Clinical Endpoint Committee Charter

Glucose Lowering in Non-diabetic hyperglycaemia Trial (GLINT)

Clinical Endpoint Committee Charter Effective Date:

10/Dec/2014
dd/mmm/yyyy

Clinical Events Committee Charter
Signature Page

Project: GLINT

Document: Clinical Endpoint Committee Charter Version 1

Your signature below shows that you have reviewed the aforementioned document, understand it, and agree with its contents.

CEC Chairperson or CEC Representative:

_____	_____	____/_____/_____
print name	signature	dd mmm yyyy

CEC Coordinator:

_____	_____	____/_____/_____
print name	signature	dd mmm yyyy

Introduction

GLINT (Glucose Lowering in Non-diabetic hyperglycaemia Trial) is a pragmatic, placebo-controlled, double blinded trial which seeks to characterise the effect of metformin on macrovascular outcomes in people with non-diabetic hyperglycaemia (NDH) at high risk over five years. The study will enrol 500 participants in a pilot study with NDH (HbA_{1c} ≥5.5% but <6.5%) and no prior history of cardiovascular disease who have an estimated 10-year CVD risk ≥20% as assessed by the Framingham or QRISK2 scores.

The primary study's objective will be to establish the effectiveness of metformin in prevention of cardiovascular events as measured by the time to first event in a primary CVD composite of CV-related death, nonfatal MI, and nonfatal stroke. Secondary objectives are to assess the effect of metformin on incident cancer, all cause mortality, and incident diabetes.

GLINT will be managed collaboratively by the MRC Epidemiology Unit at the University of Cambridge and the University of Oxford Diabetes Trials Unit (DTU) under the guidance of the GLINT Trial Steering Committee (TSC).

This charter describes the role and responsibilities of the GLINT Clinical Endpoint Committee (CEC).

1. Role of the Clinical Endpoint Committee

The Clinical Endpoint Committee (CEC) is responsible for adjudication of reported clinical events for the GLINT trial and reports to the GLINT Steering Committee. The CEC will be involved in the development of the clinical endpoint eCRF and adjudication pages which are designed to capture key data required for the efficient and accurate adjucation and final analysis of the event identified that may be one fo the following endpoints.

- Cardiovascular (CV) mortality
- Nonfatal myocardial infarction
- Nonfatal stroke
- All cause mortality
- Hospital admission for congestive heart failure
- Hospitalization for unstable angina
- Coronary, cerebrovascular , or peripheral revascularization

2. Membership

The CEC members will be comprised of at least two clinically qualified members trained in review and adjudication of clinical trial endpoint events for GLINT. The CEC members will be independent from members of the operational GLINT team and will remain blinded to study treatment assignment for the duration of the study. Overall supervision of the CEC and its activities is provided by the CEC chairperson.

3. Organisation

The CEC activities will be coordinated through the MRC Epidemiology unit according to processes outlined in the Guidance for Capturing and Adjudicating GLINT Study Endpoints.

Briefly, the MRC Epidemiology Unit is responsible for collecting relevant information for event adjudication of each probable endpoint and delivering it in an electronic format to the CEC members, along with an adjudication form. Two members of the CEC will independently adjudicate each probably case, with discrepancies resolved by consensus. Where consensus cannot be achieved, an ad hoc meeting of the CEC will be convened

and the final adjudication decision agreed.

4. Responsibilities of Members

4.1 CEC Chairperson

- To collaborate in the development of the event eCRF and adjudication pages
- To ensure proper training of all CEC members
- To oversee the day to day operations of the CEC to ensure timely case review
- To sign off on
- To communicate with the trial leadership about the status and conduct of the CEC activities
- To ensure, via ongoing Quality Control reviews of adjudicated events, that the adjudication process is being conducted according to the Guidance for Capturing and Adjudicating GLINT Study Endpoints, and that event criteria are being accurately applied
- To participate in the adjudication process

4.2 CEC Members

- To adjudicate and classify events without knowledge of the randomized treatment assignment
- To participate in discussion and training related to event criteria and the application of the criteria
- To participate in CEC conference calls and meetings
- To communicate any schedule conflicts, including extended time away from the office to the CEC Chairperson

MRC Clinical Trials Unit

GLINT: Glucose Lowering in Non-diabetic hyperglycaemia Trial

A randomised controlled trial to establish the effectiveness and cost-effectiveness of metformin in preventing cardiovascular events over five years in people with non-diabetic hyperglycaemia at high cardiovascular risk

ISRCTN 34875079
EudraCT Number 2012-005570-56

Independent Data Monitoring Committee Charter

Version 1.0, 08-Jan-2015

(developed using on MRC Clinical Trials Unit template IDMC Charter version 2.01, 13-Mar-2006; from DAMOCLES IDMC Charter template v1, Feb 2005)

IDMC CHARTER FOR GLINT

CONTENT Guidance	CHARTER DETAILS
1. Introduction	
Name (& Sponsor's ID) of trial	Glucose Lowering in Non-diabetic hyperglycaemia Trial (*GLINT*) – a randomised controlled trial to establish the effectiveness and cost-effectiveness of metformin in preventing cardiovascular events over five years in people with non-diabetic hyperglycaemia at high cardiovascular risk Sponsor ID GLINT ISRCTN 34875079 EudraCT Number 2012-005570-56
Objectives of trial, including interventions being investigated	To establish the effectiveness and cost-effectiveness of prolonged-release metformin in preventing cardiovascular events over five years in people with non-diabetic hyperglycaemia at high cardiovascular risk A study summary diagram is included in Figure 1.
Outline of scope of charter	The purpose of this document is to describe the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the independent IDMC for the feasibility phase of this trial, including the timing of meetings, methods of providing information to and from the IDMC, frequency and format of meetings, statistical issues and relationships with other committees.
2. Roles and responsibilities	
A broad statement of the aims of the committee	To safeguard the interests of trial participants, monitor the main outcome measures including safety and efficacy, and monitor the overall conduct of the trial.
Terms of reference	The IDMC should receive and review information on the progress and accruing data of this trial and provide advice on the conduct of the trial to the Trial Steering Committee (TSC). The IDMC should inform the Chair of the TSC if, in their view the results are likely to convince a broad range of clinicians, including those supporting the trial and the general clinical community, that, on balance, one trial arm is clearly indicated or contraindicated for all participants or a particular category of participants, and there was a reasonable expectation that this new evidence would materially influence patient management.
Specific roles of IDMC	Interim review of the trial's progress including updated figures on recruitment, data quality, adherence to protocol treatment and follow-up, and main outcomes and safety data. Specifically, these roles include to: • monitor evidence for treatment harm (e.g. toxicity, SAEs and SARs, deaths) • assess the impact and relevance of external evidence • decide whether to recommend that the trial continues to

CONTENT Guidance	CHARTER DETAILS
	recruit participants or whether recruitment should be terminated either for everyone or for some treatment groups and/or some participant subgroups • decide whether trial follow-up should be stopped earlier • assess data quality, including completeness (and by so doing encourage collection of high quality data) • maintain confidentiality of all trial information that is not in the public domain • examine recruitment figures and losses to follow-up • suggest additional data analyses if necessary • advise on protocol modifications proposed by investigators or sponsors (e.g. to inclusion criteria, trial endpoints, or sample size) • monitor compliance with previous IDMC recommendations
3. Before or early in the trial	
Whether the IDMC will have input into the protocol	All potential IDMC members should have sight of the protocol before agreeing to join the committee. Before recruitment begins the trial will have undergone review by the funder/sponsor (e.g. peer review for public sector trials), scrutiny by other trial committees and a research ethics committee (REC). Therefore, if a potential IDMC member has major reservations about the trial (e.g. the protocol or the logistics) they should report these to the trials unit and may decide not to accept the invitation to join. IDMC members should be independent[1] and constructively critical of the ongoing trial, but also supportive of aims and methods of the trial.
Whether the IDMC will meet before the start of the trial	The IDMC will first meet before the trial starts to discuss the protocol, the trial, future meetings, and to have the opportunity to clarify any aspects with the Chief Investigator (CI) and Trial Management Group (TMG). The IDMC should meet within one year of recruitment commencing. Any conflicts of interest should be disclosed prior to the first meeting to the GLINT Chief Investigator. **Table 1: Potential competing interests** • Stock ownership in any commercial companies involved • Stock transaction in any commercial company involved (if previously holding stock) • Consulting arrangements with the Sponsor (including CI for other MRC trials) • Frequent speaking engagements on behalf of the intervention • Career tied up in a product or technique assessed by trial • Hands-on participation in the trial • Involvement in the running of the trial • Emotional involvement in the trial • Intellectual conflict e.g. strong prior belief in the trial's experimental arm • Involvement in regulatory issues relevant to the trial procedures

CONTENT Guidance	CHARTER DETAILS
	• Investment (financial or intellectual) or career tied up in competing products • Involvement in the publication in the form of authorship
Any issues specific to the disease under study	N/A
Any specific regulatory issues	Prolonged release metformin is being used outside regular licencing. MHRA (type B) approval has been gained.
Any other issues specific to the treatment under study	Individuals with hepatic or renal impairment will not be eligible to take part in the GLINT trial. We are collecting additional safety measures in the feasibility phase of the study: B12, eGFR, creatinine and LFTs.
Whether members of the IDMC will have a contract	IDMC members will not formally sign a contract but the Chairperson should formally register his/her assent to join the group by confirming (1) that they agree to be on the IDMC and (2) that they agree with the contents of this Charter. Any competing interests by any members of the committee should be declared. The Chairperson should complete and return the form in Annexe 1. Observers attending any part of the meeting should sign a confidentiality agreement on the first occasion they attend all or part of a meeting (Annexe 2).
4. Composition	
Membership and size of the IDMC	One member each with expertise in: (1) *Cardiology* (2) *Statistics* *(3) Diabetes* *(4) Oncology* The members should be independent of the trial (should not be involved with the trial in any other way or have any competing interest(s) that could impact on the trial). Any competing interests, both real and potential, should be declared.
The Chair, how they are chosen and the Chair's role. (Likewise, if relevant, the vice-Chairman)	The Chair will have previous experience of serving on IDMCs, experience of Chairing meetings and will be able to facilitate and summarise discussions. The Chair will be nominated and agreed by the GLINT TSC, the sponsor (Cambridge University Hospitals NHS Foundation Trust and University of Cambridge) and the trial funders (NIHR HTA). The Chair is expected to facilitate and summarise discussions. A vice-Chair will not be appointed.
The responsibilities of the IDMC statistician	The IDMC membership will include a statistician to provide independent statistical expertise, especially with regards to interpretation of accumulating data and guidance through the report. The IDMC statistician will not prepare the IDMC report.
The responsibilities of the trial statistician	The trial statistician will oversee the provision of interim masked data sets for use by the IDMC and the MRC Epidemiology Unit / DTU study coordinating centres. Pre-agreed masked datasets will be transferred to the Independent Statistician who will have

Comment [AD1]: Is this necessary for observers? If not we will remove annexe 2

CONTENT Guidance	CHARTER DETAILS
	overall responsibility for the production of the unblinded report to the IDMC and will participate in IDMC meetings, guiding the IDMC through the report, participating in IDMC discussions and, on some occasions, taking notes. The Independent Statistician will hold the unblinding codes in strict confidence.
The responsibilities of the trials unit team	The trial team will help the independent statistician to produce the report to the IDMC. The Trial Manager may attend open sessions of the meeting.
The responsibilities of the Chief Investigator and other members of the Trial Management Group (TMG)	The CI should be invited and should be available, to attend open sessions of the IDMC meeting. The other TMG members will not usually be expected to attend but can attend open sessions when necessary (See Organisation of IDMC Meetings).
5. Relationships	
Relationships with Chief Investigators, other trial committees (e.g. Trial Steering Committee (TSC) or Executive Committee), sponsor and regulatory bodies	The responsibilities of each trial group are detailed in the protocol. The relationships between these groups are displayed in Figure 2.
Clarification of whether the IDMC is advisory (make recommendations) or executive (make decisions)	The TSC is the oversight body and is delegated this role by the sponsor. The IDMC is *advisory* to the TSC. Both the TMG and IDMC make comments, requests and recommendations to the TSC.
Payments to IDMC members	Members will be reimbursed for reasonable travel costs and accommodation where required. No other payments or rewards are given.
The need for IDMC members to disclose information about any competing interests	Competing interests should be disclosed. These are not restricted to financial matters – involvement in other trials or intellectual investment could be relevant. Although members may well be able to act objectively despite such connections, complete disclosure enhances credibility. IDMC members should not use interim results to inform trading in pharmaceutical shares, and careful consideration should be given to trading in stock of companies with competing products.
6. Organisation of meetings	
Expected frequency of IDMC meetings	The IDMC will meet three times during the feasibility phase. Firstly, before the trial starts. Secondly, after 250 participants have been randomised in the feasibility phase of the trial *and* when the 250th person has at least three months follow-up. And finally, when 500 participants have been randomised (end of feasibility phase). Following the feasibility phase, the IDMC will meet every six months, or more frequently if required.
Whether meetings will be face-to-face or by teleconference	The first and third IDMC meetings will be by teleconference. The second IDMC will be face-to-face.
How IDMC meetings will be	A mixture of open and closed sessions will be held. Only IDMC

CONTENT Guidance	CHARTER DETAILS
organised, especially regarding open and closed sessions, including who will be present in each session	members and others whom they specifically invite, e.g. the trial statistician/senior scientist are present in closed sessions. In open sessions, all those attending the closed session may be joined by the CI(s), other members of the trials unit team and sometimes also representatives of the sponsor, funder, or regulator, as relevant. The format of the meetings will be based on the following structure: 1. Open session: Introduction and any "open" parts of the report 2. Closed session: IDMC discussion of "closed" parts of the report and, if necessary, the trial statistician will attend only part of these discussions 3. Open session: Discussion with other attendees on any matters arising from the closed session. 4. Closed session: extra closed session (if necessary)
How and when to disclose potential conflicts of interest	1. Conflicts of interest should be disclosed to the GLINT Chief Investigator prior to the first meeting. 2. The GLINT Chief Investigator will review the conflict of interests and decide if a conflict of interest is an impediment to participation in the IDMC. 3. During each subsequent open session, the IDMC chair will ask all members if they have any additional conflicts of interest to disclose or changes to existing conflicts of interests and ensure that that are reported to the GLINT Chief Investigator. 4. Closed session: extra closed session (if necessary)
7. Trial documentation and procedures to ensure confidentiality and proper communication	
Intended content of material to be available in open sessions	Accumulating information relating to recruitment and data quality (e.g. data return rates, treatment compliance) will be presented, blinded to treatment assignment. Adverse event details based on pooled data will be presented and total numbers of events for the primary outcome measure and other outcome measures may be presented, at the discretion of the IDMC.
Intended content of material to be available in closed sessions	In addition to all the material available in the open session, the closed session material will include outcome and safety data by treatment group.
Whether or not the IDMC will be blinded to the treatment allocation	The IDMC will not be blinded to treatment allocation.
The people who will see the accumulating data and interim analysis	The accumulating data and interim analysis by randomised group will be seen by the IDMC members and trial statistician(s).

CONTENT Guidance	CHARTER DETAILS
Responsibility for identifying and circulating external evidence (e.g. from other trials/ systematic reviews)	Identification and circulation of external evidence (e.g. from other trials/ systematic reviews) is not the responsibility of the IDMC members. The CI and the trial team will collate any such information for presentation in an open session.
To whom the IDMC will communicate the decisions/ recommendations that are reached	The IDMC reports its recommendations in writing to the trial statistician who forwards the information to the TSC. A short report to the TMG to say whether the trial should remain unchanged or whether the matters will be raised with the TSC should be sent via the trial statistician. If the trial is to continue largely unchanged it is useful for the report from the IDMC to include a summary paragraph suitable for trial promotion purposes ie to be circulated to trial sites (See Annexe 3). In its communications, the IDMC should be careful not to relay any unnecessary information to the TSC: the TSC membership has independent members but also representatives from the trial team including the Chief Investigator. The IDMC should take care to protect the CI from interim trial data where possible.
Whether reports to the IDMC be available before the meeting or only at/during the meeting	The IDMC should receive the report at least 1 week and preferably at least 2 weeks before any meetings.
What will happen to the confidential papers after the meeting	The IDMC members should delete or destroy the papers after each meeting. After the trial is reported, the IDMC members should destroy all interim reports. A copy of all of the reports will be held at MRC Epidemiology Unit, University of Cambridge. Fresh copies of previous reports may be circulated (by email) with the newest report before each meeting.
8. Decision making	
What decisions/recommendations will be open to the IDMC	Possible recommendations from the IDMC include:- • No action needed, trial continues as planned • Early stopping due, for example, due to clear benefit or harm of a treatment or external evidence. (This should generally involve a recommendation to unblind the TSC to this data) • Stopping recruitment within a subgroup (care should be taken if this is not a pre-specified subgroup). (This should generally involve a recommendation to unblind the TSC to this data) • Proposing or commenting on proposed protocol changes
The role of formal statistical methods, specifically which methods will be used and whether they will be used as guidelines or rules	Formal statistical methods are more generally used as "stopping" guidelines rather than absolute rules. This is because they generally only consider one dimension of the trial. Reasons should be recorded for disregarding a stopping guideline. No pre-specified stopping guidelines have been defined.
How decisions or recommendations will be reached within the IDMC	The Chair is to summarise discussions and encourage consensus; it is usually best for the Chair to give their own opinion last. Every effort should be made for the IDMC to reach a unanimous decision. If the IDMC cannot achieve this, a vote may be taken, although details of the vote should not be routinely included in the report to the TSC as these may inappropriately convey

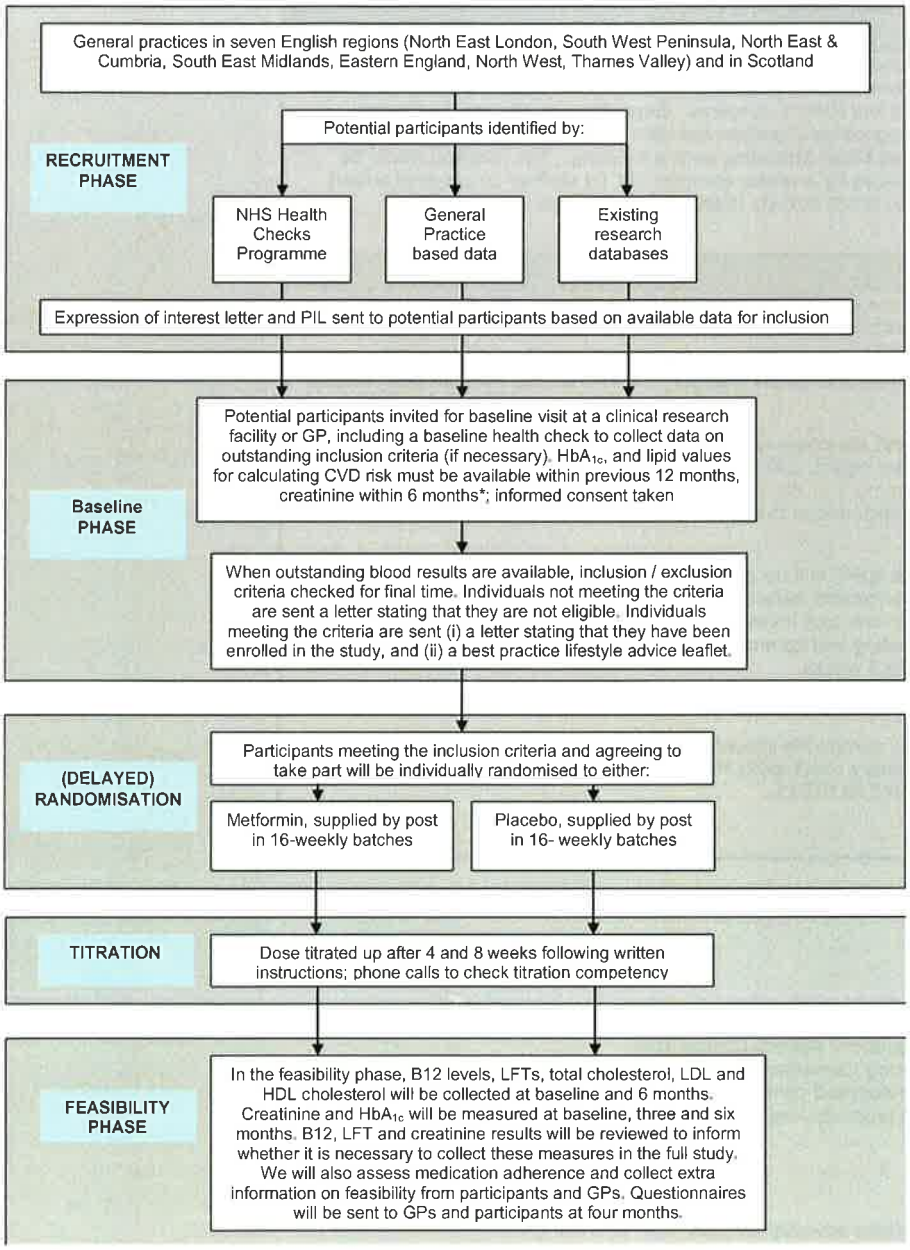
CONTENT Guidance	CHARTER DETAILS
	information about the state of the trial data. It is important that the implications (e.g. ethical, statistical, practical, financial) for the trial be considered before any recommendation is made.
When the IDMC is quorate for decision-making	Efforts should be made to ensure that all members can attend. The GLINT trial team will try to ensure that a date is chosen to enable this. Members who cannot attend in person should be encouraged to attend by teleconference. If, at short notice, any IDMC members cannot attend at all then the IDMC may still meet if at least one statistician and one clinician, including the Chair (unless otherwise agreed), will be present. If the IDMC is considering recommending major action after such a meeting the IDMC Chair should communicate with the absent members as soon after the meeting as possible to check they agree. If they do not, a further meeting should be arranged with the full IDMC.
Can IDMC members who cannot attend the meeting input	If the report is circulated before the meeting, IDMC members who will not be able to attend the meeting may pass comments to the IDMC Chair for consideration during the discussions.
What happens to members who do not attend meetings	If a member does not attend a meeting, it should be ensured that the member is available for the next meeting. If a member does not attend the following meeting, they should be asked if they wish to remain part of the IDMC. If a member does not attend a third meeting, they should be replaced.
Whether different weight will be given to different endpoints (e.g. safety/efficacy)	Different weights are not applied to endpoints.
Any specific issues relating to the trial design that might influence the proceedings, e.g. cluster trials, equivalence trials, multi-arm trials	None
Feasibility phase interim analysis reporting	See Annexe Four.
9. Reporting	
To whom will the IDMC report their recommendations/decisions, and in what form	This will be through a letter to the TSC via the trial statistician, usually within 2 weeks of the meeting (see Section 7). A copy of this will be stored at MRC Epidemiology Unit, University of Cambridge.
Whether minutes of the meeting be made and, if so, by whom and where they will be kept	Separate records will be required for open and closed sessions with minutes made by the appropriate attending member of the trial team. This will usually be the Trial Manager for the open session and the Chair or other IDMC member for the closed session. The IDMC Chair should sign off any minutes or notes.
What will be done if there is	If the IDMC has serious problems or concerns with the TSC

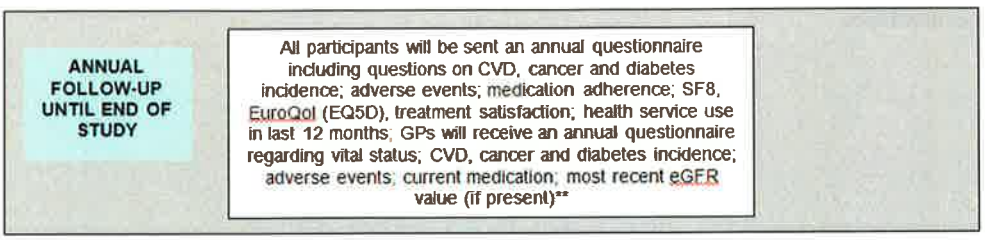
CONTENT Guidance	CHARTER DETAILS
disagreement between the IDMC and the body to which it reports	decision a meeting of these groups should be held. The information to be shown would depend upon the action proposed and the IDMC's concerns. Depending on the reason for the disagreement confidential data would often have to be revealed to all those attending such a meeting. The meeting would be Chaired by a senior member of CTU staff or an external expert who is not directly involved with the trial.
10. After the trial	
Reporting of results	At the third meeting the IDMC will discuss the data from the feasibility phase and give advice about data interpretation. The findings will be reported to the sponsor and funders in a correct and timely manner; the TSC should oversee this process.
The information about the IDMC that will be included in published trial reports	IDMC members will be named and their affiliations listed in the main report, unless they explicitly request otherwise. A brief summary of the timings and conclusions of IDMC meetings should be included in the body of this paper.
Whether the IDMC will have the opportunity to approve publications, especially with respect to reporting of any IDMC recommendation regarding termination of a trial	The IDMC will be given the opportunity to read and comment on publications before submission. This will usually be concurrent with the trial investigators and independent members of the TSC reading and commenting. The commenting period will usually be 2 to 3 weeks.
Any constraints on IDMC members divulging information about their deliberations after the trial has been published	Any comments should be made within 12 months after the primary trial results have been published *and* with the permission of the GLINT CI.

Abbreviations and glossary

AE	Adverse event
CI	Chief Investigator
CTU	Clinical Trials Unit
EUDRACT	European Union Drug Regulatory Agency Clinical Trial
IDMC	Independent Data Monitoring Committee
ISRCTN	International standard randomised controlled trial number
MHRA	Medicines and Healthcare products Regulatory Authority
MRC	Medical Research Council
PI	Principal Investigator
SAE	Serious adverse event
SAR	Serious adverse reaction
SUSAR	Suspected unexpected serious adverse reaction
TMG	Trial Management Group
TSC	Trial Steering Committee

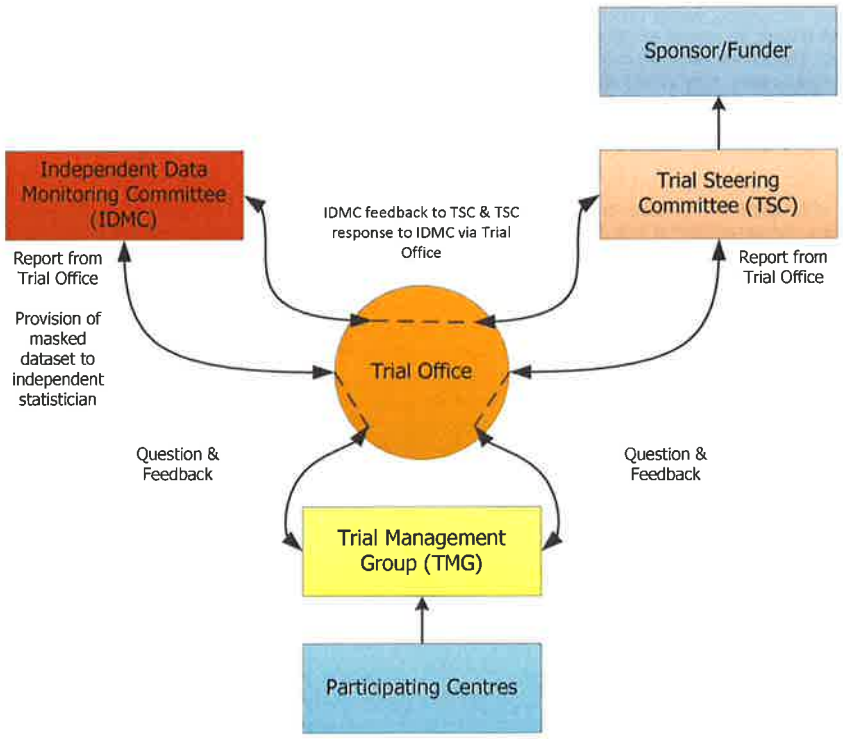
Figure 1: Diagram summarising GLINT trial


General practices in seven English regions (North East London, South West Peninsula, North East & Cumbria, South East Midlands, Eastern England, North West, Thames Valley) and in Scotland
RECRUITMENT PHASE
Potential participants identified by:
NHS Health Checks Programme
General Practice based data
Existing research databases
Expression of interest letter and PIL sent to potential participants based on available data for inclusion
Baseline PHASE
Potential participants invited for baseline visit at a clinical research facility or GP, including a baseline health check to collect data on outstanding inclusion criteria (if necessary). HbA1c, and lipid values for calculating CVD risk must be available within previous 12 months, creatinine within 6 months*; informed consent taken
When outstanding blood results are available, inclusion / exclusion criteria checked for final time. Individuals not meeting the criteria are sent a letter stating that they are not eligible. Individuals meeting the criteria are sent (i) a letter stating that they have been enrolled in the study, and (ii) a best practice lifestyle advice leaflet.
(DELAYED) RANDOMISATION
Participants meeting the inclusion criteria and agreeing to take part will be individually randomised to either:
Metformin, supplied by post in 16-weekly batches
Placebo, supplied by post in 16- weekly batches
TITRATION
Dose titrated up after 4 and 8 weeks following written instructions; phone calls to check titration competency
FEASIBILITY PHASE
In the feasibility phase, B12 levels, LFTs, total cholesterol, LDL and HDL cholesterol will be collected at baseline and 6 months. Creatinine and HbA1c will be measured at baseline, three and six months. B12, LFT and creatinine results will be reviewed to inform whether it is necessary to collect these measures in the full study. We will also assess medication adherence and collect extra information on feasibility from participants and GPs. Questionnaires will be sent to GPs and participants at four months.



*Note that we do not plan to collect LFTs or B12 at baseline in the main trial (following safety results from the feasibility phase); we do not plan to collect creatinine measures during trial follow-up, though we will ask GPs to supply this value if available
** If eGFR < 45ml/min, trial medication should be stopped

Figure 2: Relationship of trial committees



Annexe 1: Chairperson Agreement form

Glucose Lowering in Non-diabetic hyperglycaemia Trial (*GLINT*): Agreement to join the Independent Data Monitoring Committee and disclosure of potential competing interests

Please complete the following document and return to the GLINT Trial Manager (at the MRC Epidemiology Unit).

Document: IDMC Charter Version 1.0

Your signature below shows that you have reviewed the aforementioned document, understand it, and agree with its contents.

IDMC Chairperson:

PROF BRYAN WILLIAMS _____ 28/01/2015

print name signature dd mmm yyyy

Note: This DMC template was developed using on MRC CTU template DMC Charter v2.01, 13-Mar-2006; from DAMOCLES DMC Charter template v1, Feb 2005

Annexe 2: Agreement and confidentiality agreement for observers

Glucose Lowering in Non-diabetic hyperglycaemia Trial (*GLINT*) Independent Data Monitoring Committee: Agreement to attend the Independent Data Monitoring Committee and treat all information confidentially

Please complete the following document and return to the GLINT Trial Manager (at the MRC Epidemiology Unit).

Document: IDMC Charter Version 1.0

Your signature below shows that you have reviewed the aforementioned document, understand it, and agree with its contents.

Observer:

_____		____/	____/	_____
print name	signature	dd	mmm	yyyy

Note: This DMC template was developed using on MRC Clinical Trials Unit Cancer Group DMC Charter template v2.01, 13-Mar-2006; from DAMOCLES DMC Charter template v1, Feb 2005

Annexe 3: Suggested report from IDMC to TSC where no recommendations are being made

[Insert date]

To: Chair of Trial Steering Committee
Via: Trial Statistician

Dear *[Chair of Trial Steering Committee]*

The Independent Data Monitoring Committee (IDMC) for the GLINT trial met on *[meeting date]* to review its progress and interim accumulating data. *[List members] attended* the meeting and reviewed the report.

The trial question remains important and, on the basis of the data reviewed at this stage, we recommend continuation of the trial according to the current version of the protocol *[specify protocol version number and date]* with no changes.

We shall next review the progress and data *[provide approximate timing]*

Yours sincerely,

[Name of meeting Chair]
Chair of Independent Data Monitoring Committee

On behalf of the IDMC (all members listed below)

IDMC members:
<<Name>>, <<*Field of expertise*>> <<*IDMC position*>>
(1)

Annexe 4: Planned interim analyses for the feasibility phase of the GLINT trial

The analysis of the feasibility trial will be descriptive; no p-values will be calculated. It will include presentation of the following information, separately by randomised group:

- Number and percentage of individuals recruited via each of the 3 recruitment strategies.
- Summaries of baseline characteristics of recruited participants; these summaries will be means and standard deviations for continuous variables with a reasonably symmetric distribution, medians and interquartile ranges for continuous variables with a skewed distribution, and frequencies and percentages for categorical variables.
- Baseline estimate of future cardiovascular risk using Framingham risk equations
- Compliance with trial medication.
- Creatinine and HbA1c values at 0, 3 and 6 months; B12 and LFT values at 0 and 6 months
- Safety data
- Endpoint numbers

Annexe 5: Summarise changes from previous version

Version 1.0

This is version 1.0 of the IDMC charter for this trial. There are no changes to be reported.

Trial Steering Committee Charter

Glucose Lowering in Non-diabetic hyperglycaemia Trial (GLINT)

Trial Steering Committee Charter Effective Date: 08 January 2015

Introduction

GLINT (Glucose Lowering in Non-diabetic hyperglycaemia Trial) is a pragmatic, placebo-controlled, double blinded trial which seeks to characterise the effect of metformin on macrovascular outcomes in people with non-diabetic hyperglycaemia (NDH) at high risk over five years. The study will enrol 500 participants in a pilot study with NDH (HbA_{1c} ≥5.5% but <6.5%) and no prior history of cardiovascular disease who have an estimated 10-year CVD risk ≥20% as assessed by the Framingham or QRISK2 scores.

The primary objective for the study will be to establish the effectiveness of metformin in prevention of cardiovascular events as measured by the time to first event in a primary CVD composite of CV-related death, nonfatal MI, and nonfatal stroke. Secondary objectives are to assess the effect of metformin on incident cancer, all cause mortality, and incident diabetes.

GLINT will be managed collaboratively by the MRC Epidemiology Unit at the University of Cambridge and the University of Oxford Diabetes Trials Unit (DTU) under the guidance of the GLINT Trial Steering Committee (TSC).

This charter describes the role and responsibilities of the GLINT TSC. Administration of the TSC, provision of honoraria and reimbursement of reasonable expenses incurred will be the responsibility of the MRC Epidemiology Unit at the University of Cambridge.

1. Role of the Trial Steering Committee

The Trial Steering Committee (TSC) is charged with the oversight of the scientific and professional conduct of the study.

The primary functions of the TSC are to:

1. Review and approve the trial protocol and all protocol amendments.
2. Supervise the conduct of the trial in accordance with the TSC's responsibilities as described in the trial protocol.
3. Approve the Statistical Analysis Plan.
4. Oversee all trial subcommittees, including but not limited to:
    a. Clinical endpoint committee
    b. Data monitoring and ethics committee (DMEC)
    c. Operational committee
5. Approve the membership of the DMEC.
6. Review and consider recommendations from the DMEC.
7. Determine the time to terminate the trial, based on recommendations from the DMEC and other available information. The TSC may also find it necessary to terminate the trial under certain circumstances, including but not limited to the following reasons:
    a. Animal, human or toxicological test results, which in the reasonable determination of the TSC, support termination of the trial
    b. Ethical or patient safety issues occur that the TSC feels support termination of the trial
    c. Extraordinary scientific, regulatory or other events that negatively impact the rationale for the trial, such that the TSC agrees it is appropriate to terminate the trial
8. Review all sub-study requests and approve where appropriate.
9. Consider, authorise as appropriate and prioritise requests for access to GLINT trial data and genetic and biomarker samples for academic or other collaborations. After the TSC disbands, the MRC Epidemiology Unit and the Diabetes Trials Unit (DTU) will assume this responsibility.
10. Approve the strategy on how to best communicate information about the progress of the trial.
11. Ensure accurate, uniform, timely, and high quality reporting of the main trial and all approved sub-studies.
12. Approve the confidential draft manuscript describing the primary results prior to submission for publication.
13. Maintain confidentiality of all trial information that is not in the public domain.

2. Membership

The TSC will consist of nine individuals, comprising three senior independent academic experts in their field (one of whom will chair the committee), one lay representative and four GLINT PIs. If a member can no longer continue to serve on the TSC, a replacement will be selected by the TSC and approved by the Sponsor. Attendance at meetings will usually be limited to the TSC members, with observers from the MRC Epidemiology Unit and the DTU when appropriate. Other attendees may be invited for all or part of the meeting by the TSC. The observers are not members of the TSC but may be invited to provide expert input.

Independent TSC members will not be asked to sign a contract but should formally register their agreement to join the group by confirming (1) that they agree to be a member of the TSC and (2) that they agree with the contents of this Charter. Any potential competing interests should be declared at the same time. Independent members should complete and return the form in Appendix One.

Independent committee members will be reimbursed for reasonable travel expenses for attending meetings. The lay representative will be reimbursed for reasonable travel expenses and will receive an honorarium of £75 per TSC meeting attended. No other payments will be made to the professional members.

3. Organisation

The Committee will convene for at least one annual face-to-face meeting. Teleconferences will take place every three months initially, but may occur less often during the later stages of the trial as deemed necessary.

Decision making by consensus will always be the goal. In the event consensus is not achieved, votes will be taken, and the majority position will be adopted. Only independent members of the TSC are allowed to vote. The chair has the casting vote. At least three independent members must be present for the TSC to be quorate.

All TSC members are expected to participate in every meeting. If extenuating circumstances prevent a member from attending a particular meeting, the member may provide input directly to the TSC chair, or the meeting may be rescheduled for the earliest available date that all members can attend.

4. Responsibilities of Members

TSC members will be expected to:

- Attend and actively participate in meetings of the TSC
- Maintain confidentiality regarding the trial and activities of the TSC
- Intervene where appropriate to assist Operational Committee members in reaching study goals
- Participate, where appropriate, in scientific meetings providing updates of study progress
- Disclose any relevant conflicts of interest that exist at the trial outset or that arise during the conduct of the trial (Table 1)

Table 1: Potential competing interests for independent members

• Stock ownership in any commercial companies involved
• Stock transaction in any commercial company involved (if previously holding stock)
• Consulting arrangements with the Sponsor/Funder
• Ongoing advisory role to a company providing drugs to the trial
• Frequent speaking engagements on behalf of the intervention
• Career tied up in a product or technique assessed by trial
• Hands-on participation in the trial
• Involvement in the running of the trial
• Emotional involvement in the trial
• Intellectual conflict e.g. strong prior belief in the trial's experimental arm
• Involvement in regulatory issues relevant to the trial procedures
• Investment (financial or intellectual) or career tied up in competing products
• Involvement in the writing up of the main trial results in the form of authorship

5. Documentation

1) Meeting Minutes
   The MRC Epidemiology Unit at the University of Cambridge will keep a set of minutes detailing TSC Meeting decisions and action points. Once approved by the

TSC chair, the final version of the minutes for each session will be marked as such and saved as a PDF file or similar format that cannot be modified.

2) Communication Log
   The MRC Epidemiology Unit at the University of Cambridge will maintain files documenting any relevant communication between the TSC and all subcommittees or working groups and with the Sponsor or regulatory agencies.

3) Committee Recommendations
   The GLINT study coordinator at the MRC Epidemiology Unit will be the primary contact with all subcommittees or working groups and with the Sponsor.

Appendix One

Agreement and competing interests form for independent members of the GLINT Trial Steering Committee (TSC)

Document: Trial Steering Committee Charter Version 1.0

Your signature below shows that you have reviewed the aforementioned document, understand it, and agree with its contents.

Trial Steering Committee Chair:

Michael J Clarke		**26/Jan/2015**
print name	**signature**	**dd/mmm/yyyy**