer side-effects 2. Some proxies alluded to the idea that something experimental is better then current treatment alternatives, while others stated this belief explicitly. Proxies indicated that they understood that the experimental treatments may not work, but that trying something was better than nothing. Their expectations tended to be more cautious than their hopes 3. Proxies felt there was nothing to lose by participating in a drug trial, they said that a drug must be safe if it was being tested in patients	*Response rate not given*. Three proxies did not complete the second interview Qualitative study Coding of all transcripts was carried out by a single investigator, *with no reported reliability or validity checks* *Effect of variation in time of interview after enrolment was not discussed*
Tindall *et al.*, 1994[91] *Patient Education and Counselling*	Study to determine subjects' perceptions of informed consent As part of a randomised study of the effect of written versus written and verbal consent information, participants completed a questionnaire about their views on informed consent 1 week after receiving the information Australia	Participants were consecutive patients with AIDS or AIDS-related complex invited to participate in this trial (*n* = 113)	1. 88% believed that their specialist medical practitioner always acted in their best interests 2. 79% stated that people should be allowed the choice between participating in a clinical trial of unproved medication and receiving it outside the trial mechanism	*Response rate not given* Knowledge about the new medication was tested, but not about the trial design, and so it is unclear whether or not people were aware of random allocation when expressing views about their medical practitioner acting in their best interests

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Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Twomey, 1994[90] *Western Journal of Nursing Research*	Study investigating views on ethical issues involved in the conduct of clinical paediatric HIV drug research In-depth interviews were carried out with a variety of participants from relevant sample groups USA	Participants were nurses ($n = 10$), physicians ($n = 7$), IRB members ($n = 3$) and parents of children with HIV ($n = 7$)	1. Doctors emphasised the benefits of participating in a trial due to possible access to an experimental treatment. They believed that not taking a drug meant that the disease was 100% fatal, therefore taking a drug was always beneficial. Given the established treatments are far from perfect, benefits from new treatments could be expected 2. Nurses and parents were more balanced in their views of benefits and risks of research. The benefits highlighted by nurses were not drug related, such as the payment for transportation, availability of extra consultation time and care; risks were side-effects and uncomfortable procedures. Parents hoped for benefits, but would withdraw from the trial if they experienced risks	*Response rate not given* Qualitative study Content analysis performed on audio-taped interviews. *No reliability checks on analysis were reported*
Verheggen *et al.*, 1996[30] *Patient Education and Counselling*	Study to obtain insight into how informed consent is applied in the daily practice of clinical trials by studying how patients experience and evaluate clinical trial information disclosure Patients (trial participants and refusers) were interviewed by means of a questionnaire within 4 weeks of being asked for their consent to participate in a clinical trial. The interview included questions about patients' general attitudes towards medical trials. Concepts were operationalised using multiple five-point Likert items The Netherlands	Patients ($n = 172$) were randomly selected from 26 clinical trials, and refusers ($n = 26$) were included for a more representative sample of patients approached for clinical trials in a university hospital setting Same sample as Verheggen *et al.*[96] (this appendix)	1. Patients with a positive attitude towards medical experiments in general expect low risks from the new, untested treatment procedures during a clinical trial ($p < 0.001$) and randomisation ($p < 0.0001$) 2. Patients who highly value benefit that other patients might gain from the results of the clinical trial tend to anticipate low risks from new, untested treatment procedures during a clinical trial ($p < 0.001$) and receiving no treatment or only standard treatment as a consequence of randomisation ($p < 0.001$) 3. Patients who find it relevant that clinical research is being done for patient care tend to expect relatively better comfort in the trial treatment ($p < 0.05$) See also *Appendices 1* and *2*	Response rate among trial participants was 93%, among refusers it was 86%

continued

Study and journal	Purpose of study and method of assessment	Sample population (n = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
Verheggen *et al.*, 1998[96] *Patient Education and Counselling*	Study to identify reasons why some patients choose to participate in clinical trials while others decline Participants were interviewed using questionnaires just after they had been asked to participate in a clinical trial. Items used five-point Likert scales asking participants to agree or disagree with statements The Netherlands	Participants were patients (n = 198) who were approached and asked to participate in 26 prospective clinical trials in nine clinical departments Same sample as Verheggen *et al.*[30] (Appendices 1 and 2, and this appendix)	1. If patients expect high risks in the new, untested diagnostic procedures or treatment in the clinical trial, they are likely to decline participation ($p < 0.001$) 2. Patients tend to participate if they anticipate better personal comfort than experienced during their earlier treatment, or if they think that they will feel better under the trial treatment than under standard treatment ($p < 0.001$) 3. In long-term patients (problems with their health dating from more 3 months ago), 97% of trial entry could be correctly predicted by four determinants. These were the subjectively defined risks of undergoing new, untested diagnostic procedures or treatment in the trial; the patients' evaluation of the expected time involvement of the trial; the patients' evaluation of better personal comfort in participating in the trial compared with pretrial or standard treatment; and the perceived urgency to be treated 4. In short-term patients (developed symptoms only in the 3 months before the trial) 96% could be correctly predicted by two determinants. These were the patients' evaluation of the expected time involvement of the trial; and expecting a better treatment in the trial compared with previous or standard treatment	Response rate was 88% Reliability and validity of the operationalisation of concepts were conducted. Factor analysis on 40 variables from hypothetical model yielded 24 scales with Cronbach's alphas ranging from 0.6 to 0.9 (average 0.8)

continued

Study and journal	Purpose of study and method of assessment	Sample population (*n* = number of respondents to survey)	Main results	Authors' and reviewers' comments (*Reviewers' comments shown in italics*)
White *et al.*, 1984[84] *American Journal of Clinical Oncology*	Study to assess patient preference for long-, medium- or short-form consent information and whether this preference correlated with patients' characteristics of patient autonomy in decision-making or physician dependency Participants received one of the three consent forms by random assignment. All forms contained identical information about drugs and potential side effects; however, only the long form contained information about prognosis, randomisation and rationale for the randomised trial. After reading the assigned form, participants completed questionnaires including a measure of comprehension USA	Women undergoing chemotherapy for metastatic breast cancer (*n* = 75)	1. Almost two-thirds of the patients receiving the long form remained unaware that the best chemotherapy regimen was not known	Response rate was 98.7% Randomisation was mentioned in the long form and equipoise was stated in the medium and long forms *Long, medium and short are misleading terms for the information forms. The long form was the only one that contained full information, but was five paragraphs long and a single sheet. The medium form was 1 paragraph long and the short form contained two sentences* *Comprehension scores were mainly not reported, with the only exception of the awareness of equipoise in the long-form group; even then the precise percentage was not given. Given the considerable difference in content of the forms it is unclear whether the comprehension questionnaires were varied and what areas of comprehension were measured*

Appendix 5

Descriptions of randomisation and equipoise from patient information leaflets used in randomised trials and ethics guidelines

Content of description of allocation to treatment	Trial leaflets (n = 16)																	Guidelines		
	a	b	c	d	e	f	g	h	i	j	k	l	m	n	o	p	Total	MREC and *Bulletin of Medical Ethics*	University of Bristol	CERES
1. Explicitly stated 'random'	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	14 (88%)	✓	✓	✓
2. Allocation by chance									✓	✓					✓		3 (19%)	✓	✓	✓
3. Used analogy (e.g. tossing/flipping a coin)					✓					✓							2 (13%)		✓	✓
4. Described method of allocation (e.g. telephone call to trials office, computer decides or open a sealed envelope)						✓	✓		✓		✓	✓	✓			✓	7 (44%)	✓	✓	✓
5. Stated level of chance of receiving either treatment		✓	✓	✓	✓	✓	✓		✓	✓					✓	✓	10 (63%)	✓	✓	
6. Stated benefit of randomisation (e.g. best/only way to achieve similar groups/avoid bias, obtain accurate results)		✓									✓	✓		✓			4 (25%)			✓
7. Stated consequence of randomisation (e.g. neither you nor your doctor knows/choose which treatment)								✓			✓	✓					3 (19%)			✓
Total number of elements of content of description	1	3	1	2	3	3	3	2	4	4	4	4	1	2	3	3	Average 2.7, mode 3	4	5	6
Portrayal of equipoise																				
Do not know which treatment is best						✓	✓		✓						✓	✓	5 (31%)	✓	✓	✓
Possible benefits of new treatment, not certain	✓			✓						✓	✓	✓		✓		✓	7 (44%)			✓
Conflicting evidence		✓															1 (6%)			
Treatments currently used but not proven/compared								✓	✓				✓				3 (19%)			
No evidence that one treatment is better than the other																	0			

Appendix 6

Materials used in investigations 8 and 9

Fictional clinical trial information

Treating low back pain with electrotherapy using short or long heat pulses

You are being invited to take part in a research study. Before you decide whether to take part, it is important to understand why the research is being done and what it will involve. Please take time to read the following information carefully.

- **What is the purpose of the study?**
  Doctors and physiotherapists are doing an important research project. We are trying to find out how best to treat people with low back pain.

  Low back pain is a common, disabling complaint. Patients are often referred for physiotherapy which may include types of electrotherapy, using painless heat pulses for example.

  The aim of this study is to compare two different ways of giving electrotherapy, to see which way results in the best improvement. One treatment, Short Pulse Electrotherapy, uses a large number of small heat pulses through pads put on your lower back. The other treatment, Long Pulse Electrotherapy, uses a smaller number of longer heat pulses through pads put on your lower back.

- **Why have I been chosen?**
  Your GP has referred you for help with your low back pain. In total 500 patients with low back problems will take part in this study.

- **Do I have to take part?**
  Your involvement in this study is completely voluntary and if you choose not to take part in this study the care you will receive will not be affected. You may also withdraw from the study at any time without this affecting future care. If you decide to take part, you will be asked to sign a consent form.

- **What will happen to me if I take part?**
  Each patient who takes part will have one of the two electrotherapy treatments. The treatment will last for a maximum of 6 weeks. You will be assessed before you start your treatment. Both treatments take the same amount of time and need to be given for 1 hour once a week. You will be assessed again after 6 weeks when you have finished your treatment, and finally 6 months later.

CERES justification

Sometimes because we do not know which way of treating patients is best, we need to make comparisons. People will be put into groups and then compared. The groups are selected by using a computer which has no information about the individual – i.e. by chance, at random. One group will be given Short Pulse Electrotherapy and the other group will be given Long Pulse Electrotherapy.

Allocating patients to treatment groups at random is the most exact and fair way to test which treatments work best. They are less likely to have, for example, people who are older or sicker in any one group. Each year thousands of people take part in them.

The extended explanation

This study is being carried out because nobody really knows whether one treatment is better than the other. Doctors have different hunches about which is better, but they don't agree.

We need to compare the two treatments on patients with similar low back pain. Half the patients have Short Pulse Electrotherapy and the other half have Long Pulse Electrotherapy. Each patient will be followed up and we will record how well they are doing.

If doctors suggested each patient's treatment on the basis of their hunches, then the two groups might be different. For example, more of the sickest patients might end up being given Short Pulse Electrotherapy. Then Short Pulse Electrotherapy is not being given a fair chance.

But we can prevent this bias by using a computer to allocate patients to receive either Short Pulse Electrotherapy or Long Pulse Electrotherapy. The computer does not use information about individual patients to do this, it uses chance. So long as we include a large number of patients, this random allocation makes sure the results will tell us whether patients do better with one treatment than they do with the other

- **Is there any risk in taking part?**
  Electrotherapy (including painless heat pulses) is a standard treatment widely used by physiotherapists. No new, untested treatments are being tried, so there is no extra risk in taking part compared with receiving routine care.

- **What are the benefits of taking part?**
  We hope that your treatment helps you. However, we do not know which works best. The information we get from this study will help us treat future patients with low back pain better.

Cloze test used in investigations 8 and 9

Below is the consent form for the fictional clinical study that you read about. Certain words have been left out. From what you can remember about the study please fill in as many of the blanks as you can.

Treating low back pain with electrotherapy using short or long heat pulses

I have read the information leaflet. I have been informed that the _____ of this study is to compare two different electrotherapy _____ , frequent but short painless heat pulses or fewer but longer heat pulses, to see which way gives the best _____ .

I understand that these treatments are being compared because _____ knows which way of giving electrotherapy is best for lower back pain. Doctors do not agree about whether it is _____ to use a large number of short pulses or a smaller number of long pulses.

I am aware that taking _____ in this study involves an assessment before treatment starts, 6 weeks of weekly treatment and follow-up assessments when _____ ends and 6 months later.

I understand that _____ to treatment is at random, which means based on _____ . A computer with no information about _____ decides which treatment I get. This also means that my doctor _____ suggest one of the treatments for me and _____ can I. I understand that random allocation is used to _____ bias and make sure each treatment is given a _____ chance.

I am aware that the risks involved in this _____ are no more than in routine treatment as no _____ treatment is being tested.

I understand that taking part in this study is entirely _____ and that I may withdraw at any time that I _____ . If I do withdraw this will in no way affect the care and attention that I may need in the _____ .

Questionnaire on randomisation and equipoise used in investigations 8 and 9

In the research study on treatments for back pain, a computer allocated patients to receive either Short Pulse Electrotherapy or Long Pulse Electrotherapy. The computer did not use information about individual patients to do this.

Studies like this, which allocate patients to one or other treatment at random, are called randomised clinical trials. Below are some statements about randomised clinical trials. Some of them are true and some are false.

Please circle one of the three options to show whether you think each one is true or false.

(a) In a randomised clinical trial the doctors recommend who gets which one of the trial treatments.

True False I don't know

(b) In a randomised clinical trial the treatment you get is decided by chance.

True False I don't know

(c) In a randomised clinical trial doctors are already pretty sure from the start which one of the treatments is the better.

True False I don't know

(d) At the start of a randomised clinical trial doctors think that the results could equally go either way.

True False I don't know

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We look forward to hearing from you.

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