MANCHESTER 1824
The University of Manchester

Standard Operating Procedure

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Title:	Independent Data Monitoring Committee and Trial Steering Committee		
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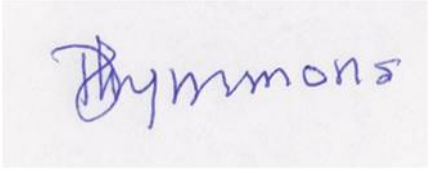
Signature: 		**Signature:** 	

Version	Date	Reason for change
1.1	**May 2014**	**Addition of version control statement for SOP**
2.0	**October 2015**	**Update of web links and office details**
3.0	**August 2016**	**Update of web links and office details**
4.0	**March 2018**	**Review and update**

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1.0 Background

The EU Good Clinical Practice (GCP) Directive 2001/20/EC was introduced to establish standardisation of research activity in Clinical Trials throughout the European Union. It was transposed into UK law as the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) which came into force on 1st May 2004. The Medicines for Human Use (Clinical Trials) Regulations together with subsequent amendments will be referred to as the Regulations in the rest of this document.

It is important to ensure that a Clinical Trial of an Investigational Medicinal Product (CTIMP) is conducted to the highest ethical and scientific standards. This means periodically reviewing the conduct and output of the trial from the perspective of patient safety, in order to ensure that patients participating in the trial are not exposed to any increased risk of harm, which could have been prevented and that ,where necessary, the trial protocol be amended or the trial ended early . This oversight can be achieved through a number of different bodies. These bodies are the Ethics committees (which are mandatory for each clinical trial), an Independent Data Monitoring Committee (which is appointed at the request of the study funder and/or Sponsor), and a Trial Steering Committee (which is required in large clinical trials and is also appointed at the request of the study funder and/or Sponsor). The key remits of these bodies are firstly to ensure that patients are not exposed to any increased risk of harm which is avoidable; and secondly to ensure the scientific integrity of data collection and analysis. The final responsibility for the conduct of the clinical trial rests with the Sponsor.

Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) comprises a group of experts who are external to the clinical trial. The IDMC reviews, in an ongoing manner, the accumulating data from the clinical trial. It mainly reviews recruitment and safety data and may also see quality and compliance data. The IDMC will usually have access to any planned interim data analysis resulting from the clinical trial. The IDMC advises the Sponsor and Trial Steering Committee (if appointed) on the future conduct of the trial. The University of Manchester, when acting as Sponsor, usually requires an IDMC to be put in place for all CTIMP and medical device clinical studies.

Trial Steering Committee

The University of Manchester, when acting as Sponsor, usually requires a Trial Steering Committee, with an independent chair, to be put in place for all CTIMP and medical device clinical investigations. The TSC acts as a body that takes responsibility for the scientific integrity of a clinical trial and will focus on trial progress including protocol adherence and subject safety. The composition of the TSC and the frequency of meetings should be specified in advance. The TSC can comprise investigators, clinical experts who are not directly involved in the clinical trial and representatives of the Sponsor. A TSC often takes responsibility for the scientific validity of the study protocol, assessment of study quality and conduct, as well as for the scientific quality of the final study report. The TSC should not usually have access to unblinded study data.

2.0 Purpose

This SOP outlines when and how the University of Manchester, as the study Sponsor, will require an IDMC to be constituted. It also describes the composition and roles of an IDMC.

The University of Manchester as a potential Sponsor will also consider and accept, where necessary, the terms and conditions of the funding body if these specify that an IDMC be established.

3.0 Procedure

The University of Manchester, in its role as the Sponsor, is responsible for the conduct of CTIMPs and Medical Device Clinical Studies.

- For all trials, the study protocol should detail in full the proposed committees
- Where a joint IDMC/TSC is deemed appropriate, all functions across both committees should be fulfilled
- It should also be noted that the UoM provide indemnity cover for IDMC and TSC members.

3.1 Independent Data Monitoring Committee

Where the University of Manchester has been approached to consider sponsorship of a CTIMP or Medical Device clinical study, a risk assessment will be undertaken. The Clinical Trial Management Group (CTMG) will then determine whether an IDMC is required based on the results of the risk assessment where this is not already a requirement of funding. It is advisable that a Charter be generated to specify the remit, composition and frequency of meetings. Again this may be subject to Funder requirements. Occasionally in smaller studies, the roles of the IDMC and TSC maybe combined.

3.1.1 Composition of an IDMC

The IDMC members must be experts in their fields and must be independent of the conduct and management of the CTIMP. The IDMC members must declare any conflicts of interest, and if there may be any major conflict of interest the IDMC member must remove his/her self immediately. Any minor conflicts of interest will be reviewed by the CI and declared to the Sponsor. All the IDMC members will be required to commit the necessary time needed to perform their duties. The IDMC must abide by any request of confidentiality as required by the funder and the Sponsor. The University Contracts team will put any relevant CDAs (Confidentiality Disclosure Agreements) in place.

The IDMC should have at least three members. The Chair of the IDMC must have previous experience of sitting on an IDMC. An IDMC should have an experienced biostatistician in their membership as well as a clinical member chosen because of their expertise in the area of medicine in which the trial is being conducted. In addition the clinical member should, ideally, have knowledge and where possible experience of potential adverse effects of the treatment being studied. The composition of the IDMC should be notified to the CTMG as well as any changes in membership during the course of the trial. For international collaborations,

international members should be considered, enabling a single IDMC group for the trial with relevant representation and expertise.

In some cases the members of the IDMC will be proposed and require review by the Trial Management Group, the CI/trials team and/or the funder.

3.1.2 Establishing the IDMC

The IDMC must be appointed as soon as possible after the trial has been funded. Ideally it should have input into the safety aspects of the protocol and the related data to be collected.

In discussion with the CI and trial statistician, the IDMC should have a 'charter' which specifies in advance their composition; frequency of meetings; who will take the minutes; communication channels with the trial team, TSC and Sponsor; and the nature of the data they will receive (including whether this will be blinded or unblinded). The charter should also specify whether the trial statistician will provide all the data for the IDMC or whether any analysis by treatment arm will be provided by another independent statistician. The charter will also detail the roles and responsibilities of the IDMC which should include reviewing and commenting on the statistical analysis plan. The charter should be agreed by all relevant trial team and IDMC members before any trial data are reviewed. All IDMC members must maintain the confidentiality of information and other intellectual property, including both blinded and unblinded clinical trial data. The Sponsor requires that the IDMC be informed of any relevant findings. In addition all reports will be circulated to the CTMG.

The Sponsor will review and approve any requirements stipulated by the Funder and/or CTU. If there are no formal requirements, the Sponsor will request the following before an IDMC can be approved:

1. Sign a confidentiality agreement, arranged through the University of Manchester Contracts Team
2. A summary of the responsibilities of the IDMC
3. A list of the proposed members of the IDMC, with contact details and areas of expertise (including CVs)
4. The structure and proposed frequency of the IDMC meetings and the flow of information between the IDMC, Sponsor, and other entities should be captured in an organisational diagram. This should also show the reporting relationship between the IDMC, the Sponsor and other functional groups (e.g. Trial Steering Committee & Chief Investigator). A copy of this diagram should be kept in the Trial Master File and provided to the CTMG.
5. Meetings must be minuted, and held within the Trial Master File (TMF) where appropriate. Where blinded information is a component of IDMC, minutes should be held outside of the TMF until the end of the trial
6. Each member should sign a conflicts of interest declaration
7. Need for a quorum for decision making procedures for making formal recommendations to the Sponsor and/or other functional body
8. The IDMC will review the Statistical Analysis Plan (SAP)

9. The IDMC will review and comment on all proposed publications before submission

Please see Appendix I for an example IDMC Charter to be referenced and amended as necessary in association with the above.

3.2 Trial Steering Committee

Where the University of Manchester has been approached to consider sponsorship of a CTIMP or Medical Device Clinical Study, a risk assessment will be undertaken. The CTMG will then determine whether a TSC is required based on the results of the risk assessment where this is not a requirement of funding. As above, occasionally in smaller studies, the roles of the IDMC and TSC maybe combined.

3.2.1 Composition of a Trial Steering Committee

Unlike the IDMC, the TSC will include some personnel who are directly involved in the trial (e.g. chief investigator, trial statistician, Sponsor) as well as independent members. The University generally requires that the TSC has an independent chair who is not directly involved in running or recruiting to the trial. The funder may also require specific members and numbers to sit on the TSC.

The TSC members must declare any conflicts of interest, and if there may be any major conflict of interest the TSC member must remove his/her self immediately. Any minor conflicts of interest will be reviewed by the CI and declared to the Sponsor. All the TSC members will be required to commit the necessary time needed to perform their duties. For external members the University Contracts team will put any relevant CDAs (Confidentiality Disclosure Agreements) in place.

3.2.2 Establishing a Trial Steering Committee

The Sponsor requires that the TSC be informed of any relevant findings. In addition all reports will be circulated to the CTMG.

The Sponsor will review and approve any requirements stipulated by the Funder and/or CTU. If there are no formal requirements, the Sponsor will request the following before a TSC can be approved:

1. Signed confidentiality agreements, arranged through the University of Manchester Contracts Team (External members only)
2. A summary of the responsibilities of the TSC including responsibility for decision making
3. A list of the members of the TSC
4. The proposed frequency of the TSC meetings
5. Details of who is responsible for TSC documentation
6. Meetings must be minuted, with copies held in the Trial Master File.
7. Each member should declare any conflicts of interest

Please see Appendix II for an example TSC Charter to be referenced and amended as necessary in association with the above.

4.0 References:

- UK Policy Framework for Health and Social Care Research
- NRES Guidance Clinical Trials and DMC
- UK Clinical Trial Regulations
- MHRA GCP Guide
- MAHSC-CTU and Cardiff CTR Charter templates and associated documents

5.0 Appendices

- **Appendix I**: IDMC Charter Template including example/guidance text
  All members must document agreement to sit on either of the relevant committees. Ideally these committees should be in place before the enrolment of any trial participants.

- **Appendix II**: TSC Charter Template including example/guidance text
  There is no formal sign off for the TSC but agreement to this document must be minuted in meeting minutes.

(Modified Courtesy of Cardiff CTR)

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Appendix I

Independent Data Monitoring Committee Charter

- The Charter should be completed before (or early into) the trial and the content should be agreed with the IDMC members
- **Guidance notes (Green highlighted) should be deleted before the document is signed off.**
- **Yellow highlighted sections should be updated and replaced as appropriate.**

Trial Title	
Short Title/Acronym	
Sponsor Reference Code (R code)	
EudraCT Number	
ISRCTN/Public Registry Number	

Created by:
Name: Role:

Signature: Date:

Abbreviations and glossary (Amend as necessary)

AE	Adverse event
AR	Adverse reaction
CF	Consent form
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trials Authorisation
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
ERC	Endpoint Review Committee
EudraCT	European Union Drug Regulatory Agency Clinical Trial
IB	Investigator's Brochure
IDMC	Independent Data Monitoring Committee
ISRCTN	International standard randomised controlled trial number
MHRA	Medicines and Healthcare products Regulatory Authority
NHS	National Health Service
PI	Principal Investigator
PIS	Patient information Sheet
QL	Quality of life
SAE	Serious adverse event
SAR	Serious adverse reaction
SOP	Standard operating procedures
SmPC	Summary of product characteristics
SSA	Site specific assessment
SUSAR	Suspected unexpected serious adverse reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected adverse reaction

CONTENT	*CHARTER DETAILS*
1. INTRODUCTION	
Objectives of trial, including interventions being investigated	[To be completed] [Please attach a flow diagram depicting the trial]
Outline of scope of charter	This charter details the roles and responsibilities, composition, relationships, meetings, trial documentation, decision making, reporting and post-trial duties of the IDMC. In brief, this document defines the communication channels within and from the IDMC, the frequency of meetings, how decisions will be made, how reports will be generated (maintaining the blind where appropriate), ensuring recommendations are fully considered and stating who is responsible for maintaining documentation throughout the trial.
2. ROLES AND RESPONSIBILITIES	
A broad statement of the aims of the IDMC	To safeguard the interests of trial participants, monitor the main outcome measures including safety and efficacy, and monitor the overall conduct of the trial/study.
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: (i) the results are likely to convince a broad range of clinicians, including those supporting the trial/study and the general clinical community, that one trial arm is clearly indicated or contraindicated for all participants or a particular category of participants, and there was a reasonable expectation that this new evidence would materially influence patient management; or (ii) It becomes clear that no clear outcome would be obtained.
Specific roles of IDMC The following roles will usually be undertaken by the IDMC.	To undertake interim review of the trial/study's progress including updated figures on recruitment, data quality, adherence to protocol treatment and follow-up, main outcomes and safety data. Specifically, these roles are to: • monitor evidence for treatment differences in the main efficacy and safety outcome measures – and thus recommending

CONTENT	CHARTER DETAILS
	action when/whether the main trial question has been answered • monitor evidence for treatment harm (e.g. toxicity, SAEs and SARs, deaths) • assess the impact and relevance of any external evidence • decide whether to recommend that the trial/study continues to recruit participants or if recruitment should be terminated either for everyone or for some treatment groups and/or some participant subgroups • recommending whether the trial should continue to recruit or continue with follow-up • 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 • monitor recruitment figures and losses to follow-up • monitor compliance with the protocol by participants and investigators • consider the ethical implications of any recommendations made by the IDMC • monitor planned sample size assumptions, preferably with regards to (i) a priori assumptions about the control arm outcome and/or (ii) emerging differences in clinically relevant subgroups, rather than on emerging, unblinded differences between treatment groups, overall[1] • 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 continuing appropriateness of patient information • monitor compliance with previous IDMC recommendations • Communicate decisions with the relevant parties set out in the organisational diagram
3. BEFORE OR EARLY IN THE TRIAL/STUDY	
Involvement/input into the protocol by the IDMC	All potential IDMC members should have sight of the protocol/outline before agreeing to join the committee. Before recruitment begins the trial will have undergone review by the funder/sponsor (e.g. peer review for public

CONTENT	CHARTER DETAILS
	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/study (e.g. the protocol or the logistics) they should report these to the Sponsor and may decide not to accept the invitation to join. IDMC members should be independent and constructively critical of the ongoing trial/study, but also supportive of aims and methods of the trial/study.
Whether the IDMC will meet before the start of the trial/study	The DMC should have a preliminary meeting before any data are reviewed and agree the frequency with which it will meet.
Any issues specific to the disease under study	[Please detail]
Any specific regulatory issues	[Please detail]
Whether members of the IDMC will have a contract	The DMC members must declare any conflicts of interest (See Annex A), and if there may be any major conflict of interest the DMC member must remove his/her self immediately. Any minor conflicts of interest will be reviewed by the CI and declared to the Sponsor. All the DMC members will be required to commit the necessary time needed to perform their duties. The DMC will be provided with blinded or un-blinded reports on study data and must abide by any request of confidentiality as required by the funder and the sponsor. The University Contracts team will put any relevant CDAs (Confidentiality Disclosure Agreements) in place.
4. COMPOSITION	
Membership and size of the IDMC Membership should consist of a small number of members with experience in clinical trials. The exact membership should reflect the needs of the trial(s) covered by the IDMC.	The members should be independent of the trial/study (should not be involved with the trial/study in any other way or have any competing interest(s) that could impact on the trial/study). Any competing interests, both real and potential, should be declared. A short competing interest form should be completed and returned by the IDMC members to the trial coordinating centre (Annex A). CVs should be collected for all IDMC members and filed appropriately with the trial team. The DMC should have at least three members. All members must be detailed in this Charter. The composition of the DMC should be notified to the CTMG as well as any changes in membership during the course of the trial.
The Chair, how they are chosen and the Chair's role. The Chair is sometimes chosen by	The Chair will have previous experience of serving on IDMCs, experience of Chairing meetings and will be able to facilitate and summarise discussions.

CONTENT	CHARTER DETAILS
the Funder or Sponsor or TMG.	
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.
Responsibilities of the trial statistician	The trial statistician will have overall responsibility for the production of the report to the IDMC and will participate in IDMC meetings guiding the IDMC through the report, participating in IDMC discussions. The statistician may also have to take notes occasionally.
Responsibilities of the members of the trial team	The other members of the trial team (i.e. Trial Manager/ Data Manager) will input to the production of the open/non-confidential sections of the IDMC report.
The responsibilities of the Chief Investigator and other members of the Trial Team	The CI and trial team should be invited and should be available to attend open sessions of the IDMC meeting.
5. RELATIONSHIPS	
Relationships with Chief Investigators, other trial/study committees (e.g. T/SSC) or Executive Committee), sponsor and regulatory bodies	[Please provide a diagram to demonstrate the organisational flow of data/information both within the IDMC and other committees/relevant parties]
Clarification of whether the IDMC is advisory (make recommendations) or executive (make decisions)	The IDMC usually provides recommendations to the TSC or Sponsor (when no TSC appointed) and in this way is advisory. It is still the responsibility of the IDMC to ensure recommendations are duly addressed.
Payments to IDMC members Members will be reimbursed for reasonable travel costs and other expenses incurred. In some instances this may be only for UK travel.	[Describe any arrangements for covering travel and relevant reimbursement policies]
IDMC member's disclosure of any competing interests	Any conflict of interest must be declared.
6. ORGANISATION OF MEETINGS	
Expected frequency of IDMC meetings	Frequency will be dependent on both the endpoints and complexity of the trial. The DMC should have a preliminary meeting before any data are reviewed and agree the frequency with which it will meet. A further meeting within the first 6 months of the trial opening should also

CONTENT	CHARTER DETAILS
	be scheduled.
Format	The first meeting should ideally be face-to-face to facilitate full discussion and allow members to get to know each other. It is recommended that all subsequent meetings should be face-to-face if possible, with teleconference as a second option.
Organisation Consideration should be taken to incorporate both closed and open sessions. Such discussions should take into account blinded/unblinded attendees. The format/agenda for each meeting should be detailed in advance of the meeting	
7. TRIAL/STUDY DOCUMENTATION AND PROCEDURES TO ENSURE CONFIDENTIALITY AND PROPER COMMUNICATION	
Accumulating data and interim analysis	The accumulating data and interim analysis by treatment group should be available only to those present in the closed sessions i.e. only members of the IDMC, the trial statistician and other members of the trial team, as agreed by the IDMC. IDMC members must **not** share confidential information with people outside the IDMC, including the CI.
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 trials unit team will collate any such information for presentation in an open session.
Providing the reports to the IDMC in readiness of discussion at the meeting.	The IDMC should receive the report at least 1 week and preferably at least 2 weeks before any meetings. The IDMC reports its recommendations in writing to the trial statistician and forwards to the TSC. This should be copied to the trial statistician and in time for consideration at a TSC meeting. A short report to the TMG to state whether the trial should remain unchanged or whether the matters will be raised with the TSC and should be sent via the trial statistician.
Destruction of confidential papers following the meeting	1. The IDMC members should destroy their reports after each meeting. Fresh copies of previous reports will be circulated with the newest report before each meeting. **OR** 2. The IDMC members should store the papers safely after each meeting so they may check the next report against them. After the trial is reported, the IDMC members should destroy all interim reports.

CONTENT	CHARTER DETAILS
8. DECISION MAKING	
Decisions/recommendations from the IDMC	Possible recommendations from the IDMC include (but are not limited too):- • No action needed, trial continues as planned • Early stopping due to, for example, clear benefit or harm of a treatment, clear lack of benefit, safety concerns, slow recruitment or external evidence. (This should generally involve a recommendation to unblind the T/SSC 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) • Extension of recruitment (based on actual control arm response rates being different to predicted rather than on emerging differences)[2] or extending follow-up • Stopping one or more arms of a multi-arm trial • Sanctioning and/or proposing protocol changes • Commenting on Statistical Analysis Plan
The role of formal statistical methods, specifically which methods will be used and whether they will be used as guidelines or rules This Charter should include or provide reference to the planned interim analyses and statistical guidelines as detailed in the Statistical Analysis Plan	
Reaching decisions or recommendations within the IDMC	The role of the Chair is to summarise discussions and encourage consensus. In each area of discussion it is usually best for the Chair to give their own opinion last. Every effort should be made for the IDMC to reach a consensus. 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 T/SSC as these may inappropriately convey information about the state of the trial data. It is important that the implications (e.g. ethical, statistical, practical, financial) for the trial/study be considered before any recommendation is made.
Ensuring quoracy for decision-making	Efforts should be made to ensure that all members can attend. The trial/study 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

CONTENT	CHARTER DETAILS
	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.
Input into IDMC meeting if not in attendance	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.
Prioritising different endpoints (e.g. safety/efficacy)	[It needs to be determined if different endpoints, namely safety and efficacy, will be given different weightings]
Any specific issues relating to the trial/study design that might influence the proceedings, e.g. cluster trials, equivalence trials, multi-arm trials	[Address any relevant issues, for example outcome measures that as a whole are spread across differing time points]
9. REPORTING	
Communicating the IDMC decisions/ recommendations that are reached A timescale should be specified	The IDMC usually reports its recommendations in writing to the trial statistician, usually within 2 weeks of the meeting, who will forward the information to the TSC. Or if agreed prior, the IDMC can report recommendations directly to the TSC or Sponsor's representative, copying in the statistician. A short report to the TMG will state whether the trial should remain unchanged or whether matters arising will be raised with the TSC. This should be sent via the trial statistician. 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.
Keeping a record of the meeting Consideration should be given to minutes being made by someone experienced in minuting or who is not otherwise involved in the meeting; else they will be made by the Trial Administrator or equivalent.	Separate records will be required for open and closed sessions. Minutes of the open session can be made by the Trials Administrator. Minutes of the closed session should be made by the attending Statistician who is authorised to attend the closed session. The IDMC Chair should sign off any minutes or notes.
What will be done if there is disagreement between the IDMC and the body to which it reports	If the IDMC identifies a serious problem or has concerns with the TSC decision a meeting of these groups should be held. The information to be shown would depend upon the action proposed and the 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

CONTENT	CHARTER DETAILS
	by a senior member of the CTR or an external expert who is not directly involved with the trial/study.
10. AFTER THE TRIAL	
Publication of results	At the end of the trial/study, there may be a meeting to allow the IDMC to discuss the final data with the Chief Investigator (or delegate) to give advice about data interpretation. The main trial results will be published in a correct and timely manner; the TSC should oversee this process.
Reference to IDMC 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.
IDMC opportunity to approve publications, especially with respect to reporting of any IDMC recommendation regarding termination of a trial/study	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 T/SSC 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 It should be specific when the IDMC may discuss issues from their involvement in the trial or trade in stock of a company making a trial drug involved e.g. 12 months after the primary trial results have been published, or when permission is agreed with the overseeing committee.	

Annex A: IDMC Conflict of Interest Declaration Form

Please complete the following document and return to the Trial Team.

(Please initial box to agree)

	I have read and understood the IDMC Charter version XX, dated XX
	I agree to join the Independent Data Monitoring Committee for this trial/study
	I agree to treat all sensitive trial/study data and discussions confidentially

The avoidance of any perception that members of an IDMC may be biased in some fashion is important for the credibility of the decisions made by the IDMC and for the integrity of the trial/study.

Possible competing interest should be disclosed via the Sponsor. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) IDMC member should remove the conflict or stop participating in the IDMC. **Table 1** lists potential competing interests.

☐ **No,** I have no competing interests to declare
☐ **Yes,** I have competing interests to declare (please detail below)

Please provide details of any competing interests:

_____

_____

_____

Name: _____

Signed: _____ Date: _____

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 CTR trials)
- Frequent speaking engagements on behalf of the intervention
- Career tied up in a product or technique assessed by trial/study
- Hands-on participation in the trial/study
- Involvement in the running of the trial/study
- Emotional involvement in the trial/study
- Intellectual conflict e.g. strong prior belief in the trial/study's experimental arm
- Involvement in regulatory issues relevant to the trial/study procedures
- Investment (financial or intellectual) or career tied up in competing products
- Involvement in the publication in the form of authorship

Annex B: IDMC confidentiality agreement - observers

Agreement to attend the Data Monitoring Committee and treat all information confidentially

Please complete the following document and return to the Trial Team.

(Please initial box to agree)

	I have received a copy of the IDMC Charter version XX, dated XX
	I agree to attend the IDMC meeting on XXX
	I agree to treat as confidential any sensitive trial information gained during this meeting unless explicitly permitted

Name: _____

Signed: _____ Date: _____

Appendix II

Trial Steering Monitoring Committee Charter

- The Charter should be completed before (or early into) the trial and the content should be agreed with the TSC members
- **Guidance notes (Green highlighted) should be deleted before the document is signed off.**
- **Yellow highlighted sections should be updated and replaced as appropriate.**

Trial Title	
Short Title/Acronym	
Sponsor Reference Code (R code)	
EudraCT Number	
ISRCTN/Public Registry Number	

Created by:

Name: Role:

Signature: Date:

Abbreviations and glossary (Amend as necessary)

CI	Chief Investigator
IDMC	Independent Data Monitoring Committee
IB	Investigator's Brochure
SAE	Serious adverse event
TMG	Trial Management Group
TSC	Trial Steering Committee

CONTENT	DETAILS OF TSC
1. INTRODUCTION	
Name (& Sponsor's ID) of trial	[To be completed]
Objectives of trial, including interventions being investigated Insert objectives of trial, including interventions being investigated from protocol	[Please provide a diagram to demonstrate the organisational flow of information both within the TSC and other committees/relevant parties]
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 Trial Steering Committee (TSC) for this trial/study, including the timing of meetings, methods of providing information to and from the TSC, frequency and format of meetings and relationships with other trial/study committees.
Facilitation	A member of the trial team will be nominated as a facilitator for the trial/study. The facilitator will be responsible for the organisation of meetings and should be copied into all communications with and between the TSC.
2. ROLES AND RESPONSIBILITIES	
A broad statement of the aims of the TSC	The primary role of the Trial Steering Committee (TSC) is to monitor and supervise the progress of the trial towards its interim and overall objectives. This includes safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and monitoring overall conduct of the trial. The TSC acts as the oversight body for this trial/study on behalf of the Sponsor/Funder.
Terms of reference	The role of the TSC is to provide oversight for the trial. It should also provide advice through its independent Chairman to the Trial Management Group (TMG), Sponsor and Funder (as necessary) on all aspects of the trial/study.
Specific roles of TSC The following roles will usually be undertaken by the TSC	• provide expert oversight of the trial/study • maintain confidentiality of all trial information that is not already in the public domain • make decisions as to the future continuation or termination(or otherwise) of the trials/studies • Monitor the main outcome measures including safety and efficacy • Monitor evidence for treatment harm (e.g. toxicity, SAEs and SARs, deaths) • assume responsibility for the assessment of the study quality and conduct (to ensure that the trial is being conducted in accordance with the principles of GCP and the relevant regulations) • monitor recruitment rates and encourage the TMG to develop strategies to deal with any recruitment problems assuming responsibility • monitor completion of CRFs data flow; comment on strategies from

CONTENT	DETAILS OF TSC
	TMG to encourage satisfactory completion in the future as well as suggesting additional data analyses if necessary • review regular reports of the trial from the Trial Management Group (TMG) • monitor follow-up rates and review strategies from TMG to deal with problems • approve any proposals by the TMG concerning any change to the design of the trial, including additional substudies – consider ethical implications, protocol modifications, appropriateness of patient info • approve amendments to the protocol, where appropriate, such as in cases of significant change to the trial design • interaction with the IDMC • receive letters of feedback from the IDMC and consider their recommendations • assess the impact and relevance of any accumulating external evidence • monitor protocol compliance by participants, investigators and sites • oversee the timely reporting of trial results • approve / comment on the publication policy (if required) • approve / comment on the main trial manuscript (if required) • be informed of any abstracts and presentations of any results *during* the running of the trial (if required) • approve external or early internal requests for release of data or subsets of data or samples including clinical data and stored biological samples • maintain confidentiality of all trial/study information that is not in the public domain • assume responsibility for the scientific integrity of the trial • assume responsibility for the scientific validity of the protocol • assume responsibility for the scientific quality of final trial report
3. BEFORE OR EARLY IN THE TRIAL/STUDY	
The involvement/input of the T/SSC into the protocol	All independent TSC members should have sight of the protocol soon after the TSC has been approached. Before recruitment begins the trial/study will have undergone review by the Sponsor/Funder (e.g. peer review for public sector trials), scrutiny by other trial committees and a research ethics committee. Therefore, if a potential independent TSC member has major reservations about the trial/study (e.g. the protocol, the logistics, ethical concerns) they should report these to the CI and may decide not to accept the invitation to join. TSC members should be constructively critical of the ongoing trial, but also supportive of aims and methods of the trial.
Whether members of the TSC will	TSC members will not be asked to formally sign a contract but should

CONTENT	DETAILS OF TSC
have a contract	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. Members should complete and return the form in Annexes A or B. Any observers (attendees who are not members) will sign a confidentiality agreement on the first occasion they attend a meeting (Annex C). It is the responsibility of the CI and Sponsor to consider any competing interests declared by a potential independent member. If they are not deemed to impair the independence of the member then the Sponsor should approve their membership by signing Annex A. If the competing interests are deemed to impair the member's independence on the TSC they should not be appointed. The TSC members must declare any conflicts of interest, and if there may be any major conflict of interest the TSC member must remove his/her self immediately. Any minor conflicts of interest will be reviewed by the CI and declared to the Sponsor. All the TSC members will be required to commit the necessary time needed to perform their duties. For external members the University Contracts team will put any relevant CDAs (Confidentiality Disclosure Agreements) in place.
4. COMPOSITION	
Membership and size of the TSC Membership should consist of a small number of members with experience in clinical trials, including a minimum of three independent members. The exact membership should reflect the needs of the trial(s) covered by the TSC. Membership should usually include lay/patient representatives. The majority of non-independent members will come from the TMG but may include PI's of key clinical sites, pathologists, representatives of relevant laboratories and other experts	The majority of members of the TSC, including the Chair, should be independent of the trial/study (see section 5). Non-independent members will also be part of the TSC. Members of the TSC must be detailed in this Charter.
The Chair, how they are chosen and the Chair's role. The Chair is sometimes chosen by the Funder or Sponsor or TMG.	The Chair should have previous experience of serving on trial/study committees and experience of Chairing meetings, and should be able to facilitate and summarise discussions; knowledge of the disease area would be beneficial.
Responsibilities of the CI and other members of the TMG	The CI (and, if appropriate, other TMG members) should be present at TSC meetings in person or by teleconference and no major decisions should be made without consultation with the CI and other appropriate members of the TMG.
The responsibilities of the observers	Additional observers may be in attendance through (parts of) the TSC meetings in order to provide input on behalf of the Sponsor, Funder or

CONTENT	DETAILS OF TSC
	to provide specific relevant expertise.
5. RELATIONSHIPS	
Relationships with Chief Investigators, other trial committees (e.g. TMG and IDMC), Sponsor/Funder and regulatory bodies	The responsibilities of each trial/study committee are detailed in the protocol and in the respective Charters.
Advisory and executive bodies	The TSC is the oversight body and is delegated the roles in Section 2 by the Sponsor. All substantial issues regarding the trial must go to the TSC for consideration. The IDMC is advisory to the TSC.
Payments to T/SSC members Members will be reimbursed for reasonable travel costs and other expenses incurred. In some instances this may be only for UK travel.	[Describe any arrangements for covering travel and relevant reimbursement policies]
The need for TSC members to disclose information about any real or potential competing interests	Any competing interests, both real or potential, should be disclosed. These are not restricted to financial matters, involvement in other trials or intellectual investment. Although members may be able to act objectively despite such connections, complete disclosure enhances credibility (See Annex A and B). TSC members should not use any trial data to inform trading in pharmaceutical shares, and careful consideration should be given to trading in stock of companies with competing products. Changes in declarations of real or potential competing interests should be minuted at the start of each meeting.
6. ORGANISATION OF MEETINGS	
Expected frequency of TSC meetings	The TSC should have an initial meeting following ethical approval, before recruitment is initiated. The TSC will meet at least yearly. At the request of the TSC, interim meetings, in person or by teleconference, will be organised. Some trial issues may need to be dealt with between meetings, by phone or by email. TSC members should be prepared for such instances.
Attendance of TSC members at meetings	The first meeting should ideally be face-to-face to facilitate full discussion and allow members to get to know each other. It is recommended that all subsequent meetings should be face-to-face if possible, with teleconference as a second option and, ideally, no two consecutive meetings by teleconference. Effort will be made to ensure that all members can attend. The Facilitator will work for a date that enables this. The CI must try to attend all meetings, especially if major actions are expected. If, at short notice, any TSC members cannot attend then the TSC may still meet if at least two independent members, including the Chair (unless otherwise agreed), will be present. A member of the trial/study team is also expected to be present, but may be asked to leave for a closed discussion at the TSC Chair request. If the TSC is considering a major action after such a meeting the TSC Chair should communicate with the absent members, including the CI, as soon after the meeting as possible to check they agree. If they do not, a further teleconference should be arranged with the full TSC.

CONTENT	DETAILS OF TSC
Meeting organisation for TSC including open and closed sessions	Presence will be usually limited to the TSC members, observers from the Sponsor/Funder, trials unit and the Facilitator. Other attendees may be invited for all or part of the meeting by the TSC including the trial/study statistician and trial/study manager. The observers are not members of the TSC but may be invited to provide expert input or to represent the funding bodies involved; other observers will be at the discretion of the TSC and the Facilitator but may include members of the TMG other than the CI.
TSC members inputting into a meeting they are unable to attend	The TSC report should be circulated before the meeting with sufficient time for members to read. TSC members who will not be able to attend the meeting may pass comments to the TSC Chair or Facilitator for consideration during the meeting.
Independent members who do not attend meetings	If an independent member does not attend a meeting or provide comments when requested between meetings, it should be ensured that the independent member is available for the next meeting. If an independent member does not attend the next meeting or provide comments when next requested, they should be asked if they wish to remain part of the TSC. If an independent member does not attend a third meeting, strong consideration should be given to replacing this member.
7. TRIAL/STUDY DOCUMENTATION AND PROCEDURES TO ENSURE CONFIDENTIALITY AND COMMUNICATION	
Intended content of material to be considered during meetings	The material may include a report from the IDMC, requests from the TMG or draft publications. No trial outcome measure data will be presented by arm unless explicitly authorised by the IDMC (eg toxicity). Where relevant, accrual, compliance with follow-up and adherence to treatment may be presented by centre.
Report dissemination	It is helpful for the TSC to receive the report at least 1 week (preferably at least 2) before any meetings. Different procedures may apply to teleconference meetings.
Access to accumulating data and interim analysis by randomised group	The accumulating data by arm and interim analyses will be confidential and viewed only by the IDMC. The TSC will not be routinely privy to these interim reports. The IDMC will make recommendations to the TSC based on the interim data. Unblinded data will only be available to the TSC if the IDMC consider this to be essential for any decisions based on their recommendations.
Responsibility for identifying and circulating external evidence (e.g. from other trials/studies/ systematic reviews)	Identification and circulation of external evidence (e.g. from other trials/ systematic reviews) is not the responsibility of the TSC members; it is a responsibility of the TMG. However, the TSC should continue to be made aware of other data that may impact on a trial/study.
Communicating decisions made by the TSC	(See Section 9)
What will happen to the papers after the meeting	TSC members would be expected to delete, destroy or store securely copies of the reports to and from the TSC, agenda and minutes, as well as copies of communications between meetings. All documentation should be considered confidential. The Facilitator will keep a central record of all minutes, reports and correspondence by the TSC.
8. DECISION MAKING	
What decisions will be open to the	Based on recommendations from the IDMC, possible decisions

CONTENT	DETAILS OF TSC
TSC	include:- • No action needed, trial/study continues as planned • Early stopping due, for example, to clear benefit or harm of a treatment, futility or external evidence (this should generally involve a recommend from the IDMC to unblind the TSC to this data • Stopping recruitment within a subgroup (this should generally involve a recommend from the IDMC to unblind the TSC to this data) • Modifying target recruitment, or pre-analysis follow-up, based on any change to the assumptions underlying the original trial/study sample size calculation (but not on any emerging differences) • Stopping one or more arms of a multi-arm trial/study • Sanctioning and/or proposing protocol changes Based on other factors, possible decisions include the decisions above and:- • Censuring centres for poor recruitment/poor data quality • Approving proposed protocol amendments or new trial sub-studies • Approving requests for early release of (subsets of) data • Approving external applications for the use of stored samples • Approving presentation of results during the trial or soon after closure • Approval of new centres or strategies to improve recruitment or follow-up
The role of formal statistical methods	Formal statistical methods may have been considered by the IDMC in making their recommendations to the TSC. These methods are usually used as guidelines rather than absolute rules. This is because they generally only consider one dimension of the trial/study. The IDMC will record reasons for disregarding a stopping guideline in the notes of their meetings and may choose to also note this in their report to the TSC if necessary.
How decisions or recommendations will be reached within the TSC	Every effort should be made to achieve consensus. The role of the Chair is to summarise discussions and encourage consensus; therefore, it is usually best for the Chair to give their own opinion last. It is important that the implications (e.g. ethical, statistical, practical, and financial) for the trial be considered before any decision is made and minuted.
Quoracy in the TSC	At least two independent members of the TSC should be present including the Chair, plus a representative of the trial tesam and, if major action is to be considered, the CI.
Any specific issues relating to the trial design that might influence the proceedings	(See Section 3)

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9. REPORTING	
To whom will the TSC report their recommendations/decisions, and in what form A timescale should be specified e.g. usually within 3 weeks	The TSC will report their decisions (via the Facilitator) to the Sponsor and TMG who will be responsible for implementing any actions resulting. This should be within 3 weeks of the meeting. The TSC may also provide feedback to the IDMC and, where appropriate, to the Sponsor/Funder. Copies of communications will pass through the Facilitator.
Minutes of the meeting Consideration should be given to minutes being made by someone experienced in minuting or who is not otherwise involved in the meeting; else they will be made by the Facilitator.	Minutes of the meeting setting out the key points and actions will be taken by the Facilitator. This will include details of whether potential competing interests have changed for any attendees since the previous meeting. The draft minutes will be initially circulated for comment to those TSC members who were present at the meeting. The TSC Chair will sign off the final version of minutes or notes. The minutes of the meeting will be kept confidentially by the Facilitator. A copy of minutes excluding any confidential issues should be stored in the relevant TMF. It is the responsibility of the CI and trial project manager to ensure all relevant issues arising from meetings are followed up and documented. Relevant participating sites must also be contacted following any significant findings. In addition, the CI and trial manager will be actively responsible for the documentation supplied in and out of the TSC, including incorporation of meeting minutes into the Trial Master File.
What will be done if there is disagreement between the TSC and other trial committees	The TSC is the oversight body for the trial. However, the TSC should have good reason before deciding not to accept requests from the TMG and recommendations from the IDMC. If there are serious problems or concerns with the TSC decision following an IDMC recommendation, a joint meeting of the TSC and IDMC should be held. The information to be shown would depend upon the action proposed and each committees' concerns. Depending on the reason for the disagreement confidential data and/or data by trial/study and may have to be revealed to all or some of those attending such a meeting: this would be minimised where possible. The meeting would be Chaired by a an external expert or appropriate personnel who is not directly involved with the trial/study.
10. AFTER THE TRIAL/STUDY	
Publication of results	The TSC will oversee the timely analysis, writing up and publication of the main trial/study results. The independent members of the TSC may have the opportunity to read and comment on the proposed main publications of trial data prior to submission and abstracts and presentations during the trial. This review may be concurrent to that of the trial/study investigators and IDMC.
TSC information included in published trial reports	TSC members will be named and their affiliations listed in the main report, unless they explicitly request otherwise.
Any constraints on TSC members divulging information about their deliberations after the trial has been published It should be specified when the TSC may discuss issues from their involvement in the trial or trade in stock of a company making a trial	TSC members should not divulge sensitive information about the ongoing trial unless specifically authorised by the TSC, depending on the nature of the information.

CONTENT	DETAILS OF TSC
drug or competitor product e.g. 12 months after the primary trial results have been published, or if permission is agreed sooner with the other trial/study committees and Trials Unit. Similarly, the TSC will decide when it is appropriate for TMG and IDMC members to trade in stock.	

Annex A: Agreement and competing interests form for independent members

Please complete the following document and return to the Trial Team.

(Please initial box to agree)

	I have read and understood the TSC Charter version XX, dated XX
	I agree to join the Trial Steering Committee for this trial/study as an independent member
	I agree to treat all sensitive trial/study data and discussions confidentially

The avoidance of any perception that independent members of a TSC may be biased in some fashion is important for the credibility of the decisions made by the TSC and for the integrity of the trial.

Potential competing interests should be disclosed via the CI. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) independent TSC member should remove the conflict or stop participating in the T/SSC. **Table 1** lists potential competing interests.

	I have no potential competing interests to declare
	I have potential competing interests to declare (please detail below)

Please provide details of any potential competing interests:

_____

_____

_____

Name: _____

Signed: _____ Date: _____

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/study
- Hands-on participation in the trial/study
- Involvement in the running of the trial/study
- Emotional involvement in the trial/study
- Intellectual conflict e.g. strong prior belief in the trial/study's experimental arm
- Involvement in regulatory issues relevant to the trial/study procedures
- Investment (financial or intellectual) or career tied up in competing products
- Involvement in the writing up of the main trial/study results in the form of authorship

Annex B: Agreement and competing interests form for non-independent members

Please complete the following document and return to the Trial Team.

(Please initial box to agree)

	I have read and understood the T/SSC Charter version XX, dated XX
	I agree to join the Trial/Study Steering Committee for this trial as an non-independent member
	I agree to treat all sensitive trial/study data and discussions confidentially

The avoidance of any perception that members of a TSC may be biased in some undisclosed fashion is important for the credibility of the decisions made by the TSC and for the integrity of the trial.

Possible competing interests should be disclosed via the CI. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) independent T/SSC member should remove the conflict or stop participating in the T/SSC. **Table 1** lists potential competing interests.

	I have no competing interests to declare other than involvement in the trial/study
	I have competing interests to declare (please detail below)

Please provide details of any competing interests:

_____

_____

_____

Name: _____

Signed: _____ Date: _____

Table 1: Potential competing interests for non-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
- Intellectual conflict e.g. strong prior belief in the trial/study's experimental arm
- Involvement in regulatory issues relevant to the trial/study procedures
- Investment (financial or intellectual) in competing products

Annex C: Agreement and confidentiality agreement for observers

Please complete the following document and return to the Trial Team.

(please initial box to agree)

	I have received a copy of the T/SSC Charter version XX, dated XX
	I agree to attend the Trial/Study Steering Committee meeting on XXX
	I agree to treat as confidential any sensitive information gained during this meeting unless explicitly permitted

Name: _____

Signed: _____ Date: _____