Queen's University Belfast

Research and Enterprise

Standard Operating Procedure

Research Governance

Title:	**Monitoring of Clinical Trials of Investigational Medicinal Products**		
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* For all University sponsored IMP research studies

Revision Log

Previous Version number	Date of Review/Modification	Reason for Review/Modification	New Version Number
Final v 1.0	10/11/09	Annual Review	Final v 1.0
Final v 1.0	10/11/10	Annual Review/ Update following MHRA GCP Inspection	Final v 2.0
Final v 2.0	21/08/12	Periodic Review	Final v 3.0
Final v 3.0	06/10/2014	Periodic Review	Final v 4.0
Final v 4.0	18/01/2017	Periodic Review	Final v 5.0

1. Purpose

This Standard Operating Procedure (SOP) provides guidance for the monitoring of clinical trials that are solely sponsored by the University.

2. Introduction

The International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP) define monitoring as "the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)."

The purpose of trial monitoring is to verify that:
1. "The rights and well-being of human subjects are protected;
2. The reported trial data are accurate, complete and verifiable from source documents;
3. The conduct of the trial is in compliance with the currently approved protocol/ amendment(s), with GCP, and with the applicable regulatory requirement(s)." (ICH-GCP 5.18.1).

3. Scope

This SOP applies to all studies where the University is acting in the capacity of Sponsor. It applies to all members of University staff; both academic and support staff as defined by Statute 1, including honorary staff and students.

4. Responsibilities

4.1 Chief Investigator (CI)

The CI is responsible for the day-to-day monitoring of a trial. This would include the following, that:
- Data collected are consistent with, and in adherence to, the trial protocol;
- Case Report Forms (CRFs) are only being completed by authorised persons;
- No key data are missing;
- Review of recruitment rates, withdrawals and losses to follow-up (overall and by clinical site).

4.2 Site Principal Investigator (SPI)

In the event of a multi-centred clinical trial, the SPI is responsible for the day-to-day monitoring of a trial, as outlined for the CI in 4.1.

4.3 Sponsor

The Sponsor must ensure that clinical trials are adequately monitored and will determine at the outset the extent and nature of the monitoring activity. Where a trial is co-sponsored with a Health and Social Care Trust, the co-sponsorship agreement will detail which organisation has lead responsibility for this process and the Memorandum of Understanding for Research Governance shall be adhered to.

5. Procedure

5.1 Extent and Nature of Monitoring

The decision regarding the extent and nature of monitoring a clinical trial should be in proportion to the objective, purpose, design, complexity, blinding, size and endpoints of

the trial. It must also be determined prior to the trial commencing. The clinical trial risk assessment can be used to determine the intensity and focus of monitoring activity, whilst the trial design can be used to inform the methods to be used for monitoring.

In general there is a need for on-site monitoring, before, during, and after a trial. However, in exceptional circumstances, such as some low risk clinical trials, the sponsor in conjunction with the CI may determine that central monitoring in conjunction with procedures such as investigators' training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP.

5.2 Oversight Committees

There are a variety of approaches that can be employed to monitor a trial. The procedures chosen should be determined at an early stage and reflect the complexity and risk involved in the trial. The potential approaches include:

5.2.1 Trial Management Group

This Group is established to monitor all aspects of the conduct and progress of the trial and it should include those persons with responsibility for the daily management of the trial. Its purpose is to ensure adherence to the protocol and take any actions necessary to safeguard trial participants. The need for a Trial Management Group and the membership should reflect the complexity and size of the trial, though it may include the Chief Investigator (CI), research nurse, data manager, statistician, trial manager and data manager.

5.2.2 Trial Steering Committee

It is recommended that a Trial Steering Committee (TSC) is established for larger, multi-centred trials as they will provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of Good Clinical Practice and in accordance with the legislative framework and relevant University Regulations. A TSC may include members who are independent of the investigators, and in particular it may have an independent chairperson.

A TSC should monitor the trial's progress e.g. recruitment, data and ensure adherence to the protocol. Decisions about the continuation or termination of the trial or substantial amendments to the protocol are usually the responsibility of the TSC.

5.2.3 Data Monitoring Committee

A Data Monitoring Committee (DMC) is established to review the accruing trial data and to assess whether there are any safety issues that should be brought to participants' attention, or any reasons why the trial should not continue. The DMC should be independent of both the investigators and the funder/sponsor and should be the only group that has access to unblinded data.

5.2.4 Coordinating Centre

Daily monitoring is carried out by those responsible for running a trial.

5.2.5 Central Monitoring

Centralised procedures can be used to confirm patient eligibility, to corroborate the existence of the patient and to determine the outcome. Examples of this might include the collection of pathology reports to substantiate a diagnosis, collection of an imaging investigation, central assessment of the results of an investigation, such as a x-ray or scan.

5.2.6 On-site monitoring

Arrangements for site visiting may vary from routine visits to all sites, visits to a random selection of sites or visits targeted at less experienced sites or those for which the central monitoring procedures suggest possible problems. On-site visits also provide an opportunity, *vis-a-viz*, to educate staff, ensure they have the relevant documentation and check that they are adhering to the protocol.

5.3 Selection and Qualification of Monitors

Following the clinical trial risk assessment and the establishment of an appropriate trial monitoring oversight committee (e.g. Trial Management Group, Trial Steering Committee or Data Monitoring Committee), monitors should be appointed. It is the responsibility of the Sponsor/lead Sponsor review and approve the monitoring plan. Where monitoring is being undertaken by a third party the sponsor must conduct due diligence on the parties contracted to complete the monitoring for the trial.

5.4 Monitor's Responsibilities

The Monitor(s) in accordance with the sponsor's requirements must ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site, through:

The verification of:

- Investigators qualifications and resources;
- Investigational products in respect of storage, supply, dispensing, control, documentation and disposal;
- Adherence to the protocol and subsequent amendments;
- Written, informed consent was obtained, prior to the subject's participation;
- Only eligible subjects are enrolled;
- Source document and other trial records are accurate, complete, kept up-to-date and maintained;
- Investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated and identify the trial.

Ensuring that:

- Investigators and trial staff are adequately informed about the trial;
- Investigators receive the current Investigator's Brochure, all documents, all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirements;
- Subject recruitment is reported;
- Checking the accuracy and completeness of the CRFs, source documents and other trial-related records against each other;
- Informing the investigator of any CRF entry error, omission, or illegibility;
- Determining whether all adverse events (AEs) are appropriately reported within the required time periods;
- Determining whether the investigator is maintaining the essential documents;
- Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

5.5 Monitoring Procedures

The Monitor(s) should follow the CI/Sponsor's established written SOPs as well as those procedures that are specified by the CI/Sponsor for monitoring a specific trial, unless the monitoring has been contracted to a third party and the Sponsor has agreed that the third parties SOPs for monitoring may be used.

5.6 Monitoring Report

Following each trial-site visit or trial-related communication, the monitor must submit a written report to the Sponsor. This report should include:

- Date, site, name of monitor;
- Name of the Investigator(s) or other individuals contacted;
- Summary of documents reviewed, along with a statement of findings, deviations, deficiencies, conclusions, actions taken or recommended to secure compliance.

Where a trial is co-sponsored, copies of monitoring reports should be received from / shared with the relevant party to enable any concerns or actions within their jurisdiction to be addressed.

6. References

Ct-Toolkit (2004) Monitoring Procedures:
http://www.ct-toolkit.ac.uk/routemap/trial-management-and-monitoring/ (last accessed January 2017)

International Conference on Harmonisation – Good Clinical Practice (ICH GCP):
http://www.ich.org/products/guidelines.html (last accessed January 2017)