STANDARD OPERATING PROCEDURE 19
Quality Control

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Version 1.4		Biennial review 2015: No changes made.
Version 1.4	25 November 2013	Addition of requirement for process audits and documentation of cross-checking procedures
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1. Purpose and Scope

The purpose of this Standard Operating Procedure (SOP) is to describe procedures for the Quality Control (QC) of research studies, particularly clinical trials. It is applicable to all staff working on any University of Warwick sponsored research studies or externally sponsored studies where quality control activities have been delegated to Warwick Clinical Trials Unit (WCTU).

2. Definitions

Quality Control (QC)	Procedures which ensure reliability of data and protection of human subjects from research risk, and thereby assures internal consistency.
Quality Assurance (QA)	Planned and systematic actions that are established to ensure that the study is performed, and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirements. QA covers all policies and systematic activities implemented within a quality system to ensure that data are recorded, analysed, and recoded in accordance with the protocol and GCP. The use of GCP guidelines ensures ethical and scientific quality standards for the design, conduct, recording, and reporting of ethically approved studies that involve research participants.
Quality Management (QM)	The overall system that includes all activities involved in QA and QC, including the assignment of roles and responsibilities, the reporting of results, and the resolution of issues identified during review procedures.

3. Background

Quality control (QC) activities are the real time ("day-to-day") observation and documentation of research work processes to ensure that accepted procedures are followed. QC is a subset of the quality assurance (QA) process. It is comprised of the following activities:

- Detection and measurement of the variability in a clinical research study.
- Detection and measurement of the characteristics of clinical study data generated.
- Corrective responses to discrepancies found during the conduct of a study.

The exact nature and timing of the QC checks that are conducted will vary, but may include:

- Cross-checking of documentation
- Recruitment processes and accumulating data (including safety data)
- Data entry
- Information and consent procedures
- Source Data Verification (SDV)
- Delivery of interventions
- Investigational medicinal products (IMP) checks
- Process audits
- Review of data used in any study reports

4. Procedure

4.1 Responsibilities

Study sponsor	Responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that studies are conducted, and data are generated, recorded, and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s) (ICH GCP section 5.1.1)
Chief Investigator (CI)	Responsible for ensuring that a study is being conducted in compliance with the approved protocol, that study documents are being maintained correctly and that all study related records are available on request to study monitors, auditors or regulatory authorities. The CI is also responsible for ensuring adequate quality control procedures are in place commensurate with the risks associated with the study.
Trial/Study Manger/Coordinator (T/SM//T/SC)	Work with CI and trial/study management group (T/SMG) to ensure QC activities are in place as appropriate. Liaise with the programming team to setup a scheduled reporting system to monitor critical data items. Resolution of queries from data checking activities.

4.2 When?

Quality control activities should be undertaken throughout the duration of a trial/research study.

The level and type of QC that should be undertaken is determined by the risk assessment of the study. Any QC activities performed must be documented and, where possible, performed by an individual who is independent of the activity e.g., study staff, Quality Assurance (QA) staff and/or statistician.

4.3 How?

Specific procedures will be developed for each trial /research study based on the risk assessment for each study and should be proportionate to the determined risk level. For further information on study risk assessment and monitoring processes, see SOP 18 ‘Risk Assessment and Monitoring’.

Written procedures detailing the requirements for QC activities should be in place (e.g., in study monitoring plan or Data Management Plan) and should include information relating to the expected scope and frequency of QC. Expectations relating to acceptable standards should be documented; this may include definition of acceptable error rates and should detail the actions to be taken where the QC checks fail to meet acceptable predefined standards. Actions may include further checking, additional site monitoring visits, increased source data verification or additional training and the level of intensity should be determined depending on the risks identified on a study-by-study basis.

4.3.1 Cross-checking of key study documents

For WCTU managed studies, the QA function will undertake a process of cross-checking key trial documents e.g., protocol against participant information sheets, consent forms and IRAS forms, to

ensure that the information is consistent and accurate. Details of documents checked, when the checks occurred and by whom should be documented and retained in the Trial/Study Master File. Other key documents which should be checked include (but are not limited to): Serious Adverse Event (SAE) forms, data flow maps, data management plans, Site Initiation Visit (SIV) presentations.

The 'Trial set-up and management checklist' spreadsheet which can be found on the WCTU website above the main list of SOPs (https://warwick.ac.uk/fac/sci/med/research/ctu/conducting/planning/sop) also lists those documents which QA are expected to check.

Where discrepancies are found between study documents, the required amendments should be documented and completed in a timely fashion. This process should begin during the set-up phase of the trial /research study as key documents are produced and be ongoing as required during the lifetime of the project.

4.3.2 Recruitment and accumulating data

Quality control checks of accumulating data should always be undertaken for several reasons:

1. to identify problems with recruitment or data collection (at a centre or from the participant)
2. to identify problems in compliance with the protocol
3. to identify patterns that may be indicative of fraud

The accumulating data should be reviewed at the Trial/Study Management Group (T/SMG) meetings. The frequency of review and the items to be checked should be determined by the CI, statistician(s) and health economists if necessary and documented in the Data Management Plan (DMP).

In addition to this, the accumulating data should also be reviewed at the independent Trial Steering Committee (TSC) and Data Monitoring Committee (DMC) meetings (where applicable).
The choice of data to be included should be made in conjunction with the committee but will normally include:

- eligibility criteria
- recruitment rates
- follow-up rates
- compliance/non-compliances/CAPA reports
- adverse events
- primary outcome(s)
- any relevant safety-related outcome data.

Whilst compiling these data from the data snapshot for review, the study statistician(s) should also carry out the associated QC checks. Moreover, a final QC check of the data should be completed by the statistician at the end of the trial /research study prior to locking the database (data do not necessarily have to be 'clean' for this purpose). Any queries from these checks should be passed onto the trial/study manager (T/SM) to investigate and resolve. This process should be clearly documented (usually in an email trail saved with any documentation of the checks).

Review of accumulating data is distinct from interim analysis. It should not involve any analysis of the study's outcomes, and blinding should be maintained if necessary to safeguard the statistical integrity of the study.

There are certain 'critical' data items determined by the risk assessment that require 100% QC checks. Critical data should be monitored at all times to ensure the protocol is not breached but most importantly to ensure the safety of the participants. The TM/C should liaise with the programming team to setup a scheduled reporting system to monitor critical data. The reporting system will be scheduled to run at specified intervals and will immediately inform the TM/C of any concerns with critical data items. If it is not possible to enter data immediately onto the study database, manual checks should be undertaken as soon as possible after receipt and any issues identified should be flagged to the study management team to ensure appropriate actions are taken. The study's data management plan should identify critical data items and detail the frequency of checks required and how to document these checks. See SOP 15 part 1 'Information Handling: Security, Protection and Management of Data for Clinical Research' for further information.

Possible fraud may be indicated by, for example, unrealistically high numbers of patients recruited by one centre, major differences in the type of patients recruited by one centre or major differences in the timing of recruitment. Suspected fraud should be reported to the CI, who should decide on appropriate action in consultation with the sponsor, Chair of the TSC and other relevant personnel as appropriate. Further guidance is available in SOP 31 ''Handling non-compliances of GCP and/or study protocol'.

4.3.3 QC of Data Entry and data quality

QC checks of data entered onto the database should be undertaken to ensure that all data are reliable and have been processed correctly. Where data are entered onto a database from a paper Case Report Form (CRF), QC checks should be undertaken to ensure accuracy. These checks may include:

- Checking the data on the database against the CRF
- Double data entry
- Sample checking to determine data entry operator competency (study statistician may be asked to determine acceptable error rate)

For studies where data are entered directly onto the database at the recruiting centre, QC checks may be undertaken at site monitoring visits as required.

All QC checks of data entry activities should be clearly documented including who did the checks, when they were done and what actions were taken. An escalation plan should be clearly stated in the case that an unacceptable error rate is identified to ensure appropriate actions are taken. This is generally documented in the DMP or study monitoring plan.

Checks to ensure that data management processes are robust should be considered and implemented.

See SOP 15 Information Handling Part 1: 'Security, Protection and Management of Data for Clinical Research' for further information.

4.3.4 Information for potential participants and consent procedures

In some studies, for example those which recruit participants in stressful situations such as emergencies, or where there is little time for eligible patients to consider participation, it may be appropriate to perform QC of information and consent procedures, to ensure that these are being conducted as expected e.g., ensuring appropriate consent to continue has been obtained in situations

where it was not possible to obtain consent prior to the commencement of study procedures. This may be undertaken during monitoring visits if determined by the study risk assessment.

4.3.5 Source Data Verification (SDV)

SDV is the act of checking the accuracy and completeness of Case Report Form (CRF) entries against the source documents to ensure:

- Assessments have been conducted and completed in accordance with the protocol and within the specified timelines
- Data from all assessments have been recorded in the source documents
- Source data have been accurately transcribed into the CRF
- Any deviations have been identified and recorded
- Adverse events, concomitant medications and intercurrent illnesses are recorded and reported in the CRF in accordance with the protocol
- Assessments have been made by appropriately qualified personnel who have been delegated that activity.

The level of SDV should be specified in the monitoring plan (what percentage of participants and what percentage of data) and will vary from study to study depending on the risk assessment and identification of data that are critical to the reliability of the results and the safety of the participants. Not all SDV checks referred to above are always necessary. Production of monitoring plans is detailed in SOP 18 'Risk Assessment and Monitoring'.

For studies where only a percentage of the data require SDV, the monitoring plan should specify the level e.g., full SDV of first participant recruited then only full SDV of certain data (e.g., primary endpoints) for a percentage of the following participants. The study statistician(s) should be consulted with to produce a random sample for SDV purposes.

4.3.6 Delivery of interventions

In many studies, including those of complex interventions and non-standard procedures being undertaken at investigator sites such as study specific laboratory processes it is necessary to ensure that the interventions are being delivered in a standard way by all practitioners and throughout the course of the study. There are three components to this:

- Training of personnel in delivery of the interventions. This is usually undertaken at the start of the study, but further sessions may be necessary later, e.g., to take account of staff changes. Details of the training delivered should be documented.
- Logbooks should be completed by those delivering the interventions to record actions.
- QC visits by study personnel. Usually these will involve observation of delivery of the interventions by members of the study team, followed by feedback to the practitioners delivering the interventions. A written report of each monitoring visit should be produced and kept on file.

4.3.7 Investigational Medicinal Products (IMPs)

In studies that involve IMPs formulated specifically for a clinical trial (e.g., drugs sourced via a clinical trials drug company), a sample of each batch of the IMP (and placebo, if used) should be retained for later testing to verify that (a) it is the correct IMP and (b) the randomisation list has recorded the allocations correctly. This is usually the responsibility of the IMP manufacturer or their contracted laboratory. See SOP 27 "Management of Investigational Medicinal Products (IMPs) for Clinical Trials" for details of IMP management.

4.3.8 Process audits

For WCTU managed studies, periodic process audits of activities e.g., data management procedures, may be undertaken by the QA function to ensure study specific procedures adhere to the relevant SOPs and study specific working instructions. A schedule of process audits will be determined and a report produced to document which activities were monitored and if any issues were noted. Further training will be given to staff where non-compliance issues are recorded. See SOP 25 'Auditing of Clinical Trials' for further details.

4.3.9 Review of data used in the final study report

Primarily it is the responsibility of the study statistician(s) and the CI to review the data presented in the final study report. In addition to this, all study co-applicants will review and comment on the study report. The DMC and TSC members will review the final results of the study to further contribute to the QC process. See SOP 22 'Publication and Dissemination' for further details.

List of abbreviations

CAPA	Corrective and Preventative Actions
CI	Chief Investigator
CRF	Case Report Form
DMC	Data Monitoring Committee
DMP	Data Monitoring Plan
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application Service
QA	Quality Assurance
QC	Quality Control
QM	Quality Management
R&IS	Research & Impact Services
SAE	Serious Adverse Event
SDV	Source Data Verification
SIV	Site Initiation Visit
SOP	Standard Operating Procedure
T/SC	Trial/Study Coordinator
T/SM	Trial/Study Manager
T/SMG	Trial/Study Management Group
TSC	Trial Steering Committee
WCTU	Warwick Clinical Trials Unit

Associated documents

T03	Critical Data Items Check Coversheet
T09	Key Document Review Approval
T25	Source Data Location Log
T58	Trial Monitoring Checklist
C02	Data Management Plan Checklist
C06	Trial Set Up & Closure Checklist
G02	Key Document Review/Approval Form