Keele Clinical Trials Unit

Standard Operating Procedure (SOP) Summary Box

Title	Study Closure
SOP Index Number	SOP 15
Version	5.0
Approval Date	08-Sept-2016
Effective Date	22-Sept-2016
Review Date	September 2018
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Reference	KCTU/SOP15/v5.0/08-Sept-2016

Signature Box

Role	Print Name	Signature	Date
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Version History Log

Version	Date Approved	Reason(s) for Change	Implementation Plan
2.0	04-10-10	Approval of version 2.0	
3.0	11-Nov-2015	Move onto updated SOP template, update roles and organisation names.	All RI staff will be notified of the revised SOP. Staff are expected to read the updated version of the SOP when it is released, as applicable to their role. The updated procedures are to be implemented from the SOP effective date.
4.0	31-Mar-2016	• Update to Section 3.3.1 (Data Cleaning) • Update to Section 3.3.2 (Database Locking Process) • Update to Section 3.3.3 (Preparing locked data for analysis) • Update to Section 3.3.4 (Removal of Sensitive Data) • Update to Section 3.3.5 (Master Flowchart (response and consent)) • Update to Section 4 (Key personnel to whom this SOP applies)	All RI staff will be notified of the revised SOP. Staff are expected to read the updated version of the SOP when it is released, as applicable to their role. The updated procedures are to be implemented from the SOP effective date.
5.0	08-Sept-2016	• Removal of the role Head of CTU IT • Addition of EudraCT reporting	All RI staff will be notified of the revised SOP. Staff are expected to read the updated version of the SOP when it is released, as applicable to their role. The updated procedures are to be implemented from the SOP effective date.

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1. Purpose

The purpose of this SOP is to describe the procedure to follow when a research study reaches its end as defined in the research protocol or is terminated early, or when research activities at a particular site are complete. This SOP covers both Clinical Trials of Investigational Medicinal Products (CTIMPs) and all other research studies hosted by Keele CTU.

2. Scope and Applicability

This SOP applies to all individuals undertaking functions outlined herein. This includes all core Keele CTU staff and all other academic, research, management or admin staff, or students working on Keele University sponsored/ Keele CTU managed clinical research projects through site agreements, service or other contractual arrangements.

This SOP must be followed in line with the NHS Research Governance Framework, and the University, Research Institute and CTU policies.

Where applicable to Clinical Trials of Investigational Medicinal Products (CTIMPs) this SOP must be followed in line with the UK Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments, and the EU Clinical Trials Directive.

Where applicable to non-CTIMP studies this SOP must be followed in line with the appropriate Good Clinical Practice guidance.

3. Procedures

The definition of the end of the study should be specified in the research protocol. In most cases, the end of study will be the date of the last visit of the last participant or the completion of any follow-up monitoring and data collection described in the protocol. Final analysis of the data and report writing should occur following the formal declaration of the closure of the study and the 'lock' of the study database.

3.1 Site Closure

Site closure occurs when recruitment is complete or is terminated, e.g. when recruitment of participants at a GP practice has ceased and there is no further follow-up activity at that site. The study may still have follow-up stages such as postal questionnaires which do not involve site activity. Site closure precedes full study closure.

3.1.1 Notification of site closure

Site closure needs to occur at all sites in which the CTU is running a research study e.g. within:

- a general practice (GP surgery)
- a physiotherapy unit
- an occupational therapy unit at a general hospital
- an X-Ray department
- a community health centre
- or any other site used to conduct a research study

Relevant personnel from the appropriate Clinical Research Network (CRN) must be notified of site closure, and can assist in implementing the appropriate site closure procedures. If a site visit is deemed unnecessary by the Study Team, e.g. when no equipment needs to be removed from the site, a confirmation letter indicating the completion of study recruitment must be sent to the local PI at the site concerned (Site Closure Notification Template). CRN personnel may be asked to support the TM/SC to ensure that all recruitment and research procedures at that site are stopped by the agreed site closure date.

Once the study is fully closed at all sites then a **Study Closure Letter** should be sent to all local PIs (Study Closure Notification Template).

These two stages (site closure, followed by full study closure) are necessary as the CRN may need to remove templates (upon site closure), but continue to visit the practices to carry out D & D checks until follow-up data collection is complete (i.e. study closure).

3.1.2 Removal of Study Specific Equipment

If removal of research equipment is required then a site visit must be made by the TM/SC (and or Research Nurse) and the following areas need to be considered:

- clearance of the physical space and any research materials, including equipment, signs and labels.
- all study phones, e-mail, IT and web services must be discontinued
- keys and identification cards must be returned
- all unused study supplies must be returned to Keele CTU.

3.1.3 Post Study Specimen Storage

Verification is needed that all protocol-specified laboratory samples have been received and laboratory testing and reporting is complete. All remaining stored specimens must be archived or destroyed in accordance with the protocol.

3.1.4 Patient Records at Site

- case report forms (CRFs) must be returned to the CTU in accordance with SOP 14 Monitoring and Audit
- all study consent forms and other essential documents must be archived in accordance with SOP 17 Archiving and Destruction
- any treatment records, which need to remain at the site should be managed according to the Service Level Agreement (SLA) (SOP 10 Study Contracts)

3.1.5 Financial Matters

All financial matters as outlined in the SLA (SOP 10 Study Contracts) should be resolved and documented.

3.2 Study Closure

The end of study is defined in the research protocol and in IRAS. If the research project has ended early for any reason the study closure procedure should still be followed as detailed in this SOP.

3.2.1 Notification of Study Closure

On study closure the CI is responsible for notifying the sponsor, the regulatory bodies, the Steering committee and the funder.

3.2.2 Notification of the End of the Study to the Regulatory Bodies

Ethics

The Research Ethics Committee (REC) that provided approval for the study should be informed when the study is closed (SOP 11 Regulatory Submission). The Health Research Authority (HRA) website describes the process, which should be undertaken.

A summary of the guidelines from this website (accessed on 10/04/15) are given below.

Once a study has ended, an **end of study declaration form** should be downloaded from the HRA website. This must be completed and emailed to the REC that gave approval for the study within 90 days of the end of the study. There are separate forms for use in CTIMPs and all other research.

In a larger programme of work which involves several sub-studies, the CI will take overall responsibility for completing the end of study declaration form (when all phases of the main study and all sub-studies are complete). In order for this to be achieved, the relevant PI or TM/SC must provide information on their sub-study to the CI, using the format provided for an end of study declaration.

A **summary of the final research report** must also be sent to the REC (and MHRA for CTIMPs) within 12 months of the end of the study. There is no standard format for final reports. As a minimum, the report should:

- inform the REC whether the study achieved its objectives
- summarise the main findings,
- summarise arrangements for publication or dissemination of the research, including any feedback to participants.

Final reports should be emailed to the REC.

For larger programmes of work, the relevant PI/TM needs to provide information on their sub-study to the CI to enable them to complete the end of study report. Final reports should be emailed to the REC.

MHRA

A 'Declaration of the end of a Clinical Trial' form should be sent to the MHRA by the sponsor within 90 days of the trial conclusion and a summary report within 12 months of the trial conclusion. See more at: HRA website.

EudraCT

It is a regulatory requirement to report the results of a CTIMP on the European Clinical Trials Database (EudraCT) within 6 to 12 months of the end of the trial. The sponsor is responsible for EudraCT reporting, however delegates this operationally to the CI with the support of Keele CTU. The Sponsor QA Manager facilitates access to the reporting system for the CI, Statistician and/or Trial Manager to report results in accordance with the required timeframes (6-12 months from end of trial) and oversees this activity.

3.2.3 Trial Steering Committee (TSC) and Data Monitoring Committee (DMC)

The Trial Statistician is responsible for preparing final reports to the TSC and DMC. A final TSC meeting will be held when the last participant has been followed-up. The format of this meeting will be identical to those conducted throughout the duration of the trial (SOP 4 Project Management).

3.2.4 Notification of the End of the Study to Funder(s)

The funding body of any study (e.g. NIHR, Arthritis Research UK, the Medical Research Council, CSP etc.) must be informed when the study has ended. The format of this notification depends on the nature of the research grant and the funding body which awarded the grant. Please check the conditions of the grant for further details.

3.3 Data Closure

3.3.1 Data Cleaning

Quantitative Studies

Once the study data has been entered into the relevant databases and Stage 1 data cleaning is considered complete (see below), preparation for Database Locking and Stage 2 data cleaning process is then undertaken.

Stage 1 data cleaning ensures:

- that the data entry databases contain data for all participants as expected by the data in the management database
- that data queries and comments have been addressed (Data Entry Log Comment and Queries template)
- that a 1 in 1 check of data entered is undertaken for Primary Outcome data and any updates complete
- that a random 1 in 10 check of data entered is undertaken for non primary outcome data and the error rate reviewed by statisticians with any necessary action undertaken.

Stage 2 data cleaning (following Database Lock) ensures that the Data Custodian will:

- verify final data numbers relating to the datasets (and equating to CONSORT flowchart requirements) and for the integrity of the included data value set following on from stage 1 checks
- generate and maintain a detailed electronic log of the issues arising
- document what action is necessary to resolve the issues
- document who has been allocated to undertake that action
- document the outcome of the action (Stage 2 Data Cleaning Log).

Although stage 2 of the data cleaning process is to be controlled by the Data Custodian, the process will require the involvement of TM/SC, Data Manager and Database Developer. Therefore, regular communication must be maintained, and where necessary liaison with the Lead Administrator for the study where administrative procedures are necessary, such as locating missing paperwork or additional data entry.

Once all the issues have been resolved and are detailed in the appropriate electronic log, the updates to source data are then carried to the original database(s) as required, and in accordance with the Database Locking process (Section 3.3.2).

3.3.2 Database Locking

Quantitative

All study databases must be locked once Stage 1 data cleaning is complete. The database locking process is outlined in the Steps 1-8 below. The Database Locking Sign Off Template is to be generated for this process (Database Locking Sign Off Template):

Step1: Notification that Data is ready to export

1.1 Once data collection queries have been addressed and Stage 1 data cleaning performed (this includes addressing data queries and undertaking 1 in 10 or 1 in 1 data checking and cleaning, as per CTU SOPs), Trial Manager/Data Manager notifies the Database Developer and Trial Manager that the Database is ready to be locked and data exported.

1.2 Database Locking Sign-off Template initiated by Data Manager.

Step 2: Users access disabled

2.1 On receipt of the Database Locking Sign-off Template, the Database Developer will ensure that all user access to the database is disabled.

2.2 Database Locking Sign-off Template updated by Database Developer.

Step 3: Database Export and Database Schema and Data Exports

3.1 Once user access has been disabled, the Database Developer exports all data tables from the database, into MSExcel (for data locking as outlined in Step 4). In addition a database schema and data export will be performed to enable reconstruction of the database at point of export, should this be necessary. All data exports and database schema are saved in the CTU secure network environment.

3.2 Database Locking Sign-off Template updated by the Database Developer.

Step 4: Data locked

4.1 As soon as data is exported, all data cells within the export tables are put into a locked state. This means that all worksheet contents are viewable, but not editable. Therefore no updates to the exported data can be made.

4.2 Database Locking Sign-off Template updated by Database Developer.

Step 5: Data copied to relevant study master file location and Stats lead notified

5.1 The locked data exports are then copied from the CTU Secure environment, to the relevant secure dedicated project network drive (w:\). The files must be version controlled and date of export to be included in the filename. Files are to be stored in a matching folder.
Filepath example: w:\projects\trials\[STUDY]\Trial_Master_File\Data Collection\Database\Database lockdownv1.0[with date]\[tablename].xlsx
NB: Each time this process is performed, the next version number and date performed will apply to the folder name and files within.

6.1 The Database Developer notifies the Stats lead (Data Custodian) of Step 5 completion and that locked data is ready for review.

5.2 Database Locking Sign-off Template updated by Database Developer.

Step 6: Locked data received by Stats (Data Custodian)

6.2 Stats Lead (Data Custodian) check files can be opened and acknowledges receipt.
6.3 Database Locking Sign-off Template updated by Stats Lead (Data Custodian).

Step 7: Stats lead reviews data

Stats lead (Data Custodian) undertakes a review of the locked data and follows either Step 8(a) or Step 8(b) below.

Step 8(a) If Stage 2 cleaning detects discrepancies/anomalies

i. Stats lead (Data Custodian) record anomalies on 'Stage 2 data cleaning Log'.
ii. Stage 2 data cleaning Log is sent to Trial Manager (or delegate) for action.
iii. Database Locking Sign-off Template updated by Stats lead (Data Custodian).
iv. Trial Manager requests the Database Developer reinstate specified user(s) to database.
v. The Database Developer reinstates database user access (as agreed by Trial Manager) to allow database updates to be performed.
vi. Database Locking template sign-off updated by Database Developer.
vii. Database updates performed as outlined in Stage 2 Data Cleaning Log.
viii. Stage 2 Data Cleaning Log updated, printed, signed and dated by Stats Lead & Trial Manager.
ix. Database Locking Sign-off Template updated by Trial Manager.
x. Return to Step 1 above and repeat the process (completing a new Database Locking Sign-off Template with exports appropriately version controlled as outlined at Step 5).

Step 8(b) If Stage 2 cleaning confirms the data is fully clean with no discrepancies/anomalies

i. Stats lead (Data Custodian) confirms the data is fully clean
ii. Database Locking Sign-off Template updated by Stats lead (Data Custodian).
iii. Database Developer ensures that the database is detached.
iv. Database Locking Sign-off updated by Database Developer.
v. Database Locking process complete. Data exports remains in locked state for Stats to commence analysis.

Please note: Throughout the process, the Database Locking Sign-off Template must to be updated and signed (wet signature) and dated accordingly. It is the responsibility of the Trial Manager to monitor the location of Sign-off Form throughout the process and ensure that final versions of all Database Locking Sign Off Templates are filed appropriately within the Trial Master File.

Qualitative

The qualitative lead is responsible for collating a complete list of study data files, anonymising transcript files, and for storing master and working versions on the relevant section of the study secure network drive. Details of study data files must be recorded and stored on the Qualitative Data Storage Location spreadsheet on the secure network drive.

The qualitative lead is also responsible for detailing the analysis procedures to be applied to individual data sets in the Qualitative Project Analysis Log (Qualitative Project Analysis Log), which will also be stored on the relevant Study Folder on the secure network drive.

3.3.3 Preparing Locked Data for Analysis

Once Stage 2 data cleaning is complete (therefore data verification complete), the dataset remains locked and is ready for the 'Data Analysis' stage. It is recommended to create a copy of this dataset that will be used as an 'analysis dataset' that will include summary scores that have been generated from algorithms/syntaxes executed on the data. At this point all identifiable data must be stripped out. For further details please see the CTU policies and procedures on the management of sensitive data (Procedures for Data Security & Managing Sensitive Data). The Data Custodian will export the locked and stripped tables to their statistical package of choice (e.g. SPSS or STATA).

Throughout the process, it is the responsibility of the Data Custodian to ensure that no sensitive data is included in any analysis database (Procedures for Data Security & Managing Sensitive Data).

A "READ ME" file (usually in Word) should be set-up by the Data Custodian and retained in the statistical master file for the analysis database. This should provide the number and details of subjects contained in the datasets along with relevant information on scoring and application of syntaxes (see SOP16). A record of issues arising from audit and the data cleaning processes, e.g. how extreme values and ambiguous data were dealt with or reasons for exclusion of subjects at a particular stage should be kept in an accompanying "READ ME" file.

Scoring Methods: Validated questionnaires should be scored using the standard scoring instructions, including instructions for dealing with missing data. If more than one method of scoring or dealing with missing data is available, then the method used should be recorded in the "READ ME" file (as outlined above). Syntax of the scoring should also be kept within the statistical master file.

Height and weight should be converted into body mass index (BMI) using the standard formula: (weight in kg) / (height in metres)^2. Extreme values that are *very unlikely* (as a guide <8 or >65) may be defined as missing. Such coding strategy needs to be decided by the study team in advance (and as part of stage 1 or 2 cleaning) and before un-blinding of treatment group allocation.

If the trial protocol states that certain members of the trial team (including trial statistician) are to be blind to treatment group, then necessary measures are required to conceal these members from treatment allocation. The data custodian / statistician and any researcher gathering outcome data should be blind, as well as anyone (e.g. PI) involved in decision making around continued participation post- treatment randomisation and entry into the trial. Un-blinding of treatment allocation should not be done until the primary outcome (and key secondary outcomes) has/have been double-analysed (i.e. independently analysed) and consensus agreement on result findings have been ratified and TSC/DMC members informed of the primary/key findings. Second-stage analysis including per-protocol comparison, evaluation of clinic case-reports, and health economic evaluation will require un-blinding of treatment arm before evaluation can be appropriately undertaken.

Qualitative Studies

Materials, such as interviews, that have been collected using audio recording equipment will need to be transcribed. To have an audio recording transcribed please follow the Process to Raise a Transcription Request.

Once the study data (e.g. interview data or diary study data) has been transcribed, strong participant identifiers such as name, address, or other personal information must be anonymised or pseudo-anonymised in the transcribed materials and these are the versions that must be used for data analysis (Procedures for Data Security & Managing Sensitive Data).

Non-anonymised transcripts will form the 'master copy' of data sets. Anonymised copies of transcripts will form the 'working copy' that will be used in data analysis. 'Master' and 'working' copies of transcripts should be stored in separate sub-folders on the respective study secure network drive. All sources of data, including master and working transcripts, and the format that they are stored in are recorded on the Qualitative Data Storage Location spreadsheet on the secure network drive. This spreadsheet is read-only and is available for review purposes only. Once a study is ready to be added to the spreadsheet, the qualitative lead completes a Qualitative Data Storage Location Template (Qualitative Data Storage Location Template) and e-mails it to the Qualitative Data Archive Superintendent (QDAS) who will ensure the details are added to the Qualitative Data Storage Location spreadsheet on the secure network drive. On completion of these procedures, the data is locked and available for analysis through the Centre's internal data request process (see SOP 16 Analysis).

Qualitative data analysis packages (such as NVivo, Framework and ATLAS TI) operate by uploading documents and 'copying' them as new files, which are then stored within the programme. Therefore the master documents are not altered and remain stored in their original location on the centre's secure network. Data analysis programme files (i.e. NVivo files relating to the study) should be archived in accordance with procedures detailed in SOP 17 Archiving and Destruction.

The PI of a study will allocate a member of the research team to be responsible for the management, labelling and storage of qualitative study data ready for archiving (SOP 17 Archiving and Destruction). The qualitative research team are also responsible for detailing the analysis procedures to be applied to individual data sets and a Qualitative Data Analysis Log must be completed (Qualitative Project Analysis Log).

3.3.4 Removal of Sensitive Data

It is the responsibility of the PI, together with other relevant members of the Study Team, to determine the point(s) in the study at which sensitive data for a study held at the CTU should be deleted, and which must be undertaken in accordance with the CTU Sensitive Data Policy (Procedures for Data Security & Managing Sensitive Data). This decision will be informed by:

- the specifics of the ethical approval granted to hold the sensitive data
- the conditions under which the sensitive data was provided
- the timing of the stages of the study.

Once it is clear that there is no further need to contact participants then the point in the study has been reached for deleting sensitive data. It is then the joint responsibility of the qualitative lead to notify the Trial Manager. The Trial Manager will liaise with the Data Custodian and Database Developer to ensure that personal identifiable data is deleted from the mailing database.

Databases Containing Participant Identifiers: Databases which include patient identifiers should NEVER be taken away from the Centre and must only be kept on the Centre's secure server (Procedures for Data Security & Managing Sensitive Data). Audits will take place to ensure all data security procedures are being adhered to.

3.3.5 Master Flowchart (response and consent)

A master flowchart of the verified number of people invited to participate and the number and percentage responding/participating at each stage should be created by the Data Custodian, along with the number and percentage consenting to follow-up contact and medical record review.

The CTU has a policy for classifying those who do not participate into "non-responders" or "exclusions", which will help when generating the flowchart for individual studies

4. Key Personnel to whom this SOP Applies

The **CI/PI** is responsible for:

- defining the end of trial/research study in the protocol
- ensuring the appropriate regulatory bodies are notified of study closure (see HRA website for guidance)
- ensuring the funder is notified of study closure
- ensuring the TSC/DMC are notified of study closure
- ensuring that this SOP is adhered to
- determining whether the study is ready to conclude as described in the Study protocol
- producing a summary report for regulatory bodies

The **Trial Manager (TM)** or **Study Co-ordinator (SC)** is responsible for:

- assisting with closure notification to regulatory bodies, funder and steering committee
- liaising with the Clinical Research Network(s) over site closure and study closure procedures
- preparing the study for archive
- liaising with the Database Developer and Data Manager through the process of Database Locking
- assisting the data manager and data custodian with data cleaning

The **Data Manager** is responsible for:

- ensuring that Stage 1 data cleaning is undertaken and complete
- initiate the process of locking of the databases (liaison with the Trial Manager)

The **Database Developer** is responsible for

- undertaking of the exporting of data and database scheme and 'locking' of data
- Disabling user access and re-instating user access

The **Data Custodian** (usually the Study Statistician) is responsible for:

- Stage 2 data cleaning
- preparation of the final report to DMC and TSC
- preparation of participant flow chart

- liaison with the Trial Manager to ensure copies of final raw and clean databases are prepared for archiving in the Keele CTU electronic archive.

The **Qualitative Lead** is responsible for:

- collating a complete list of the qualitative study data files
- anonymising transcript files
- storing master and working versions of files on the relevant section of the study secure network drive.