STANDARD OPERATING PROCEDURE FOR SET-UP IN CLINICAL TRIALS OF INVESTIGATIONAL MEDICINAL PRODUCTS

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1. PURPOSE

This Standard Operating Procedure (SOP) describes setting up a Clinical Trial of Investigational Medicinal Product (CTIMP) to ensure compliance with the Medicines for Human Use (Clinical Trial) Regulations 2004 and subsequent amendments.

2. SCOPE

This SOP applies to CTIMPs sponsored or co-sponsored by the University of Dundee (UoD) and/or NHS Tayside (NHST).

This SOP applies to all staff who have a role or responsibility in CTIMP set-up including those who manage, coordinate or advise on set-up and/or start-up procedures.

3. RESPONSIBILITIES

It is a legal requirement for CTIMPs to be set up and conducted in accordance with the UK Clinical Trial Regulations. The responsibility for set-up is the Sponsor's, however the performance of specific set-up duties will be delegated by the Sponsor to the Chief Investigator (CI) by way of a delegation agreement between the Sponsor and the CI.

4. PROCEDURE

4.1 Funding

4.1.1 The CI must secure and administer financial resources to finance the trial.

4.1.2 If the trial is externally funded, the CI must ensure an agreement is in place to confirm financial flow and oversight between the holder (recipient) of the funding and the Sponsor prior to the start of the trial.

4.2 Insurance/Indemnity

4.2.1 Adequate insurance and/or indemnity arrangements must be in place to cover liabilities.

4.2.2 The CI must ensure that evidence of insurance is held in the Trial Master File (TMF) and Investigator Site File (ISF).

4.3 Sponsorship

4.3.1 The CI must ensure that Sponsorship is in place (see TASC SOP for Sponsorship of Clinical Trials).

4.3.2 The CI will be required to sign a Co-Sponsorship Agreement and Chief Investigator Declaration which sets out the duties delegated by the Sponsor to the CI, and the duties retained by the Sponsor.

4.4 Trial Registration

4.4.1 The CI must ensure that the trial is registered on an appropriate publicly accessible research register before recruitment of the first participant. See TASC Study Registration and Publication Policy and TASC SOP for Registering and Reporting Research in a Publicly Accessible Database.

4.5 SOPs

4.5.1 The CI must adhere to the pertinent TASC SOPs and policies.

4.5.2 Where the CI wishes to use local SOPs or external SOPs, this must be agreed with the Sponsor at Risk Assessment.

4.5.3 Approval will be given only for external SOPs where adherence to such a SOP at an external Site is necessary to aid trial conduct and where the SOP is compliant with the equivalent TASC SOP.

4.6 Protocol

4.6.1 The CI should write the protocol using the latest version of the Health Research Authority (HRA) Protocol Template on the HRA website, unless previously discussed with the sponsor. (see TASC SOP Writing a Protocol to Good Clinical Practice for CTIMPs).

4.7 Establishing a TMF, ISF and Pharmacy Site File (PSF)

4.7.1 The CI or delegate is responsible for establishing a TMF

4.7.2 The Principal Investigator (PI), or delegate, at external Sites is responsible for establishing an ISF and PSF.

4.7.3 TASC SOP Establishing and Maintaining a TMF, ISF and Pharmacy Site File (PSF) for use in Clinical Research should be followed.

4.7.4 It is the responsibility of the CI and PI(s) or delegates to ensure that all essential documents as described in the TASC TMF Index (Doc Ref 018) and ISF Index (Doc Ref 019) are filed in the TMF and ISF as appropriate.

4.8 Establishing a TMF or ISF

4.8.1 The CI should contact NHST Clinical Trial Pharmacy at the earliest opportunity to discuss trial set-up. Clinical Trial Pharmacy will establish an Investigational Medicinal Product (IMP) Handling Guideline, which should be filed in the Sponsor File (SF), TMF, PSF and ISF.

4.8.2 It is the responsibility of the CI and PI(s) or delegates to ensure that all essential documents, as described in the TASC PSF Index (Doc Ref 118), are filed in the PSF as appropriate.

4.8.3 The CI/PI should ensure that an IMP Handling Guideline is in place with each Site Pharmacy and that the trial is registered with each Pharmacy as per local requirements.

4.9 Third Party Agreements

4.9.1 The CI must ensure that Agreements (contracts) or Statements of Services with third party organisations providing services such as (but not limited to); IMP supply, laboratory work, statistics, supply of equipment, trial management, data management, are approved by the TASC Legal Team and signed off by the TASC R&D Director or delegate.

4.9.2 All agreements must be instructed by the Research Governance Manager or the TASC Legal Team, and the Sponsor must be a signatory to these contracts/agreements.

4.9.3 The TASC Legal Team must be notified of any changes to any agreements and all changes must be approved by the TASC Legal Team and signed off by the TASC R&D Director or delegate.

4.9.4 The CI must ensure that all staff appointed to work on the trial and who are not employees of the Sponsor (contracted staff) have appropriate employment contracts and hold substantial or NHS honorary contracts/letters of access as appropriate.

4.10 Material Transfer Agreement (MTA) and Tissue

4.10.1 The CI must ensure that where required a Material Transfer Agreement (MTA) is in place for the transfer and storage of human tissue prior to any participant being enrolled in the trial. MTAs must be approved by the TASC Legal Team and signed off by the TASC R&D Director or delegate.

4.10.2 The CI must be aware of, and adhere to, all obligations and requirements for the storage and transfer of tissue.

4.10.3 The CI, or PIs at external Sites, must obtain agreement from NHS labs, University labs and any others for any processing, storage and handling of tissue and bloods prior to recruiting the first participant.

4.10.4 Any central labs used in the research must hold the necessary licence/accreditation, a copy of this should be stored within the TMF/ISF.

4.10.5 The CI must ensure that clear instructions are given to each participating site in the MTA Protocol.

4.11 Approvals

4.11.1 The CI must ensure that the following approvals have been obtained prior to any screening procedure for the trial and prior to the first participant being consented and entered into the trial Sponsor Approval.

- Sponsor Regulatory Green Light.
- Medicines and Healthcare products Regulatory Agency (MHRA) clinical trial authorisation or clinical trial notification acknowledgment. Equivalent authorisation should be obtained for non-UK participating countries.
- Research Ethics Committee (REC) favourable opinion. Equivalent authorisation should be obtained for non-UK participating countries.
- Scotland - NHS R&D management approval. England – HRA approval and NHS confirmation of capacity and capability. Wales - Healthcare Research Wales approval and NHS confirmation of capacity and capability Northern Ireland – Health and Social Care Trust Research Management Permission. Equivalent authorisation should be obtained for non-UK participating countries.
- Any other necessary approvals.

4.12 Training

4.12.1 The CI must ensure that all Site PIs and other research staff are fully trained on the protocol and trial procedures prior to involvement in the trial. Training may be given during pre-trial and during the course of the trial and should include but is not limited to:

- The protocol and any amendments.
- Case Report Forms (CRF) (refer to TASC SOP).
- The informed consent procedure (refer to TASC SOP), consent form, participant information sheet and other trial documents.
- Adverse event reporting (refer to TASC SOP).
- Prescribing procedures.
- Completion of source documents particularly participant's hospital or GP medical records/case notes.
- Breaking the randomisation code for a participant for safety reasons if the trial is blind (refer to TASC SOP).
- Responsibility to report breaches (refer to TASC SOP).

4.12.2 The CI/PI must keep a record of training to confirm that members of the research team are trained.

4.12.3 The CI/PI must ensure all research staff are GCP trained in a timely manner at trial set-up/start-up. Refer to TASC Policy on GCP Training.

4.12.4 The CI/PI must ensure that the TMF, PSF or ISF contains up to date GCP certificates and CVs for all research staff involved with the trial. If held separately, the location should be File Noted in the TMF, PSF or ISF.

4.13 Trial Delegation and Signature Log

4.13.1 The CI or PI is responsible for the completion and maintenance of the TASC Delegation Log (Doc Ref 057) in the TMF, PSF or ISF, prior to and during the trial. The Log should confirm all research staff involved with the trial and their duties which have been delegated to them by the CI or PI.

4.13.2 All significant duties or tasks such as taking consent, assessing eligibility, prescribing or dispensing IMP, physical examinations etc. can be delegated by the CI, or PI, to those who have the necessary education, training and experience. If the CI or PI delegates tasks to other team members, the CI and PI still retains responsibility for the trial at Site.

4.13.3 The following duties can only be delegated on the delegation log to a trial clinician:

- assess the eligibility of trial participants
- perform medical examinations
- sign-off completed Serious Adverse Event (SAE) forms
- review safety information such as line listings or Suspected Unexpected Serious Adverse Reactions (SUSARs)
- review clinical information such as NHS labs, ECG and imaging
- respond to medical queries
- approve IMP prescriptions.

4.13.4 The CI or PI must ensure that no staff member is added to the Delegation Log without appropriate training.

4.13.5 The Delegation Log must contain the signature and initials of trial staff to ensure they can then be identified on trial documents such as CRFs, case notes, and prescriptions.

4.14 Participant Screening Log and Participant Randomisation Log

4.14.1 The CI/PI (or delegate) is responsible for keeping a confidential list of names of all participants consenting to the trial (ICH GCP 8.3.21), see Doc Ref 076 (Screening Log). This is the only place where the full name, CHI/hospital number and contact details (optional) of trial participants are documented and allows the CI/PI to reveal the identity of participants if necessary.

4.14.2 The CI/PI or delegate is also responsible for keeping a list of all participants that were randomised, see Doc Ref 071 (Randomisation Log) and ICH GCP (8.3.20 & 8.3.22). Participants should be referred to by initials and/or trial number only.

4.14.3 Aside from the screening log, prescriptions or IMP request forms, participants should only be referred to by their initials and/or trial number on CRFs or elsewhere.

4.14.4 The CI or delegate must notify a TASC trial monitor of the trial start date. The trial start date will be the date when the first participant signs an Informed Consent Form.

4.15 Trial equipment

4.15.1 The CI or PI is responsible for the proper maintenance of all equipment used in the trial. This may include fridges, freezers, centrifuges, weighing scales and equipment used for medical procedures.

4.15.2 The CI is responsible for ensuring that appropriate indemnity arrangements are in place for any equipment loaned for use in the trial. The CI should seek advice regarding indemnity from the TASC Legal Office.

4.16 Trial meetings

4.16.1 A Trial Management Group (TMG) should be established, and regular meetings should be held. Meetings should be minuted or notes made of all significant decisions and follow-up actions. Copies of minutes or notes must be kept in the TMF.

4.16.2 For large multi-centre trials, trial oversight committees should also be set up e.g. a Data Monitoring Committee (DMC) and Trial Steering Committee (TSC), in order to review trial data and oversee trial management at regular pre-defined intervals during the trial. Minutes of all meetings should be maintained in the TMF.

4.17 Pharmacy responsibilities

4.17.1 The Clinical Trials Pharmacist (or delegate), at each Site is responsible for setting up and maintaining the PSF and PSF Index.

4.17.2 Where the trial pharmacy is not an NHS Pharmacy, the Sponsor will approve the use of such a pharmacy, and it will be subject to audit by the NHS Tayside Clinical Trials Pharmacist (or delegate).

4.18 Sponsor responsibilities

4.18.1 TASC is responsible for setting up and maintaining the SF.

4.18.2 The SF contains confidential documents and is kept in TASC in a locked room with restricted access.

4.18.3 All pertinent correspondence concerning the trial is filed in the SF including monitoring visit reports and action lists from monitoring.

4.19 Setting up Sites - Local Information Pack

4.19.1 To enable the set-up of participating NHS sites, the CI must complete the Local Information Pack.

4.19.2 The CI must complete the appropriate Organisation Information Document (OID) appropriate template (s). The outline OID gives information that is common to all participating NHS/Health and Social Care (HSC) organisations that are undertaking the same activities within the study. Where NHS/HSC organisations will undertake different activities to others, separate outline OIDs are required.

4.19.3 Single centre research, where the NHS organisation is acting as both the Sponsor and the sole participating site for the study does not require a Local Information Pack or an OID.

4.19.4 The outline OID(s) must be approved by Sponsor and electronically submitted as part of the combined review process.

4.19.5 The outline OID must be localised and shared with the participating NHS/HSC organisations.

5. ABBREVIATIONS & DEFINITIONS

CI	Chief Investigator
CRF	Case Report Forms
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
HRA	Health Research Authority
HSC	Health and Social Care
IMP	Investigational Medicinal Product
ISF	Investigator Site File
MHRA	Medicines & Healthcare Products Regulatory Agency
MTA	Material Transfer Agreement
NHST	NHS Tayside (Tayside Health Board)
OID	Organisation Information Document
PI	Principal Investigator
PSF	Pharmacy Site File
REC	Research Ethics Committee
SF	Sponsor File
SOP	Standard Operating Procedure
TASC	Tayside Medical Sciences Centre
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UoD	University of Dundee

6. ASSOCIATED DOCUMENTS & REFERENCES

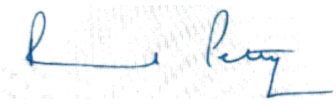
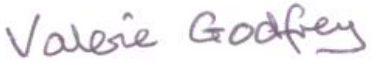
Doc Ref 018: Trial Master File index
Doc Ref 019: Investigator Site File Index
Doc Ref 057: Delegation Log

Doc Ref 071: Randomisation Log
Doc Ref 076: Screening Log
Doc Ref 118: Pharmacy Site File Index

7. DOCUMENT HISTORY

Version Number:	Reviewed By (Job Title)	Effective Date:	Details of editions made:
History of reviewers prior to 2014 is detailed in the archived SOPs			
3	Catrina Forde (SRGM)	23/09/2014	Updated in line with current practice.
4	Catrina Forde (SRGM)	23/09/2016	Scheduled review. Addition of a new numbered section (4.8.3) for changes to agreements.
5	Margaret Band (Senior Trial Manager)	23/09/2018	New TASC SOP format implemented. Minor changes to text.
6	Margaret Band (Senior Trial Manager)	26/11/2018	Reference to TASC SOP on Sponsor Regulatory Green Light and associated Checklist (Doc Ref 116) and CTIMP Protocol Template (Doc Ref 054) removed. Now use HRA Protocol template. Change of reference from TASC SOP for Approvals for CTIMPs to SOP for Sponsorship of Clinical Trials. Reference to TASC SOP for Registering and Reporting Research in a Publicly Accessible Database added.
7	Margaret Band (Senior Trial Manager) & Patricia Burns (Senior Research Governance Manager)	23/11/2020	Removal of sentence at 4.4.5, 4.7.2, 4.7.3 and 4.7.4. General tidy of the text and new TASC website address added to the footer. Addition of section 4.18 to describe Local Information Pack requirements for setting up of studies at NHS sites.
8	Margaret Band (Senior Trial Manager)	23/11/2022	Scheduled review. General tidy of the text.

8. APPROVALS

Sign		Date
APPROVED BY:	Professor Russell Petty, R&D Director, NHS Tayside	
Signature		14th November 2022
APPROVED BY:	Dr Valerie Godfrey , TASC QA Manager, Chair of Clinical Research Guidelines Committee	
Signature		14 Nov 2022