

List of key Standard Operating Procedures (SOPs) for clinical studies, aligned with the ICH Guidelines

Table of Contents	Page
Introduction	3
A. List of SOPs applicable before clinical phase of study	4
B. List of SOPs applicable during clinical phase of study	15
C. List of SOPs applicable after clinical phase of study	22
D. List of SOPs applicable for data management in clinical study	25
E. List of SOPs applicable for study site in clinical study	28
F. List of SOPs applicable for regulatory communication in clinical study	36
G. Helpful references	37

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Introduction

This document is aimed at stimulating interest and dialogue among professionals interested in the area of clinical studies and medical affairs, and contains proposals for content and wording of standard operating procedures (SOPs) to be used for clinical research activities conducted by sponsors (manufacturers) or their respective Contract Research Organisations (CROs) conducting clinical trials of medicinal products for human use, according to requirements of the International Conference on Harmonisation (ICH), the Food and Drug Administration (FDA), European Medicines Agency (EMA) and many other academic sources, openly available as 'best practice' guidance documents. It's also important to mention that every company should look at local regulations requirements as well the global guidance, and that the companies SOPs should reflect on their own processes which can be developed or improved based on the information contained in this document.

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The listed SOPs herein may be helpful when conducting clinical studies and have been aleatorily divided into six parts to facilitate reading and understanding. Their titles or headings can vary as to needs, language, institutions, countries and regions. The brief description related to each SOP does not constitute a SOP in itself, it is just a brief indication of what in general may be included in such documents. Examples are provided throughout this document under links to open access documents from various sources.

In general, the specific content of every and each SOP may include explanatory text and descriptive steps for the following items or subchapters:

- a) Title & signature page
- b) Purpose
- c) Scope
- d) Responsibility
- e) Accountability

Clinical Development and Medical Affairs Working Group - List of key SOPs for clinical operations, as of 20 February 2023

- f) Definitions
- g) Procedures
- h) Abbreviations
- i) References
- j) Annexures
- k) Document History

A. List of SOPs applicable before initiating the clinical phases of study

1. SOP for Clinical trial site selection and site selection visits

Initial Selection Process for Suitable Study Sites SOP: Current policy states that the sponsor/CRO is responsible for assuring that clinical studies are placed safely. The initial part of the selection process involves selecting study sites for formal selection visits. The sponsor (manufacturer) is responsible for organising the initial selection of investigator sites. Potential suitable investigators may be identified by the following means:

- Review of previous experience (maintenance of a file containing post-study evaluations of investigators is useful).
- Recommendations by colleagues and other investigators.
- Review of the literature to identify experts in the respective field of research.
- Contacts during professional meetings, symposia, etc.
- Reputation (e.g. an opinion leader in the field of interest).

The suitability of the study site (e.g. facilities, personnel, equipment) must be assessed before placement of the study. A formal site selection visit by the Site Monitor is required to fully assess the study site and to discuss further items with the investigator. If the investigator and facilities are known to the sponsor/CRO (i.e. a study has previously been conducted with the site under consideration), a site selection and site qualification visit is still necessary to determine that there have been no significant changes at the study site since the previous study was completed. If there has been less than a six-month interval since the completion of the previous study, it may not be necessary to confirm all items, but this must be agreed in writing between the sponsor (manufacturer) and the clinical site responsible person.

Additional information, examples and templates are openly available at

<https://onlinelibrary.wiley.com/doi/pdf/10.1002/qaj.151>

https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-8-general-considerations-clinical-trials-step-5_en.pdf

2. SOP for CRO selection

Key criteria to select a CRO include its service catalogue, experience (how many years in the market, how many trials has it managed and in which countries), knowledge of the disease under investigation, access to patients, geographical coverage, quality management, responsiveness, staff continuity and proficiency, technology, financial stability, and pricing. Clinical trials involve many tasks, so it is advisable to hire a full service CRO able to cover as many areas as possible, in order to keep the number of vendors low. The previous experience of the Sponsor with the CRO should also be taken into consideration.

More information, examples and templates available at

https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-good-clinical-practice-e6r2-step-5_en.pdf

<https://www.sofpromed.com/how-to-select-a-clinical-research-organization-cro>

3. SOP for Clinical Study Protocol and its amendments

The regulations require that clinical trials are conducted according to a pre-established protocol for Clinical Trials for Investigational Medicinal Products (CTIMPs). Subsequent amendments shall also be outlined and conducted according to the protocol. Under these regulations therefore the research protocol is a legal document that outlines the study plan.

No matter how carefully the study is designed and the procedures pre-tested, problems often appear once the study has begun and the need for an amendment becomes apparent. Once the decision has been taken to amend the protocol (or patient related documents). The study sponsor, must make a decision as to whether the intended changes constitute a minor or a substantial amendment. In general, the following steps should be followed with regards to amendments:

- Any change to the protocol will constitute an amendment either substantial or minor. The sponsor will confirm whether the change is substantial or not, according to local regulations.
- For substantial amendments, you will need to inform the regulatory authority.
- In the case of urgent safety measures the protocol can be amended without delay. Refer to PHT/RDSOP/006 'SOP for Reporting Urgent Safety Measures in Clinical Research.
- Changes must be reviewed and approved by the appropriate personnel such as PI, pharmacist, statistician, etc.

More information, examples and templates is available at

www.GlobalHealthTrials.org

<https://www.porthosp.nhs.uk/research/docs/sop/PHTRDSOP015%20-%20SOP%20for%20Protocol%20Development%20v%201.0%2026Apr16.pdf>

<https://edctpknowledgehub.tghn.org/protocol-development/protocol-development-steps/>

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200-207.

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.

4. SOP for Case Report Form (CRF) (including designing of electronic Case Report Form)

The CRF is a data capturing tool used in all Clinical Trials to record eligibility of a subject and to capture the required data as defined by the trial protocol for each individual trial subject during the course of

his/her participation in a trial. CRFs may be printed or electronic documents. CRF design should be standardized to address the needs of all users such as investigator, site coordinator, study monitor, data entry personnel, medical coder and statistician. The design of the CRF and its completion have a direct impact on the quality of the Clinical Trial data. It is subject to quality assurance and control during monitoring for GCP compliance on behalf of the Sponsor, as well as during audits and inspections. A SOP should describe the standard procedures to be followed when designing and developing CRFs for use within a Clinical Trial. Cf. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4170533/>

An electronic case report form, or eCRF is a digital, usually web-based, questionnaire for collecting data about a study participant. https://cctu.org.uk/sites/default/files/2021-05/CCTU_SOP013%20Paper%20Case%20Report%20Form%20Design_.pdf

More information available at

https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-3-structure-content-clinical-study-reports-step-5_en.pdf

https://khpcto.co.uk/SOPs/08_crfDesignSOP.php ;

<https://ichgcp.net/fr/publications/informed-consent-of-trial-subjects>

5. SOP for Informed Consent Form or Document (ICD, Assent form, AV consent form)

An SOP should describe the process for fulfilling the regulatory and ethical requirements for developing and writing the Informed Consent Form (ICF) for clinical research.

Prior to implementation of a clinical trial the PI must have IRB approval of the written ICF document and any other written information provided to subjects. The information that is given in the informed consent document to the subject or their legally authorized representative shall be in a language understandable to the subject or their representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence. The ICF will be submitted to the IRB for review and approval along with any other required and applicable documents. An ICF, provided to subjects, may include but is not limited to the following elements:

General

- A concise and focused summary of the key information that facilitates comprehension.
- A statement that the study involves research and an explanation of the purposes.
- The number of potential subjects and expected duration of subject's participation.
- A description of the procedures involved in the trial and identification of which procedures are experimental.
- The alternative procedures or courses of treatment that may be available to the subject.
- The compensation and/or treatment available to the subject in the event of trial-related injury.
- The anticipated payment, if any, to the subject for participating in the trial.
- The anticipated expenses, if any, to the subject for participating in the trial.

- For applicable clinical trials initiated on or after March 7, 2012, informed consent documents must be in compliance with the new requirement in 21 CFR § 50.25(c) and include a specific statement that refers to the trial's description on www.ClinicalTrials.gov .
- Subjects rights and responsibilities
- Risks and benefits
- Records access and review
- Special consent circumstances

More information available at

https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-good-clinical-practice-e6r2-step-5_en.pdf (page 24)

https://ccts.osu.edu/sites/default/files/inline-files/SOP%2007%20Informed%20Consent%20Form%20Development_0.pdf or

<https://www.hhs.gov/ohrp/regulations-and-policy/guidance/checklists/index.html>

6. SOP for Investigator's Brochure

A Standard Operating Procedure (SOP) describes the purpose, minimum content, creation and maintenance of an Investigator's Brochure (IB) for developed products used in clinical trials of Investigational Medicinal Products sponsored by the manufacturer and managed by the Research Office or CRO. The IB is a compilation of the clinical and non-clinical data on the Investigational Medicinal Products IMP(s) that are relevant to the study of the product(s) in human subjects. The ICH GCP E6(R2) state that the Sponsor of a clinical trial is responsible for the IB and shall ensure that the trial IB presents the information it contains in a concise, simple, objective, balanced and non-promotional form that enables a clinician or potential investigator to understand it and make an unbiased risk-benefit assessment of the appropriateness of the proposed clinical trial; and shall validate and update the IB at least once a year.

More information, examples and templates at

https://www.ucl.ac.uk/joint-research-office/sites/joint-research-office/files/11_spon_s03_sop_for_creating_and_maintaining_an_ib_v02.pdf and

https://www.health.qld.gov.au/_data/assets/pdf_file/0027/147609/gcp_sop4.pdf

<https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice-scientific-guideline>

<https://www.ich.org/page/efficacy-guidelines>

7. SOP for Translation of essential clinical study documents (ICD, Assent form, diary cards, dosing instructions etc.)

It is the responsibility of the study Sponsor/CI to decide if translation services will be required throughout the entirety of the study, based on risk, the complexity of the study procedures and the language skills of the individual. This should be discussed prior to the patient attending for their first

study visit and clearly documented in the medical and research notes, and in the study protocol. If this is not the case the trial centre/sponsor must be contacted directly to confirm if patients requiring translation services are eligible for the trial. The CI and Sponsor for each study will be responsible for determining if translated written material is to be provided to participants, and if they will be provided by the sponsor, or translated locally, and what arrangements are in place to confirm the accuracy of the translation. The purpose of an SOP is to describe Institutional Review Board (IRB) Policy for the translation of study documents into a language other than English. Examples of such policy documents and SOPs are available in links below.

More information, examples and templates available at

<https://www.nhsfife.org/media/33769/sop44-use-of-translation-services-for-research-studies-v1-final.pdf> and

<https://www.niaid.nih.gov/sites/default/files/dmidtranspol.pdf>
<https://www.neiu.edu/sites/neiu.edu/files/documents/2021/02/18/Translation%20for%20Studies%20Conducted%20in%20a%20Language%20Other%20Than%20English.pdf> and

<https://globalhealthtrials.tghn.org/articles/back-translation-clinical-trial-documentation-informed-consent-forms/>

8. SOP for Execution of clinical study agreements/contracts

The procedures described on a SOP for execution of clinical trial agreement involve an in depth budgetary, administrative and legal review of the proposals and resulting contracts and are applicable to all commercially sponsored clinical trials. The SOP should describe the key steps in creating and finalizing a Clinical Trial Agreement (CTA) and budget. When creating a budget for a clinical trial, all pertinent sponsor policies and local rules must be followed. Standard budget guidelines such as Research Floor Rates for clinical procedures/tests, standard invoiceables, and other non-patient costs shall be strictly adhered to for sponsored studies unless otherwise approved by the local regulatory authority.

More information, templates and examples of such documents are available at <https://www.epworth.org.au/-/media/project/epworth/epworthweb/documents/research/resources/sop-rg-03-developing-contracts-and-budgets-v20-21may2020-signed.pdf> and

<https://www.uhealth.com/wp-content/uploads/sites/3/2014/01/ADM-009-01-Commercially-Sponsored-Clinical-Trials-Process-SOP.pdf> and

<https://www.pif.fi/media/tiedostot/clinical-trial-agreement.pdf> and

<https://www.lsuhs.edu/administration/academic/ors/clinicaltrials/docs/SOP%201.03%20Contract%20and%20Budget%20Negotiations-signed.pdf> and

<https://www.lsuhs.edu/administration/academic/ors/clinicaltrials/docs/SOP%201.03%20Contract%20and%20Budget%20Negotiations-signed.pdf> and

<https://researchsupport.admin.ox.ac.uk/files/coresop016contractsforclinicalresearchstudiespdf>

9. SOP for Randomization, blinding & unblinding procedures

The purpose of this SOP is to describe the process that an investigator should follow to prepare a trial specific randomisation, blinding and emergency unblinding SOP. This SOP applies to a randomised controlled trial (RCT).

Clinical trials are often blinded to hide the treatment group assignment from participants and investigators (in double-blinded studies) in order to prevent the unintentional biases of either party affecting subject data. The objective of this SOP is to describe the process that an investigator should follow a trial specific randomisation, blinding and emergency unblinding SOP. It is not always necessary to randomise and/or blind treatments or assessments but these options may be appropriate when designing a study. In accordance with Good Clinical Practice each task must be conducted by appropriately qualified and trained individuals and it is expected that a statistician or other suitably qualified individual will undertake or be involved in the randomisation and blinding of a study. In order to protect the wellbeing and safety of the trial subject as required in the principles of GCP, the coding system for the Investigational Medical Product(s) in blinded trials should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency, but one that does not permit undetectable breaks of the blinding in order to protect the integrity and validity of the data. To ensure this, emergency unblinding procedures must be clearly established. At the start of any clinical trials the Principal Investigator (PI) should have a written procedure on the randomisation, blinding and process for rapidly identifying a blinded Investigational Medicinal Product(s), as well as the details of authorised personnel who will have access to unblinded data. The PI and designated study personnel are responsible for following the randomization and blinding procedures described in each clinical trial protocol.

More information, templates and examples are available at

https://royalpapworth.nhs.uk/application/files/3015/7485/1628/SOP069_Code_Breaking_in_Clinical_Trials_v3.0.pdf and

https://www.ucl.ac.uk/joint-research-office/sites/joint-research-office/files/4_inv_s06_sop_preparation_for_randomisation_blinding_and_code_breaks_v04_signed.pdf and

<https://www.porthosp.nhs.uk/research/docs/sop/PHTRDSOP014%20-%20SOP%20for%20Randomisation%20and%20blinding%20V1.0%2026Apr16.pdf> and

<https://qp.swansea.ac.uk/QPulseDocumentService/Documents.svc/documents/active/attachment?number=STU-SOP-DMS-002>

https://www.ed.ac.uk/files/atoms/files/ectu_sop_st_02_randomisation_and_blinding_procedures_v2.pdf

<https://www.porthosp.nhs.uk/research/docs/sop/PHTRDSOP014%20-%20SOP%20for%20Randomisation%20and%20blinding%20V1.0%2026Apr16.pdf>

10. SOP for Delegation of duties / responsibilities of clinical site

A SOP should describe the responsibilities of the PI and the procedures for identifying and delegating specific responsibilities to research team members for conducting clinical research. At a minimum, the Delegation of Authority Log should contain the individuals full name, signature, initials, duties assigned, date duties assigned, dates duties completed (if applicable) and signature of PI indicating that he/she has reviewed the duties delegated to an individual. Documents should include: A: Delegation of Authority Log; B: Study Team Training Log.

More information, templates and examples are available at

<https://ccts.osu.edu/sites/default/files/inline-files/SOP%2002%20Delegation%20of%20Responsibilities.pdf> and

<https://research.musc.edu/-/sm/research/resources/doing-research-files/delegation-of-authority-sop.ashx>

https://www.ucl.ac.uk/joint-research-office/sites/joint-research-office/files/UCLH_SOP_2_Definition_of_Responsibilities_V2_18_12_17.pdf

<https://www.porthosp.nhs.uk/research/docs/sop/PHTRDSOP012%20-%20SOP%20Delegation%20of%20Roles%20and%20Responsibilities%20-%20v1.1%2007%20April%202016.pdf> and

<https://www.epworth.org.au/-/media/project/epworth/epworthweb/documents/research/resources/sop-tm-14-delegation-of-duties-v10-23oct2019.pdf>

11. SOP for GCP training of site staff:

This SOP aims to provide clear guidance on the GCP training requirements so as to ensure that personnel involved in clinical research studies are aware of, and have an understanding of, the principles of GCP and the law on which they are based. This SOP should clarify the requirements for staff to be aware of the principles of Good Clinical Practice (GCP: ‘a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected’) and provide clear guidance on the frequency and type of GCP training that is required so as to comply with the regulations and policies.

More information, templates and examples are available at

https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-good-clinical-practice-e6r2-step-5_en.pdf

<https://processmap.tghn.org/mapnode/complete-training>

https://khpcto.co.uk/SOPs/02_trainingSOP.php

<https://khpcto.co.uk/includes/GCP14.php>

<https://ccts.osu.edu/sites/default/files/inline-files/2.%20TOC%20Glossary%20References.pdf>

http://s3-eu-west-1.amazonaws.com/files.royalfree.nhs.uk/SOP005_GCP_Training_v2.1_28_JUN_2021.pdf

12. SOP for Protocol training of site staff

Prior to conducting clinical research, the Principal Investigator (PI), sub-investigators, and study staff are required to receive training in the protection of human subject research participants (i.e. CITI), protection of personal health information (i.e. HIPAA), and in Good Clinical Practice (GCP) guidelines, Conflict of Interest (COI), and when applicable Biosafety Training. Additionally, the PI and all other study personnel must receive specific study/protocol training to ensure:

- Compliance with the investigational plan
- Protection of the rights, safety, and welfare of study participants, and
- Validity and integrity of study results

Protocol training is required for interventional clinical trials, including industry-sponsored trials, network trials, institutional trials, and investigator-initiated trials. The PI is responsible for all aspects of conduct for a clinical trial, but will generally delegate authority to perform certain functions or aspects of the study to sub-investigators, clinical research coordinators, study coordinators, data coordinators, or other study personnel. The PI and every other individual with a dedicated role on the study should receive adequate training prior to their involvement in the clinical trial.

This SOP should describe the processes which units will put in place to ensure that those involved in clinical research are demonstrably qualified by education, training and experience to perform their respective study roles and responsibilities.

More information, templates and examples are available at

https://qualitycompliance.research.utah.edu/resources/documents/uusop/uusop-03_protocol_training_17aug2020.pdf

<https://researchsupport.admin.ox.ac.uk/files/universitycoresop4trainingforclinicalresearchpdf>

https://siren.network/sites/default/files/docs/sop_training_of_personnel_final1b_1_.pdf

<http://www.westhertshospitals.nhs.uk/randd/documents/SOPs/gSOP-07-05%20-%20Research%20Staff%20Training.pdf>

13. SOP for Validation of software for CT data collection

The complexity of such systems has evolved rapidly during the last years from eCRF, ePROs, to various wearable devices used to continuously monitor trial participants for clinically relevant parameters and ultimately to the use of artificial intelligence (AI). All computerised systems used within a clinical trial should be subject to processes that confirm that the specified requirements of a computerised system are consistently fulfilled and that the system is fit for purpose. Validation should ensure accuracy, reliability and consistent intended performance, from design until decommissioning of the system or transition to a new system. The processes used for the validation should be decided upon by the

system owner (e.g. sponsors, investigators, technical facilities) and described, as applicable. System owners should ensure adequate oversight of validation activities and documentation (thereon) performed by contracted parties to ensure suitable procedures are in place and that they are being adhered to.

More information available at https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/draft-guideline-computerised-systems-electronic-data-clinical-trials_en.pdf

14. SOP for Registration of clinical study with clinical trial registry

The registration of all interventional trials is a scientific, ethical and moral responsibility. The procedures detailed on such SOP should cover the following aspects of clinical trial registration:

- Selecting a clinical trial registry
- Requesting a user account
- Creating a new record
- Updating and maintaining records
- Approving and releasing records
- Notifying stakeholders of registration
- Submitting summary results, protocol and statistical analysis plan

This SOP applies to the sponsor and other research team members that are involved in registering, updating, and reporting the results of a clinical trial on ClinicalTrials.gov or similar web registries. Note that the process outlined in this SOP for registering a clinical trial may also be used to register observational studies. i.e. the process is the same.

More information, templates or examples are available at

<https://apps.who.int/iris/bitstream/handle/10665/274994/9789241514743-eng.pdf>

<https://clinicaltrials.gov/ct2/manage-recs/how-register>

https://www.mcri.edu.au/images/research/training-resources/research-process-resources/sop_clinical_trial_registration.pdf

<https://www.uhhospitals.org/-/media/Files/For-Clinicians/Research/sc-401-registration-of-clinical-trials-in-ct-gov.pdf?la=en&hash=63C37947255E972D3AB10BFC9B87818F652F6749>

15. SOP for Laboratory equipment, supplies, and tests

This topic is broader than it appears, there are books and many subcategories of SOPs for laboratory research, both preclinical and clinical research, and also handling of samples. This may require more contributions from experts.

More information is available at

<https://www.pharmaguideline.com/p/sop-for-quality-control.html>

https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-q14-analytical-procedure-development-step-2b_en.pdf

16. SOP for Indemnification in clinical trials

The Regulations state that provision must be made for insurance or indemnity to cover the liability of the investigator and sponsor which may arise in relation to the clinical trial. Indemnification is a contractual agreement between the parties whereby one party, the indemnifying party, agrees to protect the other party, the indemnified party, against harms or losses brought by a third party that the indemnified party may incur. It's important to understand that indemnification protects the indemnified party against third-party claims that are brought against it, not claims by the indemnifying party against the indemnified party.

More information, templates, and examples are available at

https://khpcto.co.uk/SOPs/11_obtainingInsurance.php

<https://www.epworth.org.au/-/media/project/epworth/epworthweb/documents/research/resources/sop-rg-02-clinical-indemnity-and-insurance.pdf>

<https://cms.centerwatch.com/articles/12422-establishing-indemnification-in-a-clinical-trial-agreement-requires-precise-language>

<https://news.research.uci.edu/wp-content/uploads/2022/08/SOP-Clinical-Research-Subject-Injury.pdf>

B. List of SOPs applicable during clinical phases of study

17. SOP for Investigators' Meeting

An Investigator Meeting is a time for everyone involved with a new clinical trial to meet face to face and get familiar with the study, including learning about the roles in the study. An Investigator Meeting is usually a sponsor's responsibility, but a CRO may also be delegated with this task. It is a group meeting conducted, on behalf of sponsor, to train investigators and their lead clinical trial staff on trial related activities, standard operating procedures and to discuss the applicable regulatory picture. The content of an investigator meeting is usually trial specific, nevertheless a common agenda, on SOP's, Adverse Event Reporting, Source Documentation etc are also discussed. The meeting has multiple sessions on each aspect of the clinical trial, wherein the pros and cons of trial related activities are discussed. The discussion is also extended towards highlighting the expected issues that investigators may face and how to deal with them.

An investigator meeting is required/ helps to:

- Ensure that all investigators have an understanding of how to conduct the trial in strict compliance with the protocol, SOP's, guidelines and applicable regulations.
- To introduce the investigators with Case Report Forms (CRFs).
- Document the responsibilities of all participating investigators and its staff and train them prior to the start of the trial.
- Discuss the study protocol in detail.
- Facilitate communication between investigators.

The ICH guideline for GCP states that investigators "should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs" (4.9.1). Hence effective execution of IM is perceived as a reflection of the team's capabilities.

More information, templates and examples are available at

<https://www.jli.edu.in/blog/investigator-meeting-im-in-clinical-trials/>

https://alfresco-static-files.s3.amazonaws.com/alfresco_images/pharma/2014/08/22/ba4dead4-6bdc-4673-affe-4e36a7ee9b5c/article-15507.pdf

<https://www.openaccessjournals.com/articles/comprehensive-and-effective-system-of-standard-operating-procedures-for-investigatorinitiated-trials.pdf>

18. SOP for Site Initiation Visit

Site initiation is the process by which the sponsor is assured that the Principal Investigator (PI) at site is trained in the protocol and other instructions (as relevant) prior to issuing a 'study activation notice' which permits the site to commence the study. The study activation notice must be issued prior to obtaining consent from the first subject. This Standard Operating Procedure (SOP) describes the procedure to ensure that a site participating in a clinical trial sponsored by a manufacturer is initiated prior to the trial commencing and any procedures taking place. Site Initiation can only be conducted

after Ethics, Competent Authority [for Clinical Trials of Investigational Medicinal Products], sponsor and site permissions/ approvals have been received. Site initiation

for non-CTIMPs may be conducted using formats other than site visits (for example: a video conference, investigator meeting or teleconference). Site initiation should be conducted once all supplies (including study documentation) are available to the Investigator site. If certain supplies are not available to the site for any reason at the time of the site initiation, then this should be documented in the site initiation report (a further visit /training may be required).

More information, templates and examples available at

https://www.noclor.nhs.uk/sites/default/files/noclor-documents/Nochlor_Spon_S05_01%20Site%20Initiation%20and%20Activation%20%28Clinical%20Trials%29_uncontrolled.pdf

https://www.ed.ac.uk/files/atoms/files/ectu_sop_op_04_site_initiation_and_sponsor_authorisation_v2.0_0.pdf

https://www.westernhealth.org.au/EducationandResearch/Research/General%20Information/Documents/Standard%20Operating%20Procedures/WH_GCP/WH%20GCP%20SOP%20008%20Site%20Closure%20v3%20Jun19.pdf

https://health.ec.europa.eu/system/files/2022-02/guidanceclinicaltrials_covid19_en_1.pdf

<https://www.ncl.ac.uk/media/wwwnclacuk/newcastleclinicaltrialsunit/files/SOP%20TM-005-03%20Site%20Selection%20and%20Initiation.pdf>

19. SOP for Site Monitoring Visit (including Remote Monitoring)

Monitoring is defined 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, SOPs, The Principles of GCP, and the Medicines for Human Use (Clinical Trials) Regulations - where applicable. The purpose of monitoring is to verify that:

- The rights and well-being of the human subjects are protected
- The reported trial data are accurate, complete and verifiable from source documents
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), GCP and the applicable regulatory requirements.

Monitoring is an integral role in the quality control of a clinical trial and is designed to verify the ongoing quality of the study. All clinical trials sponsored or co-sponsored by one or more of the Partner Organisations will be monitored as described in this SOP.

More information, templates and examples are available at

https://khpcto.co.uk/SOPs/03_MonitoringSOP.php

<https://www.epworth.org.au/-/media/project/epworth/epworthweb/documents/research/resources/sop-tm-09-remote-and-on-site-monitoring-03jun2020-v2-signed.pdf>

<https://sites.veeva.com/wp-content/uploads/2020/04/Preview-of-Guide-to-Implementing-Remote-Monitoring-For-Clinical-Research-Sites.pdf>

20. SOP for Preparation and management of study files (Trial Master File & Site Master File) and Clinical study forms and logs

Investigators are responsible for maintaining strict control over investigational products to ensure that the product is used only for subjects enrolled in the study. The Accountability Log helps maintain study inventory.

Regulations require that a readily available Trial Master File is kept, which contains the essential documents relating to that clinical trial. In addition to demonstrating compliance with the principles of GCP, the filing of essential documents in an orderly, timely manner also greatly assists the smooth running of the trial and any future audit or inspection. It is the responsibility of the Principal Investigator to establish a TMF for each clinical trial they initiate, by utilising the TMF template associated with this SOP. Where there is an external Sponsor, the Principal Investigator may be provided with an ISF for their site, with the TMF being held by the Sponsor.

More information, templates and examples available at

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-content-management-archiving-clinical-trial-master-file-paper/electronic_en.pdf

<https://hub.ucsf.edu/accountability-logs>

https://khpcto.co.uk/SOPs/05_TMF.php

[https://www.westhertshospitals.nhs.uk/randd/documents/SOPs/new/SOP-06-07%20-%20TMF%20\(OCT%2021\).pdf](https://www.westhertshospitals.nhs.uk/randd/documents/SOPs/new/SOP-06-07%20-%20TMF%20(OCT%2021).pdf)

https://royalpapworth.nhs.uk/application/files/3416/0804/6415/SOP013_Trial_Master_File_Creation_and_Maintenance_v7.0_FINAL.pdf

https://www.ucl.ac.uk/joint-research-office/sites/joint-research-office/files/inv_s02_sop_for_the_preparation_and_maintenance_of_the_tmf-isf_v06_final_signed.pdf

https://www.ulh.nhs.uk/content/uploads/2016/10/SOP07_Trial_Master_File.pdf

21. SOP for Investigational Product storage, accountability & management, Shipment of Investigational Product and handling of loss or damage during shipment

The purpose of this SOP is to ensure that records of product delivery, inventory, subject use and return of drug and drug products to sponsors are maintained for clinical trials conducted. This standard operating procedure (SOP) describes the processes monitored at the investigator sites for the receipt, storage, dispensing, reconciliation and return or authorized destruction of the investigational drug (study drug).

It is responsibility of the PI to ensure appropriate management and handling of study products, including ordering, receipt, storage, use, accountability, and disposition of study products procured for use during a clinical trial, and where necessary, for labeling of study products, according to the protocol and Manual of Procedures (MOP).

More information available at

https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-responsibilities-sponsor-regard-handling-shipping-investigational-medicinal-products_en.pdf

https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/distribution/trs961-annex9-modelguidanceforstorageandtransport.pdf?sfvrsn=b80e925f_2

<https://ccts.osu.edu/sites/default/files/inline-files/SOP%2015%20Investigational%20Product%20Management.pdf>

<https://www.georgiacancerinfo.org/images/public/embedded/SM-307.01%20Investigational%20Product%20Management.pdf>

https://mhir.org/deptPages/em/downloads/GCP_SOP/SOP1106.pdf

https://www.maudsleybrc.nihr.ac.uk/media/219488/crf-stu-sop-1_management_and_accountability_ofimps_in_the_crf_v40-1.pdf

<https://www.epworth.org.au/-/media/project/epworth/epworthweb/documents/research/resources/sop-tm-05-handling-and-shipping-of-biological-samples-v1-15nov2019.pdf>

22. SOP for Adverse Event reporting and monitoring

This standard operating procedure (SOP) is intended to help facility managers/administrators and facility-based health care workers involved in index testing to 1) prevent adverse events from occurring, 2) encourage clients to report adverse events when they occur, 3) support providers [titles of relevant providers here] to respond to and document adverse events, and 4) inform site managers about how to investigate, report, and remediate adverse events.

More information, templates and examples are available at

<https://www.fhi360.org/sites/default/files/media/documents/resource-index-testing-adverse-event-sop.pdf>

https://covid19cra.org/wp-content/uploads/2021/05/5_COPCOV_SOP_AE-SAE_V2_24Feb21.pdf

https://www.ema.europa.eu/en/documents/sop/standard-operating-procedure-signal-management_en.pdf

https://mhir.org/deptPages/em/downloads/GCP_SOP/SOP1110.pdf

https://www.ucl.ac.uk/joint-research-office/sites/joint-research-office/files/5_inv_s05_sop_for_ae_sae_reporting_by_inv_v07.pdf

23. SOP for Data Safety Monitoring Board / Data Monitoring Committee

The Data and Safety Monitoring Board (DSMB) is an independent group of experts that advises NIDCR. The members of the DSMB serve in an individual capacity and provide their expertise and recommendations. The primary responsibilities of the DSMB are to 1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy, and 2) make recommendations to NIDCR concerning the continuation, modification, or termination of the trial. The DSMB considers study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study.

Prior to initiating any data review, the DSMB is responsible for defining its deliberative processes, including: event triggers that would call for an unscheduled review, stopping procedures that are consistent with the protocol, unmasking (unblinding), and voting procedures. The DSMB is also responsible for maintaining the confidentiality of its internal discussions and activities as well as the contents of reports provided to it. The DSMB should review each protocol for any major concern prior to implementation.

The DSMB should also assess the performance of overall study operations and any other relevant issues, as necessary.

Items reviewed by the DSMB include:

- Interim/cumulative data for evidence of study-related adverse events;
- Interim/cumulative data for evidence of efficacy according to pre-established statistical guidelines, if appropriate;
- Data quality, completeness, and timeliness;
- Performance of individual centers;
- Adequacy of compliance with goals for recruitment and retention, including those related to the participation of women and minorities;
- Adherence to the protocol;
- Factors that might affect the study outcome or compromise the confidentiality of the trial data (such as protocol violations, unmasking, etc.); and,
- Factors external to the study such as scientific or therapeutic developments that may impact participant safety or the ethics of the study.

More information, templates, examples are available at

<https://www.nidcr.nih.gov/research/human-subjects-research/toolkit-and-education-materials/interventional-studies/data-and-safety-monitoring-board-guidelines>

<https://www.fda.gov/media/75398/download>

24. SOP for Management of misconduct/fraud in clinical study

This procedure is designed to deal with concerns relating to research misconduct and it should be aligned with the local applicable laws. Fraud in clinical research is rare but serious. It has adopted the

following, non-exhaustive definition of misconduct and fraud which is based on guidance issued by the Wellcome Trust: “The fabrication, falsification plagiarism or deception in proposing, carrying out or reporting results of research or deliberate, dangerous or negligent deviations from accepted practices in carrying out research. It includes failure to follow established protocols or adhere to established ethical principles if this failure results in unreasonable harm to human beings, other living organisms or the environment and facilitating of misconduct in research by collusion in, or concealment of, such action by others. It includes intentional, unauthorised use, disclosure or removal of, or damage to, research-related property of another, including apparatus, materials, writings, data hardware or software or any other substance or devices used in or produced by the conduct of research. It also includes any plan or conspiracy or attempt to do any of the above.”

It does not include honest error or honest differences in the design, execution, interpretation or judgment in evaluating research methods or results or misconduct unrelated to the research process. Similarly, it does not include poor research unless this encompasses the intention to deceive.

More information, templates, examples are available at

<https://learning.eupati.eu/mod/book/view.php?id=328&chapterid=214>

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4340084/>

<https://www.jpccr.eu/Fraud-and-misconduct-in-clinical-research,71369,0,2.html>

https://www.isglobal.org/documents/10179/8829429/ISG-RES-SOP+Management+of+Suspected+Scientific+Misconduct_v1.0_17.09.202....pdf/63668f02-fd63-49cd-92de-2f8ccad3a4df

25. SOP for Premature termination or suspension of a clinical study

Premature termination is when a clinical study ends sooner than scheduled and may include how the sponsor should communicate such a decision, as in the following non-exhaustive examples:

- Determination that a study product’s efficacy is better or worse than anticipated.
- Occurrence of unforeseen study drug safety issues or if data from preclinical studies indicate a presence of unanticipated toxicity risks that cannot be adequately quantified.
- Futility: Determination that a demonstrable difference in relevant therapy/treatment proves unlikely.
- Operational futility: the protocol is determined to no longer be able to meet study objectives (e.g., fails to enrol participants within a requisite time period, study drug no longer available or usable), and is ended.

It is responsibility of the sponsor to decide, take actions and communicate to local authorities about study termination or suspension.

More information, templates, examples available at

Clinical Development and Medical Affairs Working Group - List of key SOPs for clinical operations, as of 20 February 2023

<https://www.niaid.nih.gov/sites/default/files/score-premature-termination-or-suspension-of-clinical-trial.pdf>

<https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice-scientific-guideline>

<https://www.qub.ac.uk/Research/Governance-ethics-and-integrity/FileStore/Fileupload,755683,en.pdf>

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5085068/>

<https://ichgcp.net/publications/early-discontinuation-of-a-ct>

C. List of SOPs applicable after clinical phase of study

26. SOP for Clinical Study Report

The purpose of this SOP is to describe the activities about the clinical study reports before the closure of a clinical study, e.g. preparation, review, approval and amendments, and distribution of clinical study reports.

Every clinical study must be described in a clinical study report, whether or not the study is fully completed as planned in the protocol. In the case of a study that is not fully completed as specified, the format of the report may be a shortened version, reflecting clearly the reasons why the study was not completed as planned. The clinical study report must be reviewed and approved internally to indicate formal authorisation by the sponsor/CRO before being released to the investigator, ethics committee/IRB or other reviewers external to the sponsor/CRO. The internally approved clinical study report must also be formally reviewed and approved by the external reviewers to indicate their approval. Any change to an approved clinical study report must be implemented by a formal amendment procedure. The distribution of all drafts and final versions of the clinical study report must be carefully restricted and controlled because of the confidential nature of the document and to ensure that all intended recipients have the correct final version.

More information, templates, examples available at

<https://onlinelibrary.wiley.com/doi/pdf/10.1002/qaj.314>

<https://studylib.net/doc/18443749/sop-tm-009-02-clinical-study-report>

27. SOP for Site Close-out Visit

The purpose of this SOP is to describe the procedures followed by key research personnel engaged in clinical research during a close-out visit with a sponsor representative from the time the monitor schedules the visit until all associated follow-up activities have been completed. This SOP applies to key research personnel involved in arranging, managing, participating in, and/or resolving outstanding items resulting from the study close-out visit. The Principal Investigator (PI), study coordinator, and/or other designated key personnel are responsible for study close-out visits.

More information, templates, examples available at

<https://www.umc.edu/Research/Research-Offices/Clinical-Trials/Researchers/Road-Map/Study-Closure/Study-Close-Out-Visit.html>

[https://khpcto.co.uk/SOPs/16_siteCloseOutSOP.php#:~:text=Investigator%20Site%20Close%20Out%20Procedures&text=Close%20Out%20is%20defined%20as,applicable%20regulatory%20requirement\(s\).](https://khpcto.co.uk/SOPs/16_siteCloseOutSOP.php#:~:text=Investigator%20Site%20Close%20Out%20Procedures&text=Close%20Out%20is%20defined%20as,applicable%20regulatory%20requirement(s).)

https://www.swslhd.health.nsw.gov.au/Ethics/content/pdf/SOP_CTSU_012%20Site%20Close-out.pdf

https://www.health.qld.gov.au/_data/assets/pdf_file/0021/147630/gcp_sop8.pdf

[https://www.westhertshospitals.nhs.uk/randd/documents/SOPs/new/SOP-21-05%20-%20Trial%20Closure%20\(Oct%202021\)%20.pdf](https://www.westhertshospitals.nhs.uk/randd/documents/SOPs/new/SOP-21-05%20-%20Trial%20Closure%20(Oct%202021)%20.pdf)

<https://www.epworth.org.au/-/media/project/epworth/epworthweb/documents/research/resources/sop-tm-12-trial-closeout.pdf>

28. SOP for Archival of essential documents

The purpose of this SOP is to describe the standard procedures to be followed when archiving essential documents related to clinical trials conducted under the auspices of the sponsor. The Sponsor shall ensure that the documents contained, or which have been contained, in the Trial Master File/Investigator Site File are retained for at least 5 years after the conclusion of the trial, or for a longer period where so required, and that during that period are (a) readily available to the licensing authority on request; and (b) complete and legible, as required in the Regulations and the ICH GCP guidelines (E6 - as revised). All essential documents relating to the clinical study must be archived in accordance with the SOP and the requirements of the local or international regulations:

The following may be considered for inclusion when archiving documentation (as applicable, depending on study requirements):

- Trial Master File (TMF)
- Investigator Site File (ISF)
- Pharmacy File
- Study Data (including paper CRFs, data collection sheets, clinical reports (e.g. lab reports, scan reports etc.)
- Data Management Files
- Statistics Master File
- Health Economics Files
- Clinical Files (participant files specific to any contact with clinical team may include consent forms, lab reports etc.)
- ISG (Investigational Supplies Group) Files

Site Documentation: For at least 5 years after the completion of a clinical study, as defined by the Regulations.

Trial Master File and all Essential Documentation: For a minimum of 25 years or until at least 2 years after the last approval of a marketing application in a region where the ICH guideline applies,

and

Until there are no pending or contemplating marketing applications in a region where the ICH guideline applies or as defined in the sponsor's protocol.

More information, templates, examples available at

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-content-management-archiving-clinical-trial-master-file-paper/electronic_en.pdf

https://khpcto.co.uk/SOPs/04_archivingSOP.php

<https://www.epworth.org.au/-/media/project/epworth/epworthweb/documents/research/resources/sop-tm-13-trial-archiving.pdf>

Clinical Development and Medical Affairs Working Group - List of key SOPs for clinical operations, as of 20 February 2023

<https://www.accord.scot/sites/default/files/CR009%20Study%20Closure%20and%20Archiving%20v5.0%20-%20signed.pdf>

<https://researchsupport.admin.ox.ac.uk/files/universitycoresop5archivingofessentialdocumentspdf>

<http://www.westhertshospitals.nhs.uk/randd/documents/SOPs/gSOP-17-04-%20Archiving%20Essential%20Documents.pdf>

<https://g14784.ideagenpulse.com/QPulseDocumentService/Documents.svc/documents/active/attachment?number=NJRO-GEN-SOP-012>

https://www.ucl.ac.uk/joint-research-office/sites/joint-research-office/files/12_spon_s21_sop_for_archiving_v05_signed.pdf

[https://www.westhertshospitals.nhs.uk/randd/documents/SOPs/new/SOP-17-05-%20Archiving%20Essential%20Documents%20\(OCT%202021\).pdf](https://www.westhertshospitals.nhs.uk/randd/documents/SOPs/new/SOP-17-05-%20Archiving%20Essential%20Documents%20(OCT%202021).pdf)

https://www.herts.ac.uk/_data/assets/pdf_file/0020/212492/2022-07-28-gSOP-17-02-Archiving-Essential-Documents-v2.pdf

<https://g14784.ideagenpulse.com/QPulseDocumentService/Documents.svc/documents/active/attachment?number=NJRO-GEN-SOP-012>

D. List of SOPs applicable for data management in clinical study

29. SOP for Sample size determination

Sample size determination is an essential step in planning a clinical study. It is critical to understand that different study designs need different methods of sample size estimation in order to maximise the chance that the study is large enough to estimate the primary outcome effect with sufficient precision and so that the study is not so large that far more participants than necessary are exposed to trial interventions. This SOP outlines the procedures for performing, checking and documenting the sample size determination.

The reference article reviews basic statistical concepts in sample size estimation, discusses statistical considerations in the choice of a sample size for randomized controlled trials and observational studies, and provides strategies for reducing sample size when planning a study.

To assist clinical researchers in performing sample size calculations, an online calculator for common clinical study designs was developed by some authors (cf. https://riskcalc.org/samplesize/SampleSizeEstimation_Chest2020.pdf).

More information, templates, examples are available at

https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-9-statistical-principles-clinical-trials-step-5_en.pdf

https://www.clinicaltrials.gov/ProvidedDocs/15/NCT01747915/SAP_000.pdf

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3148614/>

30. SOP for Data Management plan and activities

Data are the foundation of scientific discovery and future research. The purpose of this SOP is to provide the minimum standards required to ensure all Clinical Trial data, from the point of collection from source documents up to the point of archiving, excluding the requirements for statistical analysis, are managed, collected and verified in the appropriate manner. It describes the data collected across all Work Packages (WPs), the data collection methods, actions to secure data, and actions to secure FAIR (Findable, Accessible, Interoperable, Reusable) data. This SOP is to ensure the data are recorded correctly in order that Clinical Trials conducted within the partner institutions comply with Law.

It is important that each sponsor generate a good working plan for how to manage their data workflow and how to communicate that plan with new personnel, to ensure that the data remain intact and accessible. The scope of this Data Management Standard Operating Procedure (DMSOP) includes the Scientific Advisory, data manager, research staff, and Endpoint users, and defines both data governance and data management practices to create a specific plan that facilitates data collection, analysis, processing, and sharing.

In addition, a SOP may be needed to describe the procedures and activities for data management in clinical trials. The data management process typically encompasses: the design and production of the data capture tool for the collection of participant data from an investigator site(s); the design and construction of databases; the processing of the data, database lock and the production of the final

data set(s) for analysis. This SOP does not apply to the statistical analysis of Clinical Trial data. This SOP ensures compliance with ICH Guideline for Good Clinical Practice (ICH GCP) and national and international laws and regulations as specified in the SOP. If the sponsor is external, e.g. a pharmaceutical company, the sponsor's SOPs will be used, provided that these are in line with national and international laws, regulations and ICH Guideline for Good Clinical Practice (ICH GCP). The sponsor has overall responsibility for ensuring that data management in clinical trials is carried out in compliance with national and international laws, regulations, ICH GCP and this SOP. The sponsor's responsibilities shall be described in the quality system of the sponsor institution. Tasks can be delegated, and if so delegation of tasks should be documented.

More information, templates, examples available at

https://sops4ri.eu/wp-content/uploads/D1.2_Data-Management-Plan-1.pdf

<https://acdmglobal.org/wp-content/uploads/2022/01/ACDM22-Data-Management-Plan.pdf>

https://khpcto.co.uk/SOPs/18_DataSOP.php

https://medschool.duke.edu/sites/default/files/2021-10/data_management_sop_guidance_shared_resource.pdf

https://www.researchgate.net/publication/277630123_A_Model_Data_Management_Plan_Standard_Operating_Procedure_Results_From_the_DIA_Clinical_Data_Management_Community_Committee_on_Clinical_Data_Management_Plan

https://www.norcrin.no/documents/2013/05/data-management.pdf/?show_document

<https://researchsupport.admin.ox.ac.uk/files/coresop015datamanagementpdf>

31. SOP for Statistical Analysis Plan, Statistical analysis and Statistical report

The purpose of this SOP is to describe the procedure for the preparation of a statistical analysis plan (SAP) and report for a trial or study. The SAP contains the pre-specified statistical analyses to be performed upon completion of the study and detail of any interim analyses planned. Statistical analysis of a study should comply with the study protocol, GCP guidelines and other statutory and regulatory requirements. It is important that all analyses are repeatable, and that there are processes to ensure that the final report is accurate and to minimise bias. This SOP also applies to the statisticians performing the trial analyses and producing statistical reports.

The purpose of this SOP is to describe the procedure for the preparation of a statistical analysis plan (SAP) and to define the purpose and content of the SAP for a trial or study. The SAP contains the pre-specified statistical analyses to be performed upon completion of the study and detail of any interim analyses planned. Statistical analysis of a study should comply with the study protocol, GCP guidelines and other statutory and regulatory requirements. The details provided in the protocol may be sufficient for data analysis and reporting, but if not, a separate statistical analysis plan that provides full details may be written.

More information, templates, examples are available at

Clinical Development and Medical Affairs Working Group - List of key SOPs for clinical operations, as of 20 February 2023

https://cctu.org.uk/sites/default/files/2017-10/CCTU_SOP023%20Statistical%20Analysis%20Plan_1.pdf

https://www.ed.ac.uk/sites/default/files/atoms/files/ectu_sop_st_04_statistical_analysis_plans_v6.0_0.pdf

<https://g14784.ideagenpulse.com/QPulseDocumentService/Documents.svc/documents/active/attachment?number=NJRO-REG-SOP-010>

<https://qp.swansea.ac.uk/QPulseDocumentService/Documents.svc/documents/active/attachment?number=STU-SOP-DMS-004>

https://www.ema.europa.eu/en/documents/sop/standard-operating-procedure-data-analysis-eudravigilance_en.pdf

https://cctu.org.uk/sites/default/files/2017-10/CCTU_SOP023%20Statistical%20Analysis%20Plan_1.pdf

<https://irma.nps.gov/DataStore/DownloadFile/549067>

https://www.ed.ac.uk/sites/default/files/atoms/files/ectu_sop_st_05_statistical_analysis_and_reporting_v5.0.pdf

E. List of SOPs applicable for study site in clinical study

32. SOP for Ethics Committee submission & communication

A clinical study may not proceed before review and approval by a local independent ethics committee/IRB. The sponsor/CRO must facilitate the initial review by an ethics committee/IRB by submitting all the necessary documentation.

Interactions with the Institutional Ethics Committee (IEC) continue throughout the duration of a research study. Establishing effective ongoing IEC communication and reporting procedures are essential to the successful management of research studies. An effective working relationship with the IEC strengthens the team approach to the protection of participant safety in addition to enhancing compliance with applicable SOPs, guidelines and regulations governing research studies.

Any events that have an impact on the assessment of risk to the study subjects must be brought to the attention of the ethics committee/IRB. The sponsor/CRO must obtain documentation of the membership and working procedures of the ethics committee/IRB to ensure that there is no serious conflict of interest for any members, that the committee has sufficiently qualified members to enable a medical and scientific review of the proposed study and a review of all other ethical aspects of the study, and that the committee operates in accordance with international and local requirements, in the best interests of the study subjects.

Note: The sponsor is not responsible for preparing the SOP of the IEC/REC/IRB. However, sponsor needs to check if the REC have an SOP. The REC shall be constituted as per the prevailing rules of the country, and the flow of submissions and communications.

More information, templates or examples are available at

https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-good-clinical-practice-e6r2-step-5_en.pdf

<https://onlinelibrary.wiley.com/doi/epdf/10.1002/1099-1786%28200009%294%3A3%3C151%3A%3AAID-QAJ103%3E3.0.CO%3B2-K>

<https://apps.who.int/iris/handle/10665/207611>

<https://www.who.int/publications/i/item/9789240006218>

<http://www.dcs.gov.za/wp-content/uploads/2017/12/Amended-Standard-Operating-Procedures-February-2019-.pdf>

https://www.ema.europa.eu/en/documents/presentation/ethical-review-process-perspectives-ethics-committee-david-neal_en.pdf

https://s3.eu-west-2.amazonaws.com/www.hra.nhs.uk/media/documents/RES_Standard_Operating_Procedures_Version_7.5.1_August_2021_Final_Accessible_07IVkXt.pdf

<https://www.eoc.ch/dms/site-eoc/documenti/documenti/SCTO20good20operational20practice.pdf>

<https://onlinelibrary.wiley.com/doi/pdf/10.1002/1099-1786%28200009%294%3A3%3C151%3A%3AAID-QAJ103%3E3.0.CO%3B2-K>

https://www.health.qld.gov.au/_data/assets/pdf_file/0022/836221/AUSTRALIAN-ICH-GCP-SOP-50_V4.0.pdf

https://www.westernhealth.org.au/EducationandResearch/Research/General%20Information/Documents/Standard%20Operating%20Procedures/WH_GCP/WH%20GCP%20SOP%20003%20Notification%20to%20HREC%20Sponsor%20Insurer%20v3%20Jun19.pdf

https://cdn.pfizer.com/pfizercom/research/research_clinical_trials/ethics_committee_guide.pdf

33. SOP for Subject screening & recruitment and for Eligibility confirmation

The recruitment and screening phase of eligible subjects for a clinical study is frequently challenging. This standard operating procedure (SOP) should describe the processes for developing a recruitment plan and provides recommended recruitment definitions, strategies and activities covering the entire recruitment period, screening and rescreening. This SOP covers the study recruitment process starting from a base population of patients or healthy volunteers through to enrolled study participants.

In addition, a SOP should describe the process of handling requests for eligibility to the centralised procedure for medicinal products for human use, including the preparation of the eligibility report, the discussion of the requests and report at regulatory meeting and the preparation and sending of eligibility letters to applicants, as applicable.

More information, templates, examples are available at

https://mhir.org/deptPages/em/downloads/GCP_SOP/SOP1108.pdf

<http://kledeemeduniversity.edu.in/ethics/SOP/25-Patients-recruitment.pdf>

<https://ccts.osu.edu/sites/default/files/inline-files/SOP%2010%20Subject%20Screening%20and%20Recruitment.pdf>

https://medschool.cuanschutz.edu/docs/librariesprovider66/human-subject/sop-fda/oto-201---subject-recruitment-and-screening.pdf?sfvrsn=1aa95bb9_2

<https://www.beaumont.org/docs/default-source/policies-and-procedures/clinical-research-standard-operating-procedures/participant-recruitment-and-screening.pdf?sfvrsn=2>

<https://cctoblog.stanford.edu/2022/07/update-of-sop-determination-of-participant-eligibility-in-clinical-trials-effective-25-july-2022/>

https://www.hopkinsmedicine.org/institutional_review_board/about/compliance_monitoring/researchers_tool_kit/standard_operating_procedure.pdf

34. SOP for Informed consent process and documentation

In the clinical research context, informed consent is a person's voluntary agreement, based upon adequate knowledge and understanding of relevant information, to participate in a research study. This SOP describes the procedures for obtaining and documenting informed consent from a study

subject or the subject's legal representative for enrolment in a Clinical Trial of an Investigational Medicinal Product (CTIMP) study. A verbal explanation is given and an informed consent document is provided to a subject to ensure that he or she understands what he or she is signing. The consent process continues throughout the subject's participation in the study.

More information, templates and examples available at

<https://www.uthscsa.edu/sites/default/files/Services/forms/informedconsentprocess.pdf>

https://khpcto.co.uk/SOPs/07_consentSOP.php

<https://research.ucdavis.edu/wp-content/uploads/HRP-090-SOP-Informed-Consent-Process-for-Research.pdf>

https://mhir.org/deptPages/em/downloads/GCP_SOP/SOP1107.pdf

35. SOP for Source documentation

The medical record of the subject before, after, and during the clinical trial is a Source Document. One of the most common inspection findings in investigator site inspections is lack of reliable, accurate and adequate source documentation, being the most common pitfall identified during sponsor audits. The importance of good documentation practice needs to be emphasized to investigator sites to ensure that the study results are built on the foundation of credible and valid data. This means that there are various types of data that are classed as source data. For example:

- Information which the investigator writes down in the patient's record.
- Values in a lab result sheet or direct printout from a measuring device (e.g. analysis scale, spectrophotometer).
- Answers which a patient enters into a questionnaire.

More information, templates, examples available at

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3121265/>

<https://www.niaid.nih.gov/sites/default/files/score-source-documentation.pdf>

<https://ccrps.org/clinical-research-blog/tag/what+is+a+source+document>

<https://ccts.osu.edu/content/data-management-crfs-and-source>

36. SOP for Biological sample processing, storage & shipment

The purpose of this Standard Operating Procedure (SOP) is to describe the processes for the safe processing, storage and shipment of samples within the Clinical Research Facility (CRF). This SOP applies to all samples collected from study subjects, which are to be processed and/or stored by CRF staff in the sample processing areas. This SOP also applies to users of the CRF using the sample processing areas to process and/or store samples.

More information, templates, examples available at

<https://www.nhsfife.org/media/33755/sop25-sample-processing-and-storage-v3-final.pdf>

<https://www.kcl.ac.uk/cveda/assets/cveda-biologicalsampling-sop-mar2017.pdf>

https://link.springer.com/chapter/10.1007/978-3-319-98857-3_4

<https://www.usf.edu/research-innovation/comparative-medicine/documents/sops/s616-shipping-samples-for-b-virus-testing.pdf>

<https://www.researchsop.com/2022/03/STANDARD-OPERATING-PROCEDURE-FOR-MANAGING-BIOLOGICAL-SAMPLES-DURING-CLINICAL-TRIALS.html>

37. SOP for Dispensing of Investigational Products

This SOP should describe the process for the receipt, storage, dispensing, reconciliation and return or authorized destruction of an investigational product (IP; e.g., drug or device).

More information, templates, examples available at

<https://ccts.osu.edu/sites/default/files/inline-files/SOP%2015%20Investigational%20Product%20Management.pdf>

<https://www.epworth.org.au/-/media/project/epworth/epworthweb/documents/research/resources/sop-tm-04-imp-receipt-storage-dispensing-return-and-destruction.pdf>

https://www.health.qld.gov.au/_data/assets/pdf_file/0027/147654/gcp_sop5.pdf

38. SOP for Handling and reporting of adverse events and serious adverse events

The purpose of this standard operating procedure (SOP) is to ensure that adverse and serious adverse events are defined, recorded, reported, and evaluated as required by the Institutional Review Board (IRB). Adverse events are not necessarily physical in nature; attention must be paid to psychological harm (such as depression, thoughts of suicide, etc.), threats to privacy, or participant safety. An event is considered serious and must be reported when the participant experiences an unusually strong response, recurring problems, and/or Serious Adverse Event (SAE), as defined by ICH:

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Application of this SOP starts at the time the subject signs the initial Informed Consent Form and continues through 30 days after the subject completes the active part of the study, unless otherwise stated. Investigators are responsible for prompt reporting to the IRB of "any unanticipated problems involving risks to participants or others."

More information, templates, examples available at

https://covid19crc.org/wp-content/uploads/2021/05/5_COPCOV_SOP_AE-SAE_V2_24Feb21.pdf

<https://www.southalabama.edu/departments/research/compliance/humansubjects/resources/601.adverse.event.reporting.pdf>

https://www.ohri.ca/ohsn-reb/forms/SOP012_08_SADRRreporting_FINAL_15May2019.pdf

<https://www.karger.com/Article/Pdf/75011>

39. SOP for Handling of acute clinical emergency

A medical emergency is an acute, unplanned event that has the potential for serious harm or death. This includes for example anaphylaxis and cardiorespiratory arrest. The purpose of this Standard Operating Procedure (SOP) is to describe how medical emergencies are managed in the CRF. In particular, the SOP should describe the procedure to un-blind subjects in an emergency situation. This SOP should be referred to code breaking procedures, whenever a situation arises whereby it becomes necessary to unblind subjects in an emergency situation.

More information, templates, examples available at

<https://www.maudsleybrc.nihr.ac.uk/media/181816/crf-cl-sop-6-management-of-medical-emergencies-in-the-crf-v30.pdf>

https://buckup-cuh-production.s3.amazonaws.com/documents/RDSOP008_Emergency_Unblinding_VCe15S9.pdf

<https://www.health.gov.au/sites/default/files/documents/2021/02/national-standard-operating-procedures-for-clinical-trials-national-standard-operating-procedures-for-clinical-trials-including-teletrials-in-australia.pdf>

<https://www.cdc.gov/vhf/ebola/clinicians/emergency-services/patient-handoff.html>

https://royalpapworth.nhs.uk/application/files/3015/7485/1628/SOP069_Code_Breaking_in_Clinical_Trials_v3.0.pdf

40. SOP for Handling of subject withdrawal or dropout during the study

This SOP should clarify the steps research personnel must take and the documentation required when a study participant withdraws consent, the principal investigator (PI) removes a participant from the study, or when the participant is lost to follow-up. When a subject chooses to withdraw from (i.e., discontinue his/her participation in) an ongoing research study, or when an investigator terminates a subject's participation in such a research study without regard to the subject's consent, the investigator may retain and analyze already collected data relating to that subject, even if that data includes identifiable private information about the subject.

More information, templates, examples available at

<https://www.hhs.gov/ohrp/sites/default/files/ohrp/policy/subjectwithdrawal.pdf>

<https://www.beaumont.org/docs/default-source/policies-and-procedures/clinical-research-standard-operating-procedures/participants-removed-withdrawn-or-lost-to-follow-up.pdf?sfvrsn=2>

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3737004/>

<https://www.mcw.edu/-/media/MCW/Departments/Human-Research-Protection-Program/Researchers/IRB-SOPs/IRB-SOP-Withdrawal-of-Informed-Consent-FINAL.pdf>

41. SOP for Handling and reporting of Protocol deviations and violations

The purpose of this Standard Operating Procedure (SOP) is to describe the process for detecting, documenting, assessing, tracking, and closing of protocol deviations (PDs) detected by study personnel at site or by sponsor, e.g. during monitoring (including data monitoring by data managers) of clinical trials. This SOP ensures that issues are managed in compliance with ICH Guideline for Good Clinical Practice (ICHGCP) and national and international laws and regulations.

More information, templates, examples available at

https://www.norcrin.no/documents/2020/03/protocol-deviation-handling.pdf/?show_document

https://www.uts.edu.au/sites/default/files/2018-02/NEW_FINAL_4.5%20Protocol%20Deviations%20and%20Violations%202018.pdf

42. SOP for Remuneration of clinical study participants

The purpose of this SOP is to facilitate the management of payments to study subjects participating in human subject research (HSR). Payments for participation in research studies should not be considered a benefit; rather it is compensation for a subject's time, effort and for study-related expenses. Patient stipend is to cover cost associated with participation in the research study. This may include cost of travel to and from Center/Clinic, bus fare, taxi, gas, child care, meals. This SOP should detail available payment options, procedures for disbursement, requirements for social security number collection, and tax reporting.

More information, templates, examples available at

https://www.research.vt.edu/content/dam/research_vt_edu/hrpp/files/sops/sop-hrpp-092.1-payments-to-research-participants.pdf

<https://www.nova.edu/ocr/forms/OCR-RR-005%20%20Compensation%20For%20Research%20Subjects.pdf>

<https://www.mcw.edu/-/media/MCW/Departments/Human-Research-Protection-Program/Researchers/IRB-SOPs/IRB-SOP-Subject-Payments-for-Research-Participation.pdf?la=en>

<https://ctsi.wakehealth.edu/announcements/2019/10/new-clinical-research-participant-compensation-policy-and-sop>

https://siren.network/sites/default/files/siren_sop_participant_reimbursement_.pdf

43. SOP for Maintenance of Site Master File

Regulations require that a readily available Clinical Trial Master File is kept, which contains the essential documents relating to that clinical trial. In addition to demonstrating compliance with the principles of GCP, the filing of essential documents in an orderly, timely manner also greatly assists the smooth running of the trial and any future audit or inspection.

More information, templates, examples available at

https://khpcto.co.uk/SOPs/05_TMF.php

https://www.ucl.ac.uk/joint-research-office/sites/joint-research-office/files/inv_s02_sop_for_the_preparation_and_maintenance_of_the_tmf-isf_v06_final_signed.pdf

<https://www.gmpsop.com/sample/QMS-030-Preparation-Maintenance-and-Change-Control-of-Master-Documents-sample.pdf>

44. SOP for Maintenance of confidentiality of information

This Standard Operating Procedure (SOP) describes the procedure to ensure the integrity and confidentiality of data collected within the framework of a study and the privacy of study participants.

More information, templates, examples available at

https://www.uwo.ca/research/docs/ethics/SOPs/REB_N107.002_Privacy_and_Confidentiality_of_Personal_Information-Investigator.pdf

<https://www.bcpft.nhs.uk/documents/policies/i/1626-information-governance-sop-01-confidentiality-procedure/file>

<https://researchsupport.admin.ox.ac.uk/files/universitycoresop13confidentialityandsecurityofpersonaldata.pdf>

<https://proceduresonline.com/trixcms1/media/11377/standard-operating-procedure-handling-personal-information.pdf>

45. SOP for Audit of clinical study (by sponsor, EC or regulatory agency)

An audit is “A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor’s Standard Operating Procedures (SOPs), Good Clinical Practice (GCP) and the applicable regulatory requirements.” (ICH GCP 1.6) The purpose of auditing is to:

- Ensure participant and staff safety.
- Assist researchers with compliance to regulatory requirements and policy.
- Improve research systems and data quality.
- Prepare researchers for external audit processes.
- Demonstrate robust research processes to external funders and industry.

More information, templates, examples available at

https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/annex-iv-procedure-conducting-gcp-inspections-requested-chmp-sponsor-contract-research-organisations_en.pdf

https://www.herts.ac.uk/_data/assets/pdf_file/0006/212496/2022-08-10-gSOP-23-02-Quality-Assurance-Audit-v2.pdf

F. List of SOPs applicable for regulatory communication in clinical study

46. SOP for Regulatory submission and communication

The purpose of this SOP is to describe procedures for timely, transparent, and effective communications between investigational new drug application (IND) sponsors and regulators at critical junctures in product development, which may facilitate earlier availability of safe and effective medicinal products to the public.

More information, templates, examples available at

<https://www.fda.gov/files/drugs/published/Best-Practices-for-Communication-Between-IND-Sponsors-and-FDA-During-Drug-Development.pdf>

https://www.hopkinsmedicine.org/institutional_review_board/about/compliance_monitoring/researchers_tool_kit/standard_operating_procedure.pdf

List of key SOPs for clinical operations v3, by Sonia Pagliusi, 10 Jan 2023, for comments

List of key SOPs for clinical operations v5, edited by Sonia Villasenor & Sonia Pagliusi, as to the meeting of CDMA WG, on 09 Feb 2023, 12 pm to 1:30 pm. 10 February 2023, for final WG approval.

List of key SOPs for clinical operations v6, edited by Sonia Pagliusi, following comments by Dr. Sahoo, 19 Feb 2023

Helpful References

1. <https://onlinelibrary.wiley.com/doi/epdf/10.1002/%28SICI%291099-1786%28199809%293%3A3%3C137%3A%3AAID-QAJ76%3E3.0.CO%3B2-E>
2. <https://onlinelibrary.wiley.com/doi/epdf/10.1002/1099-1786%28200003%294%3A1%3C31%3A%3AAID-QAJ98%3E3.0.CO%3B2-G>
3. <https://onlinelibrary.wiley.com/doi/epdf/10.1002/1099-1786%28200006%294%3A2%3C95%3A%3AAID-QAJ100%3E3.0.CO%3B2-7>
4. <https://onlinelibrary.wiley.com/doi/epdf/10.1002/1099-1786%28200009%294%3A3%3C151%3A%3AAID-QAJ103%3E3.0.CO%3B2-K>
5. <https://onlinelibrary.wiley.com/doi/epdf/10.1002/1099-1786%28200012%294%3A4%3C211%3A%3AAID-QAJ122%3E3.0.CO%3B2-2>
6. <https://onlinelibrary.wiley.com/doi/epdf/10.1002/qaj.125>
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8. <https://onlinelibrary.wiley.com/doi/epdf/10.1002/qaj.144>
9. <https://onlinelibrary.wiley.com/doi/epdf/10.1002/qaj.151>
10. https://www.researchgate.net/publication/250566569_Standard_operating_procedures_for_clinical_research_personnel_-_Part_10
11. <https://onlinelibrary.wiley.com/doi/epdf/10.1002/qaj.168>
12. <https://onlinelibrary.wiley.com/doi/10.1002/qaj.172>
13. <https://onlinelibrary.wiley.com/doi/epdf/10.1002/qaj.187>
14. <https://onlinelibrary.wiley.com/doi/epdf/10.1002/qaj.198>
15. <https://onlinelibrary.wiley.com/doi/epdf/10.1002/qaj.204>
16. <https://onlinelibrary.wiley.com/doi/epdf/10.1002/qaj.222>
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18. <https://onlinelibrary.wiley.com/doi/abs/10.1002/qaj.243>
19. <https://onlinelibrary.wiley.com/doi/epdf/10.1002/qaj.253>
20. <https://onlinelibrary.wiley.com/doi/epdf/10.1002/qaj.266>

Clinical Development and Medical Affairs Working Group - List of key SOPs for clinical operations, as of 20 February 2023

21. <https://onlinelibrary.wiley.com/doi/epdf/10.1002/qaj.280>

22. <https://onlinelibrary.wiley.com/doi/epdf/10.1002/qaj.292>

23. <https://onlinelibrary.wiley.com/doi/epdf/10.1002/qaj.314>

Compilation of many parts of the above SOPs

[https://www.sciencegate.app/document/10.1002/1099-1786\(200003\)4:1%3C31::aid-qaj98%3E3.0.co;2-g](https://www.sciencegate.app/document/10.1002/1099-1786(200003)4:1%3C31::aid-qaj98%3E3.0.co;2-g)

<https://www.openaccessjournals.com/articles/comprehensive-and-effective-system-of-standard-operating-procedures-for-investigatorinitiated-trials.pdf>

John's Hopkins Essential Standard Operating Procedures & Sample Templates

https://www.hopkinsmedicine.org/institutional_review_board/about/compliance_monitoring/researchers_tool_kit/standard_operating_procedure.pdf

EMA GUIDANCE ON THE MANAGEMENT OF CLINICAL TRIALS DURING THE COVID-19 (CORONAVIRUS) PANDEMIC

https://health.ec.europa.eu/system/files/2022-02/guidanceclinicaltrials_covid19_en_1.pdf