Writing a GCP Compliant Trial Protocol

DOCUMENT DETAILS	
Document Type	Standard Operating Procedure
Document Name	KHP-CTO/CT/SOP 9.0 Writing a Trial Protocol
Version	v8.0
Effective from	28 Apr 2026
Review date	28 Apr 2029
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1. BACKGROUND AND PURPOSE

The Clinical Trial should be described in a clear, concise, scientifically sound and operationally feasible protocol (ICH GCP E6 (R3): Principle 8).

A protocol is 'a document that describes the objectives, design, methodology, statistical considerations and organisation of a clinical trial' (definition from the Regulations).

'The design and procedure of the research are clearly described and justified in a research proposal or protocol' (UK Policy Framework: Principle 6). 'This is important so that the researchers can all understand consistently what they are supposed to do and so that the research can be properly analysed and, if necessary, reproduced' (UK Policy Framework: Paragraph 9.4).

'A research project is started only if a research ethics committee and any other relevant body or the Medicines and Healthcare products Regulatory Agency (MHRA) have favourably reviewed the research proposal or protocol and related information…' (UK Policy Framework: Principle 9).

The purpose of this SOP is to describe the process for writing the protocol for a Clinical Trial.

2. SCOPE

This SOP applies to all Clinical Trials (CTIMPs) sponsored by KHP.

3. PROCEDURE

3.1 Writing the protocol for the Clinical Trial Authorisation (CTA) submission

Task	Responsibility	Activity
1	Chief Investigator	Overall responsibility for the development, content, accuracy, and maintenance of the trial protocol.
2	Chief Investigator	Ensure that the protocol contains all required information to support CTA submission. • The KHP-CTO protocol template (See **CTIMP Protocol Template.docx**) includes all required sections and may be used without further approval • If the CI wishes to use an alternative protocol template, the template must be submitted to the Setup CRA for review prior to use

3	Setup CRA	Review any alternative protocol template proposed by the CI. Where all elements contained in the KHP-CTO protocol template (See **CTIMP Protocol Template.docx**) are present, confirm approval of the template for use for the Clinical Trial.
4	Chief Investigator or delegate	Complete the protocol using the approved template. The CI remains responsible for the content of the protocol, although the drafting of specific sections may be delegated to appropriately qualified individuals. The protocol must contain sufficient detail to ensure that the Clinical Trial can be conducted as described without the need for Clinical Trial-specific SOPs. Supporting documents (e.g. worksheets or guidance documents) may be produced where appropriate. <u>Informed Consent Process</u> The protocol should explicitly state: • Any Clinical Trial-specific consent process requirements. • The minimum qualifications or requirements for individuals involved in obtaining consent. Where consent involves multiple stages, different minimum qualifications or requirements may be specified for each stage. • Any Clinical Trial-specific requirements for verifying participant identity, including where consent is obtained remotely (e.g. use of video, in line with ICH GCP E6 (R3) principles). • Where participants are expected to lack capacity, any Clinical Trial-specific requirements for identifying and appointing a suitable Legally Acceptable Representative. • Any Clinical Trial-specific requirements for the use of translators and/or Witnesses, including how suitability should be determined. <u>Clinical Trial Activities</u> State any Clinical Trial-specific requirements for carrying out protocol-mandated activities, including where these differ from local standard practice. <u>Adverse Event (AE) Reporting</u> State any Clinical Trial-specific AE reporting requirements. • Unless otherwise stated in the protocol, AE reporting begins when informed consent is first obtained from the participant.

		• AE reporting ends at the participant's final protocol-defined visit, or at the end of the participant-specific data collection period where no visits are specified. <u>Serious Adverse Event (SAE) Reporting</u> Define any Clinical Trial-specific SAE reporting requirements. Where applicable, specify: • Any AEs that meet regulatory seriousness criteria but should not be reported as SAEs for the purposes of the Clinical Trial; and • Any AEs that do not meet seriousness criteria but must be reported to the KHP-CTO within 24 hours (e.g. Important Medical Events). In accordance with the Regulations, such requirements must be stated in the protocol even where they are also described in the Investigator's Brochure. **Please note**: Avoid defining hospitalisation solely by duration (e.g. "24 hours or more"). Regulatory seriousness relates to inpatient admission, not elapsed time, and duration-based definitions may cause inconsistency with regulatory expectations. <u>Minimising Burden</u> Where possible, the protocol should minimise burden on participants and Trial Location Teams, for example by: • Using data collected during routine clinical care • Using local laboratories where appropriate • Reducing unnecessary transcription or duplication of data <u>Default Practice</u> Where no Clinical Trial-specific instruction is stated in the protocol, Principal Investigators will follow: • Local SOPs; or • Local custom and practice where no SOP exists. <u>Human Biological Sample (HBS) Sampling Order</u> Where multiple HBS are required at a single timepoint, consider specifying the order of sampling to demonstrate the following considerations have been addressed: • Protection of participants' rights, safety, and wellbeing; and • Reliability and credibility of the Clinical Trial results

5	Trial Statistician or delegate	Complete the statistical section of the protocol. Detailed statistical methods may be documented separately (e.g. in a Statistical Analysis Plan), where appropriate.
6	Chief Investigator	Ensure that the Clinical Trial objectives, participant selection criteria, efficacy and/or safety assessments, and schedule of activities are peer reviewed prior to finalisation of the protocol. Where peer review of a Clinical Trial summary was completed as part of funder assessment and is consistent with the draft protocol, repeat peer review is not required. In such cases, existing peer review documentation should be filed in the TMF.
7	Chief Investigator	In accordance with the UK Policy Framework: Paragraph 9.2 (a), the CI must be satisfied that appropriate and effective PPIE has been considered. Where appropriate, arrange PPIE review of the Clinical Trial objectives, participant selection criteria, assessments, and schedule of activities prior to protocol finalisation. Record PPIE review outcomes in the TMF.
8	Chief Investigator	Finalise the first draft of the protocol and send to the Sponsor for review. File Sponsor correspondence in the TMF.
9	Sole Sponsor/NHS Co-Sponsor R&D Dept.	Review the draft protocol and provide feedback to the CI, as appropriate. If there's no feedback to be given to the CI, send written approval of the protocol to the CI.
10	Setup CRA	Review the protocol and provide feedback to the CI, as appropriate. Ensure feedback is saved to the TMF. If there's no feedback to be given to the CI, send written approval of the protocol to the CI. Save written approval in the TMF.
11	Chief Investigator	If the Sole Sponsor/NHS Co-Sponsor R&D Dept. requires changes to be made to the protocol, the CI should make such changes and send back to the Sole Sponsor/NHS Co-Sponsor R&D Dept. for review. The CI should repeat this process until the Sole Sponsor/NHS Co-Sponsor R&D Dept. approves the protocol. If the Setup CRA requires changes to be made to the protocol, the CI should make such changes and send back to the Setup CRA for review. The CI should repeat this process until the Setup CRA approves the protocol.

12	Chief Investigator	Save written approval of the protocol from the Sole Sponsor/NHS Co-Sponsor R&D Dept. in the TMF. Save written approval of the protocol from the Setup CRA in the TMF. Save written approval of the protocol from the Sole Sponsor/NHS Co-Sponsor R&D Dept. and the Setup CRA in the CTA Submission Package.
13	Chief Investigator	Sign the final protocol for CTA submission. Wet-ink signatures must be scanned and included with the submission (photographs are not acceptable). Electronic signatures must include a timestamp. Ensure the signed protocol is included in the CTA Submission Package and filed in the TMF.

3.2 Modifying the protocol

Task	Responsibility	Activity
1	Chief Investigator	Modifications to the protocol can be made at any point before the End of Trial (EoT) notification is submitted. The CI is responsible for making sure the appropriate Modifications are made. Information about Modifications can be found in **SOP 12.0 Application & Maintenance of a Clinical Trial Authorisation** The protocol must be periodically reviewed in accordance with **SOP 22.0 Proportionality and Risk Assessment for Clinical Trials of Investigational Medicinal Products**
2	Chief Investigator	Sign the modified protocol for the Modification submission package. Wet-ink signatures must be scanned and included with the submission (photographs are not acceptable). Electronic signatures must include a timestamp. Ensure the signed protocol is included in the Modification submission package and filed in the TMF.

4. RELATED TEMPLATES

- CTIMP Protocol Template.docx

5. RELATED DOCUMENTS

SOPs

SOP 12.0 Application & Maintenance of a Clinical Trial Authorisation
SOP 22.0 Proportionality and Risk Assessment for Clinical Trials of Investigational Medicinal Products

Other Documents

HRA Protocol Guidance
https://www.hra.nhs.uk/planning-and-improving-research/research-planning/protocol/

The HRA CTIMP Protocol Development Tool
https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Fs3.eu-west-2.amazonaws.com%2Fwww.hra.nhs.uk%2Fmedia%2Fdocuments%2Fctimp-protocol-development-tool.docx&wdOrigin=BROWSELINK

6. CHANGE HISTORY

CHANGE HISTORY			
Date	Version Number	Change details	Approved by
01 Oct 2010	2.0	Transfer to King's Health Partners Livery, clarification that all study specific procedures must be defined in the trial protocol. Minor amendments to remove duplication in SOP.	Jackie Powell
01 Oct 2012	3.0	Scheduled review and re-branding of JCTO to KHP-CTO.	Jackie Powell
19 Dec 2014	4.0	Scheduled review and consistency check.	Jackie Pullen
28 Feb 2017	5.0	Scheduled review, glossary update and inclusion of HRA changes.	Jackie Pullen
24 Oct 2018	5.1	Minor amendment to include trials managed by KHP-CTO.	Jackie Pullen
24 Feb 2020	6.0	Minor amendment to replace the word 'subject' with 'participant'. Additional text added relating to consent, randomisation and use of CRFs as source data.	Jackie Pullen
01 Jun 2023	7.0	Scheduled review. Updates to protocol content including data confidentiality statement, database lock as EoT definition, IRAS number to be main	Kirsty Hough

		identifier, removal of lab and site details on the cover page.	
23 Apr 2026	8.0	SOP transposed into new SOP template. ICH GCP E6 (R3) and Regulations updates including: • Removing information from the SOP which is already included in the KHP-CTO protocol template (to reduce duplication) • Adding requirements for generalisability, proportionality and assessment of burden per the Regulations	Ann-Marie Murtagh

7. GLOSSARY

Adverse Event (AE) - Any untoward medical occurrence in a participant who has been administered an IMP, which does not necessarily have a causal relationship with that IMP.

Chief Investigator (CI) – The overall lead researcher for a Clinical Trial (Outside the UK the term 'Coordinating Investigator', 'Principal Investigator' or 'Investigator' may be used for the overall lead researcher for a Clinical Trial). Chief Investigators are responsible for the overall conduct of a Clinical Trial.

Clinical Research Associate (CRA) – A staff member employed by the KHP-CTO who conducts monitoring activities for a Clinical Trial, including but not limited to the initiation phase, routine phase, and close down phase.

Clinical Trial of an Investigational Medicinal Product (CTIMP) - Any investigation in human participants (other than a non-interventional trial) intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more medicinal products and/or to identify any adverse reactions to one or more such products and to study absorption, distribution, metabolism and excretion of one or more such products with the object of ascertaining the safety and/or efficacy of those products. Includes clinical trials of ATMPs.

Clinical Trial Authorisation (CTA) – Authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA) to conduct a Clinical Trial. No Clinical Trial can commence in the UK without both a CTA and a favourable ethical opinion. Applications to the MHRA and the Research Ethics Committee (REC) may be made in parallel.

Co-Sponsors – Two organisations that take responsibility for the initiation, management and financing (or arranging of the financing) in relation to a Clinical Trial. The Co-Sponsors agree how the Sponsor functions for the Clinical Trial are divided between themselves and document this accordingly.

CTA Submission Package - The CTA submission form and all necessary supporting documents for the CTA submission.

End of Trial (EoT) – The end of the Clinical Trial as defined in the protocol. The end of the Clinical Trial is typically expressed as a condition-based event, not a predetermined date.

Good Clinical Practice (GCP) - An international ethical and scientific quality standard for designing, conducting, recording, and reporting Clinical Trials that involve human participants. It ensures the safety, well-being, and rights of participants are protected while maintaining the credibility and accuracy of trial data. GCP is crucial for safeguarding participants and ensuring Clinical Trials produce reliable, scientifically valid results.

Health Research Authority (HRA) – The national body in England responsible for protecting and promoting the interests of patients and the public in health and social care research.

Human Biological Samples (HBS) – Materials of human origin collected for clinical care or research purposes, which contain biological information about an individual. They typically include tissues, cells, blood, blood components, bodily fluids, DNA, RNA, and other derivatives obtained directly or indirectly from a human body.

ICH GCP E6 (R3) – The International Council for Harmonisation – Good Clinical Practice, Guideline E6 (Revision 3). This is an internationally recognised ethical and scientific quality standard for the design, conduct, oversight, recording, and reporting of Clinical Trials.

Important Medical Event (IME) - An Adverse Event or Adverse Reaction that may not immediately result in death, be life-threatening, or require hospitalisation, but which, in the judgement of a medically qualified individual, may jeopardise the participant or require medical or surgical intervention to prevent one of those serious outcomes.

Investigator's Brochure (IB) - A Sponsor-prepared reference document that compiles the clinical and non-clinical data on an IMP that are relevant to its use in a Clinical Trial. It's intended to provide Clinical Trial staff with sufficient information to understand the rationale for the Clinical Trial, the known and potential risks and benefits of the IMP, including Adverse Reactions, and the appropriate management of participants. Where the IMP has a Marketing Authorisation, an SmPC will be available and it will supersede the IB as the RSI.

King's Health Partners (KHP) - King's College London, Guy's and St Thomas' NHS Foundation Trust, King's College Hospital NHS Foundation Trust, and South London and Maudsley NHS Foundation Trust.

King's Health Partners Clinical Trials Office (KHP-CTO) – The department established by King's College London, Guy's and St Thomas' NHS Foundation Trust, King's College Hospital NHS Foundation Trust, and South London and Maudsley NHS Foundation Trust to 1) undertake the set up and financial Management of commercial research hosted by one or more of the KHP Partners, and 2) undertake the regulatory submissions and oversight, as well as monitoring activity for non-commercial research studies sponsored by one of the KHP Partners.

Legally Acceptable Representative (LAR) – An individual or body authorised under applicable UK law to give informed consent on behalf of a prospective Clinical Trial participant who lacks the capacity to consent for themselves.

Modification - Any change to a Clinical Trial after initial approval that affects the information or conditions on which the Clinical Trial was authorised. Includes minor modifications, Modifications of an Important Detail (MOIDs), Route A and Route B substantial modifications.

Patient and Public Involvement and Engagement (PPIE) - The active involvement of patients, service users, carers, and members of the public in the design, conduct, management, and dissemination of research, rather than their participation as research subjects.

Principal Investigator (PI) – The individual at a Trial Location who has primary responsibility for the conduct of the Clinical Trial at that Trial Location.

Regulations – The Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended including the Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025).

Research & Development Department (R&D Dept.) – The department at a Trial Location that's responsible for research and development at that Trial Location.

Serious Adverse Event (SAE) - An Adverse Event that results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or consists of a congenital anomaly or birth defect.

Setup CRA – The CRA who is responsible for Clinical Trial setup activities on behalf of the KHP-CTO.

Sponsor - The person or body who takes on ultimate responsibility for the initiation, management and financing (or arranging of the financing) of a Clinical Trial. The Regulations allow for two or more persons or bodies to take on responsibility for Sponsor functions.

Standard Operating Procedures (SOPs) - Detailed, written instructions to achieve uniformity of the performance of a specific function. SOPs are the basis upon which Quality Systems and Processes are conducted and monitored against.

Statistical Analysis Plan (SAP) - A detailed, pre-specified document that describes the planned statistical methods and analyses to be applied to a Clinical Trial's data.

Trial Location - Means a hospital, health centre, surgery or other establishment, or facility or premises at or from which a Clinical Trial, or any part of such a Clinical Trial, is conducted.

Trial Location Team - The team selected by the PI to undertake the Trial Location functions of the Clinical Trial.

Trial Master File (TMF) - A standard filing system which contains all essential documents which individually and collectively permits the evaluation of the conduct of a Clinical Trial and the quality of the data produced. The filing system can be in the form of a single project file or a number of files/filing cabinets, depending on what is deemed most appropriate for a particular Clinical Trial given its size and complexity. The regulatory documents and approvals within the TMF will be maintained alongside Case Report Forms and Source Records.

Trial Statistician - A suitably qualified individual with responsibility for the statistical design, analysis, and interpretation of data generated in a Clinical Trial, ensuring that the Clinical Trial is scientifically robust and that its results are reliable and unbiased.

UK Policy Framework – The UK Policy Framework for Health and Social Care Research.

Witness – A third party who's not involved in the Clinical Trial, such as a Trial Location employee who's not involved in the Clinical Trial, a relative of the participant, or a person similarly uninvolved in the Clinical Trial.