| Standard Operating Procedures (SOP) for: | | | |
|---|---|---|---|
| **Trial Committees** | | | |
| SOP Number: | **47** | Version Number: | **2.0** |
| Effective Date: | **01/02/2017** | Review Date: | **01/02/2019** |

| | |
|---|---|
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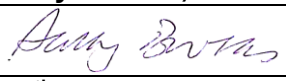
| Signature: |  |
| Date: | **12th January 2017** |

| Purpose and Objective: |
|---|
| The role of trial committees is to give independent and expert oversight of the conduct of clinical trials. Bart's Health NHS Trust (BH) and Queen Mary University of London (QMUL), as sponsors of clinical trials and research, have produced this SOP to provide procedural guidance on the set-up of trial committees, trial committee conduct and their remits.<br><br>The purpose of this SOP is to outline what committees are necessary for Clinical Trials of Medicinal Products (CTIMPs), Advanced Therapies of Medicinal Products (ATIMPs), Clinical Trials of Medical Devices, and Clinical Investigation Trials that are sponsored by BH or QMUL.<br><br>This SOP also gives guidance on trial committee composition and committee charters. |
| Scope: |
| The scope of this SOP is for CTIMPs, ATIMPs, and non-CE marked device trials that fall under the Clinical Device regulations and Clinical Investigation Trials sponsored by BH/QMUL.<br><br>This SOP should be considered best practice for all QMUL and BH sponsored research and should be applied proportionately to other types of clinical research that do not fall within the scope above. |

| Abbreviations: | |
|---|---|
| APR | Annual Progress Report |
| ATIMP | Advanced Therapy Investigational Medicinal Product(s) |
| BH | Barts Health NHS Trust |
| CE | Conformité Européene (mark denoting a product complies with European regulations) |
| CI | Chief Investigator |
| CRF | Case Report Form |
| CTIMP | Clinical Trial of an Investigational Medicinal Product |
| DMC | Data Monitoring Committee |
| DMEC | Data Monitoring and Ethics Committee |
| DSMB | Data and Safety Monitoring Board |
| DSMC | Data and Safety Monitoring Committee |
| DSUR | Development Safety Update Report |
| EOT | End of Trial |
| GCP | Good Clinical Practice |
| IDMC | Independent Data Monitoring Committee |
| IMP | Investigational Medicinal Product |
| IRAS | Integrated Research Application System |
| JRMO | Joint Research Management Office |
| MHRA | Medicines and Healthcare Regulatory Agency |

| | |
|---|---|
| PI | Principal Investigator |
| QMUL | Queen Mary University of London |
| REC | Research Ethics Committee |
| ReDA | Research Database Application |
| SAE | Serious Adverse Event |
| SOP | Standard Operating Procedures |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TMF | Trial Master File |
| TMG | Trial Management Group |
| TSC | Trial Steering Committee |

Definitions:

**Trial Management Group (TMG):**

The role of the Trial Management Group (TMG) is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to, and take appropriate action to safeguard participants and the quality of the trial itself. TMGs meet regularly but their frequency may vary depending on the phase of the trial. The TMG normally includes those individuals responsible for the day-to-day management of the trial, such as the CI, Statistician, Trial Manager and Data Manager. Every trial should have a TMG but if the trial increases in complexity and risk, additional committee or oversight mechanisms may be required.

**Data Monitoring Committee (DMC):**

An Independent DMC (IDMC) - also referred to as Data Monitoring and Ethics Committee (DMEC), Data Safety and Monitoring Committee (DSMC), or Data Safety and Monitoring Board (DSMB) - is a group of experts independent of the study team who review accumulating data from an on-going clinical trial. The broad remit of a DMC is to safeguard the interests of the trial participants by monitoring their safety and the treatment efficacy of the interventions during the trial. The DMC may also assess other aspects of a clinical trial such as efficacy, study integrity, design aspects, recruitment and some ethical considerations (such as early analysis and publication). In general a DMC is required when a randomised trial is double-blinded (i.e. neither the participant nor the researchers know what treatment they are receiving), so an independent review of (unblinded) participants' safety reports is required during the treatment phase, whilst protecting the blinding of the research team. Rather than making decisions, the DMC makes recommendations to the TMG which may include recommending the termination of a trial for safety reasons, due to evidence of the trial's futility, or the trial's overwhelming statically proven benefit.

**Trial Steering Committee (TSC):**

A Trial Steering Committee (TSC) provides overall trial supervision and advice through its Chair, on behalf of the Trial Sponsor. Its role is to ensure that the trial is conducted in accordance with the protocol, GCP, and relevant regulations. The TSC should include members who are independent of the trial investigators, their employing organisations, funders, and sponsor. The TSC concentrates on the progress of the trial, adherence to the protocol, patient welfare, and considers new information of relevance to the research question. The TSC may meet at the beginning of the trial to approve the final protocol and, once active, considers any new relevant information, including recommendations from the DMC or results from other studies. Based on any such information, the TSC may make recommendations to change the trial documents (i.e. the protocol or patient documents) or to stop or extend the trial. Where the Sponsor and protocol permits, the TSC may consider requests to publish data before the end of trial. All trials require a TSC.

**Independent** (in relation to TSC Chair)**:**

The Chair should not be an employee of BH or QMUL. They should not be named on any funding application associated with the trial and should not have been involved in the trial design or trial planning stages.

**Independent** (in relation the Statistician)**:**

The Statistician can be an employee of QMUL or BH but should not be directly related or involved with

the trial design or funding application, the day to day running of the trial, or its final analysis. It is acceptable to contract a suitably qualified statistician to perform this role.

**Independent** (in relation to the DMC and TSC)**:**

Individuals who are not credited on the protocol and/or the grant application, and who are not research investigators for the study or employed as part of the trial management/coordination team.

**Charter:**

A document which describes the role and function of the committee. The charter (also referred to as the "Terms of Reference") should also cover the committee's membership, how often it meets, how decisions are reached and whether they are "advisory" (which is the norm) or "executive". The charter will make clear the need for confidentiality, the liability of the committee members, and the obligation to declare any conflicts of interests. The members of the committee will formally register their assent by confirming that they agree to be on the committee, and that they agree with the contents of the charter.

| Relevant SOPs |
|---|
| SOP 11a: BH/QMUL Sponsorship of CTIMPs, ATMPs and Clinical Trials of Non-CE Marked Medicinal Devices – Process for Researchers |

| SOP text | | |
|---|---|---|
| | Responsibility | Activity |
| 1. | CI | **All CTIMPs must have a TSC.**<br>All CTIMPs, ATIMPs and Clinical Investigation Trials (including device trials) must have a TSC with an independent Chairperson. For details of the TSC purpose, composition and general guidance see *Appendix 1*.<br>It is the CI's responsibility to set-up a TSC.<br>For further detailed guidance, see the NIHR's TSC/SSC Guidelines (*Associated Document 4*). |
| 2. | CI and named trial statistician | **CI and trial statistician must assess the need for a DMC.**<br>For all CTIMPs, ATIMPs and Clinical Investigation Trials (including device trials), a justification from the named statistician and CI should be provided at the trial design stage to ascertain if a DMC is needed. The CI should consider whether the funder has any requirements during this decision making process. See *Appendix 2*. |
| 3. | CI | **All CTIMPs, ATIMPs and Clinical Investigation Trials (including device trials) require a TMG**.<br>It is best practice for all trials to have a TMG.<br>It is the CI's responsibility to set-up a TMG. |
| 4. | CI | **Trial committees must be documented within the protocol.**<br>All CTIMPs, ATIMPs and Clinical Investigation Trials (including device trials) must outline their trial committees within the protocol. Individuals should not be named but committee roles (i.e. Chair, Statistician, etc.) should be indicated in the protocol. For all committees convened the following should be produced and retained:<br>• Charter (*Associated Documents 1 and 2*); located within Sponsor Over-sight File and the TMF<br>• Conflict of Interest Declarations from all members and attendees (*Associated Documented 3: Competing Interests Form*); located within |

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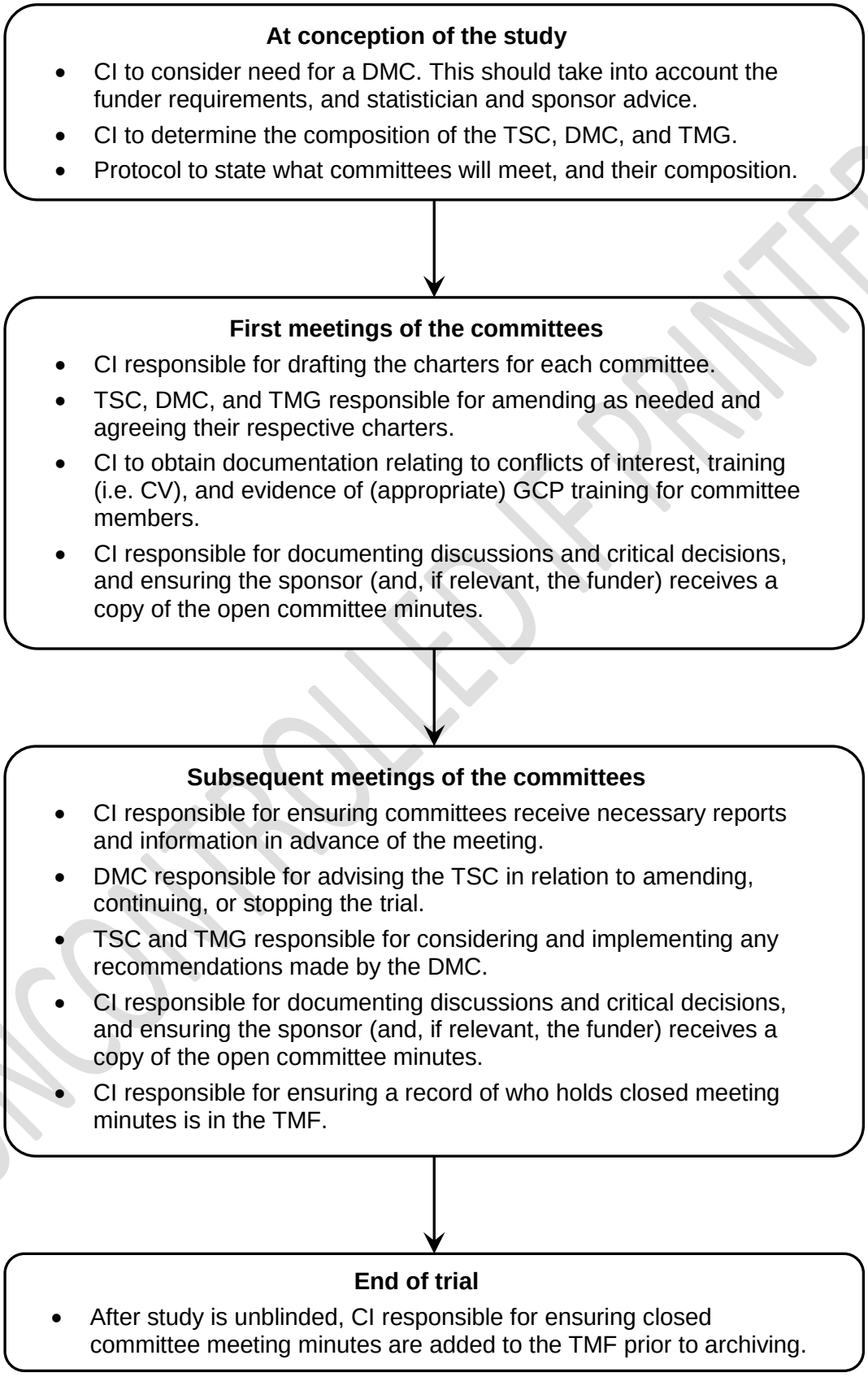
|---|---|---|
| | | Sponsor Oversight File and TMF<br>• CV and GCP training (all members); located within TMF only |
| 5. | CI | **Committees should be set up prior to trial green light.**<br>Membership of committees should be agreed, the charter drafted and first meeting scheduled prior to the sponsor issuing "the green-light to activate sites".<br>(See *SOP 11a: BH/QMUL Sponsorship of CTIMPs, ATMPs and Clinical Trials of Non-CE Marked Medicinal Devices – Process for Researchers.*)<br>Committees should continue to meet until the End of Trial Notification is submitted, in accordance with the protocol and charter. |
| 6. | CI | **All members of any committee should receive appropriate GCP training**.<br>This can be the JRMO's GCP training or the NIHR's online GCP course. BH and QMUL committee members are welcome to attend the JRMO training at no cost.<br>(See the JRMO website for booking details or email: research.training@bartshealth.nhs.uk)<br>It is the CI's responsibility to ensure all committee members are appropriately trained.<br>**EXCEPTION:** Any consumer / public / patient representatives on the committee do not need to attend a certified GCP course, but the CI should ensure they are given a level of understanding of the research environment and GCP. This training should be documented within the TMF. |
| 7. | CI or delegate | **All meetings and critical decisions must be documented.**<br>All meetings (blinded sections and unblinded), discussions and decision making must be documented and retained in the TMF. Blinded reports, and discussions surrounding blinded reports, must be retained by the independent committee chairman until the study team is formally unblinded. After this point the chairman must ensure the blinded documentation is added to the TMF prior to archiving.<br>For CTIMPs, ATMPs and Clinical Trials of Non-CE Marked Medicinal Devices *only*, minutes should be sent to the GCP team. The timing of this will vary depending on the type of reporting a team is performing. Minutes will either be attached to quarterly reports and/or disseminated as part of the main minutes distribution list. |
| 8. | GCP team staff | **Minutes should be chased, reviewed (where appropriate), saved and filed appropriately.**<br>The timing of the distribution/receipt of minutes should be agreed at the final CTIMP meeting or when trial green light is issued. Minutes will be chased at each monitoring visit and/or on receipt of quarterly reports.<br>Where possible, or where concerns are raised, minutes will be reviewed by a member of the GCP team.<br>Minutes will be saved as per *SOP 10 – JRMO Internal Filling Process*. |

**Flow chart**



**Change Control**

This section outlines changes from version 1.0 to version 2.0.

| Section changed | Summary and description of changes |
|---|---|
| Abbreviations | Further abbreviations added. |
| Definitions | Independent statistician: amended definition to clarify this individual can be contracted, but must not be involved in the final study analysis. |
| 3 | Updated to state that all trials (including non-CTIMPs) must have a TMG. |
| 7 | Added information regarding blinded reports and decisions, stating the chairman is responsible for retaining these documents and adding them to the TMF after the study team is unblinded but before archiving. |
| 8 | Section added to detail GCP Team responsibilities regarding receipt, review and saving of meeting minutes. |
| Flow chart | Added. |
| Associated Document 4 | NIHR TSC & SSC Guidance added as Associated Document 4 |

**List of Appendices**

| | Appendix Name |
|---|---|
| Appendix A | Trial Steering Committees Guidance |
| Appendix B | Data Monitoring Committee Guidance |
| Appendix C | Trial Management Group Guidance |
| Appendix D | References, Related External SOPs, Web links |

**Appendix A**

**Trial Steering Committees (TSC)**

The role of the TSC is to provide overall supervision of the trial on behalf of the trial Sponsor and trial funder and to ensure that the trial is conducted in accordance with the principles of GCP and relevant regulations. The CI is responsible for convening an appropriate TSC. The CI is also responsible for liaising with the funding body to ascertain whether they require a TSC or have committee guidance as a funding condition.

**Composition:**

The TSC will normally be limited to:

- An independent chair (mandatory).
- At least two other independent members, usually representing clinical areas under study.
- One or two Principal or Co-investigators.
- Two service / patient representatives (where possible).
- Independent statistician (where possible and deemed necessary).

Whilst independence is strongly recommended it is not mandatory unless required by the sponsor, funder or other regulatory body.

Trial Statisticians, Data Manager, Trial Manager etc. should attend TSC meetings as appropriate.

Document the TSC membership in the protocol

**Prior to commencement of trial**

- Meet (ideally face to face) and agree roles and responsibilities. This meeting may be held jointly with the DMC.
- Review and agree the final study protocol before regulatory submission.
- Agree an appropriate timescale for meetings, at least annually.
- Agree the minimum quoracy for meeting to conduct business (see *Associated Document 2: Damocles Charter* for more details).
- Agree data that should be presented at each meeting.
- Create and agree a committee charter.

**During the trial**

The TSC will meet according to its charter (at least annually) in order to:

- Monitor the progress of the trial.
- Monitor adherence to protocol.
- Review available information relating to patient safety.
- Consider new information of relevance from other sources.
- Make executive decisions about the trial as suggested by the TMG (e.g. protocol amendments where practical).
- Consider and act on the recommendations of the DMC, Research Ethics Committee and competent authority (MHRA) as appropriate, including the termination the trial.

If the TSC charter identifies a need for statistical reports to be prepared in order to advise the committee, it is the CI's responsibility to ensure the TSC receives this information. It is the responsibility of the statistician named on the protocol to advise the CI on data to be presented at the TSC meetings and appropriate timescales, so that there is sufficient time to check the data and carry out the analysis before circulation to the committee.

**Appendix B**

**Data Monitoring Committee (DMC)**

The role of the DMC is to review unblinded accruing trial data, and is the only body that has access to unblinded data. The DMC may also be asked by the TSC, Trial Sponsor or Trial Funder to consider data emerging from other studies. The DMC should advise the TSC. The DMC should be independent of the investigators and the funder / sponsor.

The CI is responsible for liaising with the funding body to establish if they require a DMC as a condition of funding (or have guidance on such committees), and where appropriate liaising with the trial statistician and / or sponsor to determine the need for a DMC. Where it is necessary or appropriate for the trial to have a DMC, the CI is responsible for identifying appropriate members. The membership of a DMC, or a justification of why a DMC has not been formed, should be documented in the protocol.

**Composition**

- Small, usually 3-4 members.
- At least one clinician experienced in the clinical area.
- At least one expert trial statistician.
- A chair with previous experience of serving on DMCs.
- All members should be independent of the investigators, funder / sponsor, the host institution and the TSC.

**Prior to commencement of the trial**

- Meet (ideally face to face) and agree a DMC charter. This meeting may be held jointly with the TSC.
- Review study protocol.
- Determine a schedule of meetings at least annually and timed so that reports can feed into TSC meetings.
- Agree the minimum quoracy for meetings to conduct business (see *Associated Document 2: DAMOCLES Charter* for more details).
- Agree a DMC charter specific to the trial (see *Associated Document 1: Sample DMC Charter Template*).
- Provide the study team with details of any potential conflicts of interest for each committee member (or confirmation that no such conflicts exist) and a copy of their CV and evidence of GCP training.

**During the trial**

The DMC will meet regularly in accordance with the agreed protocol and charter. It is the responsibility of the CI / delegated study staff to provide DMC with a comprehensive report for each meeting as agreed in the DMC charter. It is the responsibility of the statistician named on the protocol to advise the CI on data to be presented at the DMC meetings and appropriate timescales, so that there is sufficient time to check the data and carry out the analysis before circulation to the committee. The DMC will review the trial's progress which may be through the following information:

- Review whether there are any safety concerns on one or more treatment arms (by considering e.g. toxicity data, SAEs/SUSARs, deaths), or any ethical reasons why the trial should not continue.
- View whether the data shows significant benefit on one or more treatment arms.
- Whether there is evidence that, should the trial continue, it would fail to show clear benefit on any treatment arm.

- Suggest any additional data analyses (using unblinded data where necessary) where it is relevant to advising whether the trial should continue or be terminated early.
- Monitor the sample size (including recruitment targets and losses to follow-up) and make recommendations.
- Advise on substantial protocol amendments that may impact upon data or safety, such as changing the primary end points.
- Consider any new information relevant to the trial, including reports from TSC and any related external research.
- Make recommendations to the TSC and / or TMG whether to continue, modify or stop the trial.

**Additional considerations**

- In conjunction with the Trial Manager / Coordinator, the DMC chair may prepare reports for the TSC and open reports for the DMC, in accordance with the agreed charter or terms of reference.
- The DMC may arrange for any interim statistical analysis to be carried out by a statistician independent of the trial and assist as appropriate.
- If an unblinded interim statistical analysis is required by the DMC this should be undertaken by a qualified statistician independent of the trial. There are various ways that this can be arranged; it is acceptable for this person to be an independent statistician within the sponsor's organisation.
- It is the responsibility of the CI to arrange regular meetings of the DMC and it is the Chair's responsibility to retain copies of the minutes for future reference.
- Copies of open DMC minutes should be filed in the TMF and the Statistical Master File along with a note of who holds the closed report and minutes.
- It is the responsibility of the CI to circulate copies of the minutes to the sponsor (JRMO) and to the funder if required.

**Format of the DMC meeting**

The format of the DMC meeting may have two parts:

1. **Open DMC session** which all TMG members (blinded and unblinded) may attend to review general trial progress and pooled data.
2. **Closed DMC sessions** to review unblinded results (see *Associated Document 1: Sample DMC Charter Template*). During the closed session, blinded members (e.g. investigators) cannot be present.

Attendance of the CI or co-investigators at the open session of the DMC meetings should only be at the invitation of the DMC Chair.

**Appendix C**

**Trial Management Group (TMG)**

The role of the TMG is to monitor all aspects of the conduct and progress of the trial, and to ensure that the protocol is adhered to and that appropriate action is taken to safeguard participants and the quality of the trial itself. The TMG should meet as frequently as is required by the progress of the trial, and as determined by the members of the group.

The TMG should:

- Ensure the protocol is adhered to and take action as necessary to remedy any difficulties.
- Consider and act on the recommendations of the TSC and DMC, REC and competent authority (MHRA) as appropriate.
- Consult co-investigators prior to protocol amendments in a timely and efficient manner.
- Refer any possible protocol amendments to the TSC.

It is the CI and TMG groups' responsibility to inform the sponsor (and where applicable the funder) of decisions made by the TSC or DMC.

**Appendix D**

## References, Related External SOPs, Web links

With thanks and acknowledgements to:

- Pragmatic Clinical Trials Unit SOP on trial committees: PCTU_TM_02
- Barts Clinical Trials Unit SOP on trial committees: SOP BARTS CTU GEN TM 14
- Centre for Experimental Cancer Medicine SOP on trial committees
- Committee for medicinal products for human use (CHMP), Guideline on data monitoring committees, July 2005
- ICH Topic E6 (R1) Guideline for Good Clinical Practice, July 1996. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf
- DAMOCLES study group. A proposed charter for clinical trial data monitoring committees: helping them to do their job well. Lancet, 2005. 365: 711-22.
- Clinical Trials Toolkit: http://www.ct-toolkit.ac.uk/glossary
- Medical Research Council. MRC Guidelines for Good Clinical Practice in Clinical Trials 1998. Available from: http://www.mrc.ac.uk/documents/pdf/good-clinical-practice-in-clinical-trials/

## List of Associated Documents

| | Document name |
|---|---|
| Associated Document 1 | Sample DMC Charter template |
| Associated Document 2 | Damocles Charter for DMCs: template |
| Associated Document 3 | Competing Interests Form |
| Associated Document 4 | NIHR Trial Steering Committee and Study Steering Committee Guidance |