STANDARD OPERATING PROCEDURE 26

Clinical Research Study Activation, Site Selection and Initiation

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Author:	Claire Daffern, Quality Assurance (QA) Manager, Warwick Clinical Trials Unit (WCTU)		
WCTU Reviewers:	Louisa Edwards, Clinical Trials Coordinator, WCTU Lucy Eggleston, Clinical Trials Coordinator, WCTU		
Sponsor Reviewers:	Mathew Gane, Research Governance & QA Manager, Research & Impact Services (R&IS)		
WCTU approval:	Natalie Strickland, Head of Operations, WCTU		
Sponsor approval:	Carole Harris, Assistant Director, R&IS (Systems & Strategic Projects) & Head of Research Governance		
Review Lead:	WCTU QA Team		

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Version 4.0	17 May 2023	Biennial Review: change to new format. Minor amends to text.
Version 3.0	18 February 2021	Biennial Review: change to new format. Minor amends to text.
Version 2.2	8 January 2019	Updates to guidance and additions to process text. Clarification regarding evidence of qualifications and training. Clarification between Green light for commencing the study and green light for individual recruitment sites.
Version 2.1	3 May 2016	Minor changes to text. Change to new format
Version 2.0	9 December 2013	Addition of text to include site selection and change of title.
Version 1.1	5 March 2012	Biennial review: Format change to comply with SOP 1.
Biennial review February 2010		No changes.
Version 1.0	29th February 2008	

STANDARD OPERATING PROCEDURE 26
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1. Purpose and Scope

This Standard Operating Procedure (SOP) describes the procedure for permissions required for a University of Warwick clinical research study to commence (Green Light), the process for selection of suitable clinical study sites and conducting site initiation to ensure the investigator and site team have the capacity to participate in the study and are fully prepared to commence recruitment.

This SOP is applicable to all staff involved in the set-up of a new research study or new research sites.

Researchers working on non-Warwick sponsored studies must ensure they are compliant with the external sponsors requirements.

2. Definitions

Clinical study	A research study involving human volunteers (also called participants) that is intended to add to medical knowledge.
Recruitment site	A location at which research study participants are enrolled into a study.
Participant Identification Centres (PICs)	NHS/HSC organisations that identify potential research participants for a research study (e.g., through search of patient databases) and have no other involvement in the research.
Principal Investigator (PI)	The person responsible for the conduct of a research study at a participating site.

3. Background

The International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines state that 'the sponsor of a clinical trial is responsible for selecting the investigator(s)/institution(s) and to ensure they are qualified by training and experience and should have adequate resources' (section 5.6.1).

The Medical Research Council (MRC) Guidelines for Management of Global Health Trials (2017, updated 2022) section 5.4.1 entitled 'Trial Management' states that: The Principal Investigator (PI) should ensure that all the persons involved in implementing the protocol are adequately informed about the protocol, the nature of any intervention and their trial-related duties; that all trial-related functions are clearly defined, allocated and documented and that the responsibilities of participating investigators are clearly understood."

ICH GCP section 5.7: 'Allocation of duties and functions' states that prior to initiating a trial, "The sponsor should define, establish and allocate all trial related duties and functions".
For multi-site trials, the careful selection and evaluation of investigator sites is critical for the successful completion of a trial within budget and timelines and to ensure the generation of high-quality data.

It is therefore essential that there is appropriate communication between the coordinating centre and each study site prior to initiation to ensure that site staff are aware of their responsibilities and all documentation is in place to enable the first participant to be recruited. This is especially important when working with new or inexperienced teams to ensure that they are prepared, organised and adequately staffed to commence the trial.

4. Procedure

4.1 Responsibilities

Sponsor	• Ensure all required approvals are in place to commence the study • Sign 'green light' form (T18) to commence protocol activities • Review and sign localised mNCA agreement for each site • Approve non-substantial amendments for the addition of new sites.
Chief Investigator (CI)	• Support TM/C to identify recruitment sites • Attend SIVs where possible to provide clinical/scientific information • Delegate study management tasks to appropriately trained and qualified individuals.
Trial Manager/Coordinator (TM/C)/Research Facilitators	• Identify potential recruitment sites • Develop and distribute feasibility questionnaires • Preparation of the Site Initiation Visit (SIV) presentation • Liaise with sites to arrange SIV meetings • Delivery of SIV presentation • Preparation of essential documents to obtain green light from sponsors • Ensure site activation checklist is completed • Communicate with sites to activate for recruitment • (If applicable) Work with external study sponsors to ensure appropriate 'green lighting' of the study including agreement on which documentation is required
Trial Management Group (TMG)	• Support TM/C with site selection • Review/assess feasibility questionnaires • Document decisions on site selection in meeting minutes
Quality Assurance (QA) team (WCTU studies)	• Review study-specific green light form • Review site initiation presentation slides

4.2 When?

Site selection should be considered at the very early stages of setting up a new study, although additional sites may be identified at later stages (e.g., after recruitment has commenced).

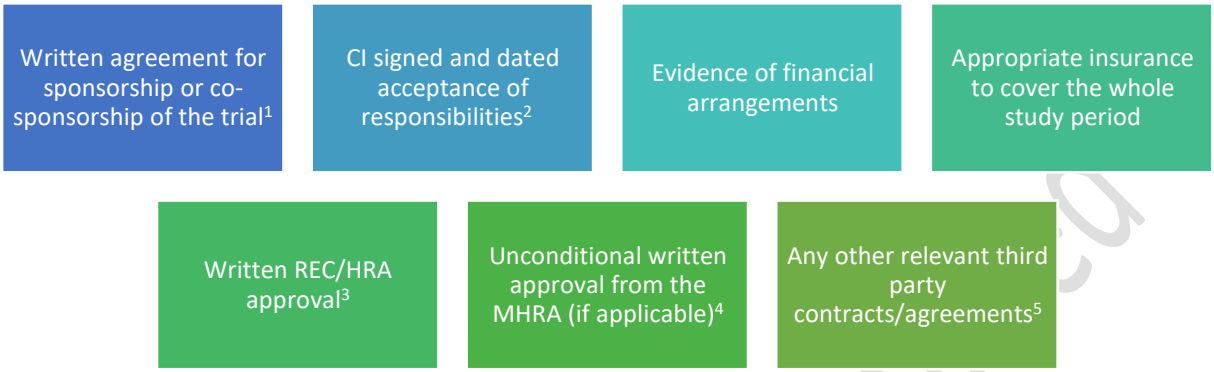
The permissions required for a clinical research study to commence (Green Light) form (T18) must be completed prior to any protocol required activities commencing and requires Sponsor approval.

Individual site activation checklists (C09) must be completed before site initiation confirmation letters/emails are sent to activate a site.

4.3 How?

4.3.1 Activation of a clinical research study

It is essential that the following documentation is in place at the coordinating centre and the Sponsor (or their delegate) has given their written approval for recruitment to begin:



1 See SOP 3 'Research Sponsorship'

2 For Warwick sponsored studies contact the Research and Governance team in R&IS using sponsorship@warwick.ac.uk. (For non-Warwick sponsored research, ensure sponsor requirements are followed)

3 See SOP 5 part 1 'Gaining Initial Ethical Approval for Research Studies'

4 See SOP 5 part 2 'Gaining Initial Regulatory Approvals'

5 Where applicable e.g., Investigational Medicinal Product (IMP) manufacturer/distributor

Documentation of RCT activation should be via a green light form, a template is available to adapt to suit the needs of the study (T18). The Sponsor should have oversight of its contents and final approval to commence activity. External sponsors may require the study coordination centre to use the sponsors own green light form, but it should be ensured that the requirements are consistent with the minimum requirements of the Warwick form.

For Warwick Sponsored research, QA should review the form and requests for approval should be submitted to sponsorship@warwick.ac.uk along with any supporting documentation.

The CI must delegate study management tasks to appropriately trained and qualified individuals and continues to retain oversight of this throughout the study. A template coordination centre delegation log can be located on the WCTU website (T23).

4.3.2 Site selection

Failure to assess feasibility of potential sites may result in recruitment targets not being achieved and/or poor-quality data being collected.

Potential sites may be identified by:

- contacting investigators with previous experience in the therapeutic area
- recommendations by colleagues
- Publications
- professional groups
- conferences
- clinical research networks (CRNs)

- National Institute for Health and Care Research (NIHR) Hub Open Data Platform (ODP)
    - To access: https://odp.nihr.ac.uk/qlikview/ via the LCRN NENC Portfolio ODP.qvw application in the dashboard
    - Guidance can be obtained via nencbusinessintelligence@nihr.ac.uk.

An 'expression of interest' form can be a useful way of establishing a site's interest. This is usually an outline of the study, and a summary of the patient population, study timelines and the expectations on sites.

A feasibility questionnaire should be sent to assess the site's suitability to participate in a study against the protocol requirements. A list of potential considerations can be found below:

- Interest in the research question
- Availability of staff to manage the site tasks
- Experience and qualifications of the investigator and site team *
- Ability to comply with the study protocol
- Availability of suitable population:
    - Anticipated rate of recruitment
    - Conflicting studies (competing for the patient population and potentially introducing recruitment bias)
    - Compatible standard care offering
- Adequate time to conduct and oversee the study:
    - Screening and recruitment of participants
    - Scheduling of study-related visits, including follow-up requirements
    - Completion of Case Report Forms (CRF) throughout study duration
- Suitable facilities:
    - Availability of any specialised diagnostic or therapeutic equipment required
    - IT requirements
    - Satisfactory space (for recruitment/clinics/assessments/follow-up visits etc.,) and storage conditions (including archive)
    - Available resources in NHS support departments (including weekend cover if applicable)
    - Other departmental involvement (e.g., pharmacy, radiology, pathology)
    - Unblinding requirements
    - Space/resources for trial monitoring purposes
- History of recruiting
- Geographic location
- Contractual and budgetary negotiations and arrangements
- Equipoise at site.

*Guidance on GCP training requirements is available from the Health Research Authority (HRA) website: https://www.hra.nhs.uk/about-us/news-updates/updated-guidance-good-clinical-practice-gcp-training/

Feasibility responses should be considered by the TMG to assess the site's capacity and capability to recruit, and where there is any area of concern regarding a site's ability to participate, this should be taken into account in the decision to continue. Guidance may be sought from other study teams who have experience of working with a site. When a site is rejected at the feasibility stage, this should be

sensitively discussed with the Principal Investigator and site team. It may be possible to consider the site at a later date if the local concerns are resolved.

Any decision making around the inclusion or rejection of sites at the feasibility stage should be clearly documented in TMG meeting minutes. Both minutes and the completed questionnaires should be available in the Trial Master File (TMF).

The site selection process should also consider study limitations e.g.:

- Limited drug supply
- Funding available for site visits
- additional consultations or investigations).

The preparation of 'reserve' investigator sites or Patient Identification Centres (PICs) should be considered as part of proactive study planning (so that the study may be extended to these sites if recruitment issues arise).

Once the TMG agrees that the site is suitable, site set up can commence.

4.3.3 Site set up, initiation & activation

4.3.3.1. Ethical approval:

All clinical research studies will gain ethical and site level approvals via the HRA approval system (See SOP 5 part 1 Gaining Initial Ethical Approvals).

Adding recruitment sites once initial approvals are in place must be done using the IRAS Amendment Tool (see https://www.myresearchproject.org.uk/help/hlpamendments.aspx#Amendment-Tool and SOP 6 'Amendments to Approved Study Documents' for further details.)

4.3.3.2. Local Information Pack (LIP):

A local information pack contains the Organisation Information Document (OID) and the Schedule of Costs Attribution Template (SoECAT) and should be submitted via email to the following people once the Sponsor received the Initial Assessment Letter or Approval Letter from HRA/HCRW:

- PI
- local research staff/study coordinators,
- the NHS R&D office
- Lead Clinical Research Network (LCRN) contact.

Full details of the requirements for site set up can be found via the IRAS website 'Help' section.

4.3.3.2.1 Organisation Information Document (OID):

The OID is a component of the IRAS form submission for non-commercial funded research which details site activities. The OID details information that will be common to all participating NHS/HSC organisations that are undertaking the same activities within the study. Multiple OIDs will be needed to be issued to groups of sites doing the same activities. For help, guidance and suggested pack and email templates for England and Wales visit: https://www.hra.nhs.uk/planning-and-improving-research/best-practice/nhs-site-set-up-in-england/ or for Scottish and Northern Irish sites visit: https://www.myresearchproject.org.uk/help/hlpsitespecific.aspx#UK-Local-Information-Pack-Sharing

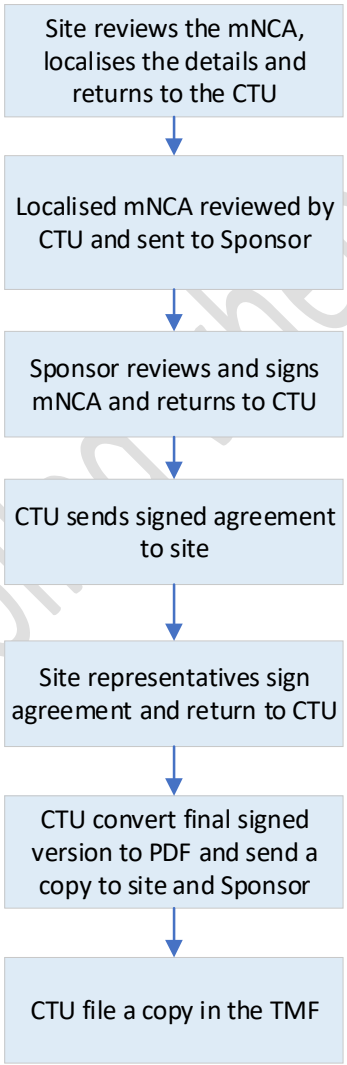
4.3.3.2.2. Schedule of Events Cost Attribution Template (SoECAT):

The SoECAT form is used to attribute research costs. However, is not intended primarily as a study costing tool. It provides the Excess Treatment Costs (ETCs).

4.3.3.3 Contract/Agreement

The study sponsor (or their delegate) will commence negotiations with each site once their involvement is confirmed and provide contracts/agreements to exchange. For non-commercial studies, the model Non-Commercial Agreement (mNCA) is likely to be used.

Completion of a model Non-Commercial Agreement



N.B. For non-commercial studies that are not clinical trials or clinical investigations, the agreed final Organisation Information Document (taken together with the documents in the Local Information Pack and the exchange of correspondence) forms the agreement between the participating NHS / HSC organisation and the Sponsor, once confirmed by the participating NHS / HSC organisation. For all other non-commercial studies, it is expected that the model Non-Commercial Agreement (mNCA) is

used as the agreement (although the localised Organisation Information Document is still needed in the Local Information Pack, for the information it contains).

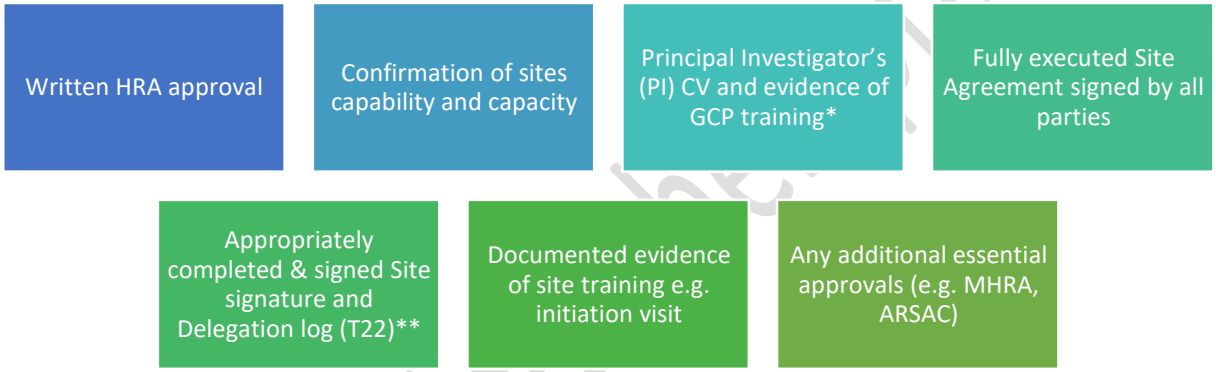
4.3.3.4. Investigator Site File (ISF)

Once the site agreement is in place or nearing completion, the Investigator Site File (ISF) may be sent to sites, if applicable. The ISF can be paper or electronic. A template ISF index is available (T08)

4.3.3.5. Capacity and Capability

The R&D offices at each site will assess and confirm their capacity and capability to undertake the study and recruitment can commence as soon as the contract/agreement has been signed. This can't be done until the HRA Approval letter is issued (N.B. There may not be a formal R&D permission letter issued.)

As a minimum, the following documentation should be in place at the study site prior to the site being opened to recruitment:



**A CV, proportionate GCP and/or relevant training is also expected to be in place for each person named on the site delegation log. Unless deemed necessary these should be retained at site and made available on request. However, if evidence of specific training is required for any member of staff based on the study risk assessment, this should be sent to the coordinating team to confirm the training has been completed.*
*** For guidance of appropriate completion of a delegation log see Guidance Document G15.*

Following site activation, new members of staff working on the study must be added to the site signature & delegation log and a CV and training evidence retained at the site.

4.3.3.6 Site initiation

When a site is close to signing the agreement/contract, a mutually convenient time for the initiation should be arranged. The format will depend on the complexity of the study and the experience of the site staff but could include:

- site visit
- Remote Teams meeting,
- detailed written instructions
- Presentation at a study launch meeting
- Regularly hosted site initiation drop in sessions
- Online or refresher packages for new members of the team who join after initiation (It is the responsibility of the site PI to ensure any new members of their team have received the relevant training before being added to the delegation log)

For WCTU managed studies, Site Initiation slides should be prepared by the TM/C, and reviewed by the following people prior to use:

- the QA team
- CI and/or TMG members (to ensure clarity of message)

A Site Initiation Visit (SIV) Checklist (C05) is available to guide expected content of the initiation. Additional site initiation guidance (G14) is also available.

The site initiation presentation should be delivered by an appropriate member of the coordinating team/WCTU. It may be appropriate for different members of staff to deliver different sections according to expertise.

Where possible all members of the study team should attend the site initiation, but it can be done in a number of sessions or parts to accommodate individuals or specialties. Attendance at the site initiation meeting should include:

- PI
- co-investigators
- research nurses
- and any other member of staff who will be involved with study related activities. Additional personnel e.g., pharmacists, radiologists etc. should be included as required.

Attendance of site staff at initiation visits/teleconferences should be recorded (e.g., by using an attendee's signature log, TEAMS attendance log or detailed in the site activation letter) and a copy should be stored in both the TMF and ISF.

4.3.3.7 Site Activation

A summary of the initiation should be sent to the site and should include:

- who attended and when
- issues discussed
- questions raised with responses showing resolution
- confirmation the site is now ready to start recruitment. Further correspondence may be required if the site is not in a position to be opened to recruitment immediately after the initiation meeting (e.g., final sign-off of contracts remains outstanding).

If there is a delay between the initiation meeting and site activation, steps should be taken to ensure the ISF is up to date with current documentation and any additional staff training requirements have been addressed. This may include repeated training if major changes have been made or if new staff members join the team.

Prior to confirming that a site can open to recruitment, the TM/TC must complete the site activation checklist (checklist C09) to document that all the required documentation and approvals are in place.

All Site activation confirmation correspondence should be filed in the Investigator Site File (ISF) and a copy filed in the TMF.

The original site signature and delegation log should be stored in the ISF. If an electronic delegation log will be used, the collection of signatures should follow the considerations in G33 Email approval guidance to ensure electronic signatures are attributable to the individual. Copies should be sent to

the coordination team and filed in the TMF. Amended/updated versions should be retained alongside the original in the ISF and a copy sent to the coordinating team to file in the TMF.

Available Templates and Guidance Documents

Template T08	ISF Index
Template T18	Permissions Required to Commence a Clinical Research Study (Green Light Form)
Template T22	Site signature and delegation log
Template T23	Coordinating centre delegation log
Checklist C05	SIV presentation checklist
Checklist C09	Site activation checklist
Guidance G13	Site training and qualification Guidance
Guidance G14	SIV guidance
Guidance G15	Delegation Log review guidance

List of Abbreviations

ARSAC	Administration of Radioactive Substances Advisory Committee
CI	Chief Investigator
CRF	Case Report Form
CRN	Clinical Research Network
CV	Curriculum Vitae
GCP	Good Clinical Practice
EDC	Electronic Data Capture
ETC	Excess Treatment Costs
HRA	Heath Research Authority
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
ISF	Investigator Site File
LIP	Local Information Pack
MHRA	Medicines and Healthcare products Regulatory Agency
mNCA	Model Non-Commercial Agreement
MRC	Medical Research Council
NIHR	National Institute for Health and Care Research
OID	Organisation Information Document
PI	Principal Investigator
PIC	Participant Identification Centre
QA	Quality Assurance
REC	Research Ethics Committee
R&D	Research & Development
R&IS	Research & Impact Services
SIV	Site Initiation Visit
SoECAT	Schedule of Events Cost Attribution Template
SOP	Standard Operating Procedure
TM/C	Trial Manager/Coordinator
TMF	Trial Master File
TMG	Trial Management Group
WCTU	Warwick Clinical Trials Unit