UNIVERSITY OF LINCOLN

CLINICAL GOVERNANCE - STANDARD OPERATING PROCEDURE

DATA MONITORING COMMITTEE

CG-QMS

Version Final 1.0 Date 01 May 2021

Effective Date: 01 August 2021

Next review: 2 years

Author:	Elise Rowan Clinical Data Manager
Approved by: Signature:	UREC See original

Version History	**Reason for change**

NOTE: All SOPs are subject to regular review.

Please ensure that the version of this SOP is the most up-to-date.

OUT OF DATE DOCUMENTS MUST NOT BE USED AND HARD COPIES SHOULD BE DESTROYED

1. PURPOSE

This SOP describes the use and role of a Data Monitoring Committee (DMC) for assessing data during interim analyses of clinical trials and studies, and how such a committee should operate.

2. SCOPE

This SOP is applicable to all staff involved in setting up and conducting research e.g. Chief Investigators (CI), Principal Investigators (PI), medical staff, Health Care Assistants (HCA), Research Governance Managers and Clinical Trial Administrative staff. The SOP is also relevant to members of the DMC, Trial Management Group (TMG) and TSC.

3. BACKGROUND

3.1 The Chief Investigator is ultimately responsible for the study's data integrity.

3.2 All Clinical Trials of Investigational Medicinal Products (CTIMPs) and device studies which are blinded studies shall have an independent DMC. It is recommended that large, complex trials also have an Independent DMC to carry out reviews of trial data at staged intervals during the study. The DMC should include experienced trial investigators, statisticians and clinicians; all of whom must be independent to the research team.

3.3 Prior to each DMC review, a summary of the data should be prepared by the research team's data manager (with the support of the research team statistician (if there is no risk of unblinding) or the DMC statistician) and this should be as up to date as possible and should be validated up to the point of the interim analysis.

3.4 The remit of the DMC is to make recommendations for action (or not) to the TSC based on the outcome of their review(s). TSCs then can take decisions based on the DMC recommendations.

4. CROSS REFERENCES

4.1 CG-QMS Data Monitoring Committee

4.2 CG-QMS Trial Management Group

4.3 CG-QMS Trial Steering Committee

5. PROCEDURE

ROLE OF THE DMC

The general roles of the DMC are as follows:

5.1 The DMC members will be required to commit the necessary time needed to perform their duties.

5.2 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.

5.3 The DMC must have input into the safety aspects of the protocol and the related data to be collected.

5.4 The DMC will review data at regular intervals as sufficient data accumulate.

5.5 The DMC should mainly review the safety and efficacy data and may also see quality and compliance data.

5.6 The DMC will determine whether there are any safety issues or any reasons why the study should not continue.

5.7 The DMC will make recommendations for action through the Trial Steering Committee (TSC) for the study, cc'd to the Sponsor.

Specific Tasks to be undertaken by the DMC

5.8 To agree a pre-defined format for DMC/DMEC reports in collaboration with the TSC and TMG.

5.9 To regularly review summary data on (but not limited to) the number of adverse events, deaths and withdrawals of trial participants.

5.10 To keep the CI, TSC and TMG informed about planned dates for DMC meetings.

5.11 To keep minutes of DMC meetings.

5.12 To make recommendations that improve participant safety or enhance the safety reporting for the study/trial.

5.13 To make recommendations if necessary, about the future continuation (or otherwise) of the trial/study.

5.14 To feedback all recommendations for actions from all DMC meetings to the TSC (via the TSC chair), chief investigator and trial sponsor (and the funder if required).

DMC MEMBERSHIP

5.15 Potential DMC members will be selected by the Sponsor, TMG and sometimes by the TSC as soon as possible after the trial has been funded.

5.16 The composition of the DMC should be notified to the TMG as should any change in membership during the course of the trial.

5.17 The DMC members must be experts in their fields and must be independent of the conduct and management of the trial.

5.18 The DMC members must declare any conflicts of interest that could interfere with their role in the DMC before being formally accepted to join the committee.

5.19 If conflicts of interest arise after a member has joined the DMC, then the DMC member must declare these and remove themselves immediately.

5.20 The DMC should have at least three members:

5.21 The chair -The Chair of the DMC must have previous experience of sitting on a DMC.

5.22 Statistician -A DMC should have an experienced biostatistician in their membership. This statistician should not be the same statistician with voting rights on the TSC.

5.23 Clinical member (s) -Clinical members should be selected based on their expertise in the area of medicine in which the trial/study is being conducted. In addition, clinical members should have knowledge and where possible experience of, potential adverse effects of the treatment(s) being studied.

5.24 A list of the members of the DMC, with contact details and areas of expertise should be provided to the sponsor, CI, TSC and TMG. A copy of this should be maintained in the Trial Master File.

DMC MEETINGS

Establishing the DMC

5.25 The DMC should have their first meeting before any data are reviewed, in order to:

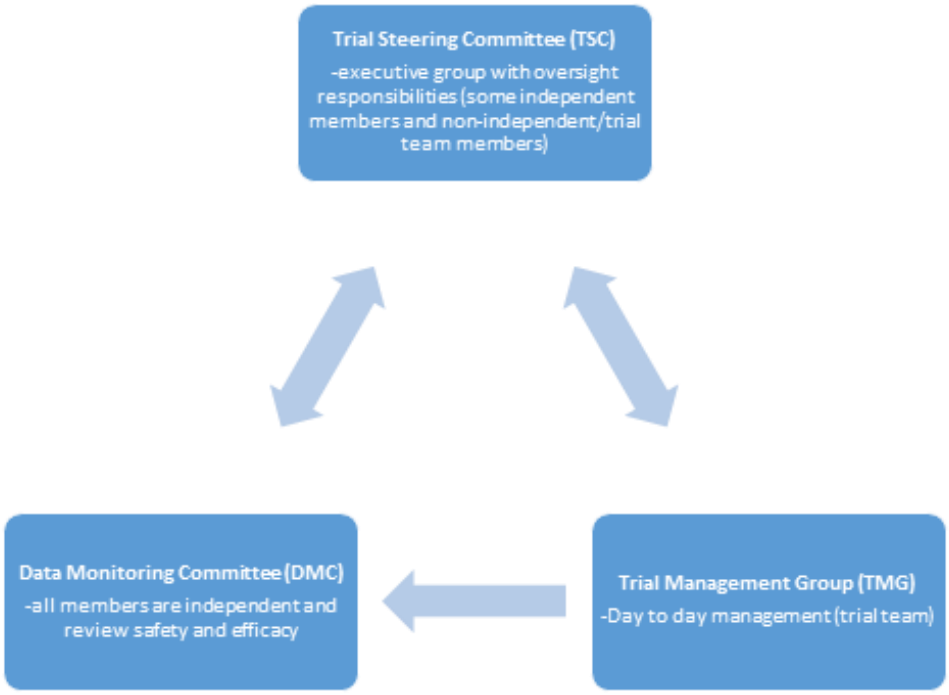
- have a clear understanding of their responsibilities

- agree the frequency with which the DMC will meet
- agree how and to whom the DMC will report its findings.
- agree a pre-defined format for DMC reports in collaboration with the TSC and TMG.

5.26 The above steps can be achieved by developing a trial/study specific DMC Charter –see the Damocles Charter template provided in Appendix 1 below.

6. FLOW CHART

This oversight and management structure should be followed unless otherwise agreed with the Sponsor, funder and Trial Management Group:



Appendix 1: DMC Charter Template (Damocles Charter)

The Damocles Charter is derived from the following publication:

A proposed charter for clinical trial data monitoring committees: helping them to do their job well. DAMOCLES Study Group, NHS Health Technology Assessment Programme. Lancet, 2005 Feb 19-25;365(9460):711-22. doi: 10.1016/S0140-6736(05)17965-3.

Italic text: illustrative examples *: based on real trial protocols

1. CHARTER FOR DMCs: TEMPLATE

2. CONTENT	3. COMMENTS FROM DAMOCLES AND ILLUSTRATIVE EXAMPLES
1. INTRODUCTION	
Name (and sponsor's ID) of trial plus ISRCTN and/or EUDRACT number	Insert name (and sponsor's ID) of trial and registration number (egISRCTN and/or EUDRACT number)
Objectives of trial, including interventions being investigated	Insert objectives of trial, including interventions being investigated from protocol. Suggest including a flow chart of the trial design (insert as Figure 1).
Outline of scope of charter	Summary of the purpose and content of this document. *Illustrative example:* *The purpose of this document is to describe the roles and responsibilities of the independent DMC for the ### #### trial, including the timing of meetings, methods of providing information to and from the DMC, frequency and format of meetings, statistical issues and relationships with other committees.*
2. ROLES AND RESPONSIBILITIES	
A broad statement of the aims of the committee	*Illustrative example:** *"To protect and serve [trial] patients (especially re: safety) and to assist and advise Principal Investigators so as to protect the validity and credibility of the trial."* *"To safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, and monitor the overall conduct of the clinical trial."*

2. CONTENT	3. COMMENTS FROM DAMOCLES AND ILLUSTRATIVE EXAMPLES
Terms of reference	*Illustrative example:** *The DMC should receive and review the progress and accruing data of this trial and provide advice on the conduct of the trial to the Trial Steering Committee.* *The DMC should inform the Chair of the steering committee if, in their view:* *(i) the results are likely to convince a broad range of clinicians, including those supporting the trial and the general clinical community, that one trial arm is clearly indicated or contraindicated, and there was a reasonable expectation that this new evidence would materially influence patient management;* ***or*** *(ii) it becomes evident that no clear outcome would be obtained."*
Specific roles of DMC	Interim review of the trial's progress including updated figures on recruitment, data quality, and main outcomes and safety data. A selection of specific aspects could be compiled from the following list:- • assess data quality, including completeness (and by so doing encourage collection of high quality data) • monitor recruitment figures and losses to follow-up • monitor compliance with the protocol by participants and investigators • monitor trial conduct – organisation and implementation of trial protocol (the DMC should only perform this role in the absence of other trial oversight committees) • monitoring evidence for treatment differences in the main efficacy outcome measures • monitor evidence for treatment harm (eg toxicity data, SAEs, deaths) • decide whether to recommend that the trial continues to recruit participants or whether recruitment should be terminated either for everyone or for some treatment groups and/or some participant subgroups • suggest additional data analyses • advise on protocol modifications suggested by investigators or sponsors (eg to inclusion criteria, trial endpoints, or sample size) • monitor planned sample size assumptions • monitor continuing appropriateness of patient information • monitor compliance with previous DMC recommendations • considering the ethical implications of any recommendations made by the DMC • assess the impact and relevance of external evidence

2. CONTENT	3. COMMENTS FROM DAMOCLES AND ILLUSTRATIVE EXAMPLES
3. BEFORE OR EARLY IN THE TRIAL	
Whether the DMC will have input into the protocol	All potential DMC members should have sight of the protocol/outline before agreeing to join the committee. Before recruitment begins the trial will have undergone review by the funder/sponsor (eg peer review for public sector trials), scrutiny by other trial committees and a research ethics committee. Therefore, if a potential DMC member has major reservations about the trial (eg the protocol or the logistics) they should report these to the trial office and may decide not to accept the invitation to join. DMC members should be independent and constructively critical of the ongoing trial, but also supportive of aims and methods of the trial.
Whether the DMC will meet before the start of the trial	It is recommended that, if possible, the DMC meets before the trial starts or early in the course of the trial, to discuss the protocol, the trial, any analysis plan, future meetings, and to have the opportunity to clarify any aspects with the principal investigators. The DMC should meet within one year of recruitment commencing. Consideration should be given to an initial "dummy" report, including the use of shell (empty) tables, to familiarise the DMC members with the format that will be used in the reports.
Any issues specific to the disease under study	Issues specific to the disease under study should be described.
Any specific regulatory issues	The DMC should be aware of any regulatory implications of their recommendations.
Any other issues specific to the treatment under study	Issues specific to the treatment under study should be described.
Whether members of the DMC will have a contract	Members of a DMC particularly for a commercially sponsored trial may be advised to have a contract making clear the need for confidentiality and the liability status of the DMC members. When there is no such contract, DMC members could formally register their assent by confirming (1) that they agree to be on the DMC and (2) that they agree with the contents of this Charter.
4. COMPOSITION	
Membership and size of the DMC	Membership should consist of a small number of members, who include at least one clinician experienced in the clinical area and at least one statistician. Additional members experienced in clinical trials should reflect the other specialities involved in the trial. Consideration may be given to consumer representation, although they may be best represented on other committees. In the case of intergroup trials or trials with international collaboration consideration should be given to overseas members. The members should be independent of the trial (eg should not be involved with the trial in any other way or have some competing interest that could impact on the trial). Any competing interests, both real and potential, should be declared. A short competing interest form should be completed and returned by the DMC members to the trial coordinating centre (Annex 1). The members of the DMC for this trial are: (1) *[---give name---]* (2) *[---give name---]* (3) *[---give name---]* It may be helpful to provide the trial coordinating centre with brief personal details (say, one paragraph) of all DMC members especially relating to experience relevant to the trial and to the operation of DMCs (such information need not be contained within the Charter).

2. CONTENT	3. COMMENTS FROM DAMOCLES AND ILLUSTRATIVE EXAMPLES
The Chair, how they are chosen and the Chair's role. (Likewise, if relevant, the vice-Chairman)	The Chair should have previous experience of serving on DMCs and experience of chairing meetings, and should be able to facilitate and summarise discussions. The Chair is sometimes chosen by the sponsor or the investigators running the trial and sometimes by the DMC members themselves. The Chair is expected to facilitate and summarise discussions.
The responsibilities of the DMC statistician	The DMC membership will include a statistician to provide independent statistical expertise.
The responsibilities of the trial statistician	The trial statistician, *[---give name---]* will produce (or oversee the production of) the report to the DMC and will participate in DMC meetings, guiding the DMC through the report, participating in DMC discussions and, on some occasions, taking notes.
The responsibilities of the trial office team	The trial office team (eg Trial Manager, etc) usually only inputs to the production of the non-confidential sections of the DMC report.
The responsibilities of the PI and other members of the Trial Management Group (TMG)	The PI, may be asked, and should be available, to attend open sessions of the DMC meeting. The other TMG members will not usually be expected to attend but can attend open sessions when necessary (See Organisation of DMC Meetings).
5. RELATIONSHIPS	
Relationships with Principal Investigators, other trial committees (eg Trial Steering Committee (TSC) or Executive Committee), sponsor and regulatory bodies	A diagram can help to clarify relationships when there are several inter-related committees. A short statement of the responsibilities of the other committees should be given if these are not provided in the protocol.
Clarification of whether the DMC are advisory (make recommendations) or executive (make decisions)	It is customary that the DMC does not make decisions about the trial, but rather makes recommendations to an appropriate executive committee or its Chair.
Payments to DMC members	Members should be reimbursed for travel and accommodation. Any other payments or rewards should be specified.
The need for DMC members to disclose information about any competing interests	Competing interests should be disclosed. These are not restricted to financial matters – involvement in other trials or intellectual investment could be relevant. Although members may well be able to act objectively despite such connections, complete disclosure enhances credibility. (See Annex 1) DMC members should not use interim results to inform trading in pharmaceutical shares, and careful consideration should be given to trading in stock of companies with competing products.
6. ORGANISATION OF DMC MEETINGS	
Expected frequency of DMC meetings	The exact frequency of meetings will depend upon any statistical plans specified, and otherwise on trial events. The wishes of the DMC and needs of the trial office will be considered when planning each meeting. It is recommended that the DMC meet at least yearly.
Whether meetings will be face-to-face or by teleconference	The first meeting should ideally be face-to-face to facilitate full discussion and allow members to get to know each other. It is recommended that all subsequent meetings should be face-to-face if possible, with teleconference as a second option.

2. CONTENT	3. COMMENTS FROM DAMOCLES AND ILLUSTRATIVE EXAMPLES
How DMC meetings will be organised, especially regarding open and closed sessions, including who will be present in each session	A mixture of open and closed sessions is recommended. Closed and open sessions should be defined. Commonly, only DMC members and others whom they specifically invite, eg the trial statistician, are present in closed sessions. In open sessions, all those attending the closed session are joined by the PI(s), and/or the head of the trials office, and sometimes also representatives of the sponsor, funder, or regulator, as relevant. The format of the meetings should be described. *Illustrative example:* 1. *Open session: Introduction and any "open" parts of the report* 2. *Closed session: DMC discussion of "closed" parts of the report* *and, if necessary,* 3. *Open session: Discussion with other attendees on any matters arising from the previous session(s).* 4. *Closed session: extra closed session*
7. TRIAL DOCUMENTATION AND PROCEDURES TO ENSURE CONFIDENTIALITY AND PROPER COMMUNICATION	
Intended content of material to be available in open sessions	*Illustrative example:* *<u>Open sessions</u>: Accumulating information relating to recruitment and data quality (eg data return rates, treatment compliance) will be presented. Toxicity details based on pooled data will be presented and total numbers of events for the primary outcome measure and other outcome measures may be presented, at the discretion of the DMC.*
Intended content of material to be available in closed sessions	*Illustrative example:* *<u>Closed sessions</u>: In addition to all the material available in the open session, the closed session material will include efficacy and safety data by treatment group.*
Will the DMC be blinded to the treatment allocation	Blinding is generally not recommended for DMC members, although opinions vary.
Who will see the accumulating data and interim analysis	The people who will see the accumulating data and interim analysis should be specified. DMC members do **not** have the right to share confidential information with anyone outside the DMC, including the PI.
Who will be responsible for identifying and circulating external evidence (eg from other trials/ systematic reviews)	Identification and circulation of external evidence (eg from other trials/ systematic reviews) is not the responsibility of the DMC members. The PI or the trials office team will usually collate any such information.
To whom the DMC will communicate the decisions/ recommendations that are reached	The DMC usually reports its recommendations in writing to the Trial Steering Committee or sponsor's representative. This should be copied to the trial statistician (or trial manager) and if possible should be sent via the trials office in time for consideration at a TSC meeting. If the trial is to continue largely unchanged then it is often useful for the report from the DMC to include a summary paragraph suitable for trial promotion purposes. (See Annex 2.)

2. CONTENT	3. COMMENTS FROM DAMOCLES AND ILLUSTRATIVE EXAMPLES
Whether reports to the DMC be available before the meeting or only at/during the meeting	It is usually helpful for the DMC to receive the report at least 2 weeks before any meetings. Depending on the trial, it may sometimes be preferable for all papers to be brought to face-to-face meetings by the trial statistician; time would then be needed for DMC members to assimilate the report.
What will happen to the confidential papers after the meeting	*Illustrative examples:* 1. *The DMC members should destroy their reports after each meetings. Fresh copies of previous reports will be circulated with the newest report before each meeting.* 2. *The DMC members should store the papers safely after each meeting so they may check the next report against them. After the trial is reported, the DMC members should destroy all interim reports.*
8. DECISION MAKING	
What decisions/recommendations will be open to the DMC	Possible recommendations could include:- • No action needed, trial continues as planned • Early stopping due, for example, to clear benefit or harm of a treatment, futility, or external evidence • Stopping recruitment within a subgroup • Extending recruitment (based on actual control arm response rates being different to predicted rather than on emerging differences) or extending follow-up • Stopping a single arm of a multi-arm trial • Sanctioning and/or proposing protocol changes
The role of formal statistical methods, specifically which methods will be used and whether they will be used as guidelines or rules	This Charter should include or provide reference to the planned interim analyses and statistical guidelines, ie the DMC should review and agree any interim analysis plan. Formal statistical methods are more generally used as guidelines rather than absolute rules. This is because they generally only consider one dimension of the trial. Reasons should be recorded for disregarding a stopping guideline.

How decisions or recommendations will be reached within the DMC	Issues to be specified can include: • The decision making methods and criteria that will be adopted for guiding deliberations • The process of decision making, including whether there will be voting or other formal methods of achieving consensus. The method of deliberation should not be revealed to the overseeing committee as this may reveal information about the status of the trial's data. • The role of the Chair - to summarise discussions and encourage consensus; it may be best for the Chair to give their own opinion last. It is recommended that every effort should be made for the DMC to reach a unanimous decision. If the DMC cannot achieve this, a vote may be taken, although details of the vote should not be routinely included in the report to the TSC as these may inappropriately convey information about the state of the trial data. It is important that the implications (eg ethical, statisticial, practical, financial) for the trial be considered before any recommendation is made.
When the DMC is quorate for decision-making	There should be a minimum number of attendees before the DMC is quorate for decision-making; this should be specified. *Illustrative example*:* *"Effort should be made for all members to attend. The trials office team will try to ensure that a date is chosen to enable this. Members who cannot attend in person should be encouraged to attend by teleconference. If, at short notice, any DMC members cannot attend at all then the DMC may still meet if at least one statistician and one clinician, including the Chair (unless otherwise agreed), will be present. If the DMC is considering recommending major action after such a meeting the DMC Chair should talk with the absent members as soon after the meeting as possible to check they agree. If they do not, a further teleconference should be arranged with the full DMC."*
Can DMC members who cannot attend the meeting input	If the report is circulated before the meeting, DMC members who will not be able to attend the meeting may pass comments to the DMC Chair for consideration during the discussions.
What happens to members who do not attend meetings	*Illustrative example:* *If a member does not attend a meeting, it should be ensured that the member is available for the next meeting. If a member does not attend a second meeting, they should be asked if they wish to remain part of the DMC. If a member does not attend a third meeting, they should be replaced.*
Whether different weight will be given to different endpoints (eg safety/efficacy)	This should be specified and will depend on the trial.
Any specific issues relating to the trial design that might influence the proceedings, eg cluster trials, equivalence trials, multi-arm trials	This should be specified and will depend on the trial.

9. REPORTING	
To whom will the DMC report their recommendations/decisions, and in what form	Usually, this will be a letter to the Trial Steering Committee or Sponsor's representative. A timescale should be specified eg usually within 3 weeks. It is helpful if a copy of this is lodged with the trial office.
Whether minutes of the meeting be made and, if so, by whom and where they will be kept	These details should be specified (separate records may be required for open and closed sessions). The DMC Chair should sign off any minutes or notes.
What will be done if there is disagreement between the DMC and the body to which it reports	Specify which committee has primacy or how disagreement will be resolved, eg a further committee may be convened to adjudicate. *Illustrative example:* *"If the DMC has serious problems or concerns with the TSC decision a meeting of these groups should be held. The information to be shown would depend upon the action proposed and the DMC's concerns. Depending on the reason for the disagreement confidential data will often have to be revealed to all those attending such a meeting. The meeting should be chaired by a senior member of the trials office staff or an external expert who is not directly involved with the trial."*
10. AFTER THE TRIAL	
Publication of results	At the end of the trial there may be a meeting to allow the DMC to discuss the final data with principal trial investigators/sponsors and give advice about data interpretation The DMC may wish to see a statement that the trial results will be published in a correct and timely manner.
The information about the DMC that will be included in published trial reports	DMC members should be named and their affiliations listed in the main report, unless they explicitly request otherwise. A brief summary of the timings and conclusions of DMC meetings should be included in the body of this paper.
Whether the DMC will have the opportunity to approve publications, especially with respect to reporting of any DMC recommendation regarding termination of a trial	The DMC may wish to be given the opportunity to read and comment on any publications before submission.
Any constraints on DMC members divulging information about their deliberations after the trial has been published	It should be specific when the DMC may discuss issues from their involvement in the trial eg 12 months after the primary trial results have been published, or when permission is agreed with the overseeing committee.

Insert figures and appendices

Figure summarising trial
Figure showing relationship of trial committees, including DMC
List of abbreviations, and glossary
Annex 1: Competing interest form
Annex 2: Suggested letter from DMC to TSC
Annex 3: Details of interim analysis plan (if not in protocol).

Annex 1: Suggested competing interests form

Potential competing interests of Data Monitoring Committee members for *[Insert trial name (and sponsor's ID)]*

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

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

Table 1: Potential competing interests

- Stock ownership in any commercial companies involved
- Stock transaction in any commercial company involved (if previously holding stock)
- Consulting arrangements with the sponsor
- Frequent speaking engagements on behalf of the intervention
- Career tied up in a product or technique assessed by trial
- Hands-on participation in the trial
- Involvement in the running of the trial
- Emotional involvement in the trial
- Intellectual conflict eg strong prior belief in the trial's experimental arm
- Involvement in regulatory issues relevant to the trial procedures
- Investment (financial or intellectual) in competing products
- Involvement in the publication

Please complete the following section and return to the trials office.

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

Please provide details of any competing interests:

_____

_____

_____

_____

Name: _____

Signed: _____ Date: _____

Annex 2: Suggested report from DMC to TSC where no recommendations are being made

[Insert date]

To: Chair of Trial Steering Committee

Dear *[Chair of Trial Steering Committee]*

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

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

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

Yours sincerely,

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

On behalf of the DMC (all members listed below)

DMC members:
(1) [*Insert name and role*]
(2) [*Insert name and role*]
(3) [*Insert name and role*]