Proportionality and Associated Risk Assessment for Clinical Trials

DOCUMENT DETAILS	
Document Type	Standard Operating Procedure
Document Name	KHP-CTO/CT/SOP 22.0 Proportionality and Associated Risk Assessment
Version	v1.0
Effective from	28 Apr 2026
Review date	28 Apr 2029
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1. BACKGROUND AND PURPOSE

The purpose of this SOP is to describe procedures for proportionality assessment, and the risk assessment of proportionality measures, for Clinical Trials. Such procedures must be followed to ensure Clinical Trials are compliant with the Regulations.

The following Paragraphs in the Regulations have been used to prepare this SOP:

- *2 (1) "conditions and principles of good clinical practice" means the conditions and principles specified in Schedule 1;*

- *28 (1)* ***No person shall (a) conduct a clinical trial****; or (b) perform the functions of the sponsor of a clinical trial (whether that person is the sponsor or is acting under arrangements made with that sponsor),* ***otherwise than in accordance with the conditions and principles of good clinical practice****.*

The following Principles of ICH GCP E6 (R3) have been used to prepare this SOP:

- Principle 1.3: 'Foreseeable risks and inconveniences should be weighed against the anticipated benefits for the individual participants and society. A trial should be initiated and continued only if the **anticipated benefits justify the known and anticipated risks**.'

- Principle 1.4: When designing a clinical trial, the scientific goal and purpose should be carefully considered so as not to unnecessarily exclude particular participant populations. The participant selection process should be representative of the population groups that the investigational product is intended to benefit, once authorised, to allow for **generalising the results across the broader population.** Certain trials (e.g., early phase, proof of concept trials, bioequivalence studies) may not require such a heterogeneous population.

- Principle 4: Clinical trials should be **scientifically sound for their intended purpose** and based on adequate and **current scientific knowledge and approaches**.

- Principle 6: Quality should be built into the scientific and operational design and conduct of clinical trials.

- Principle 7: Clinical trial processes, measures and approaches should be implemented in a way that is proportionate to the risks to participants and to the importance of the data collected and that **avoids unnecessary burden on participants and investigators.**

- Principle 8: Clinical trials should be described in a clear, concise, scientifically sound and operationally feasible protocol.

2. SCOPE

This SOP applies to all Clinical Trials (CTIMPs) sponsored by KHP, that are overseen by the KHP-CTO.

Trial Location-level evaluation of risk is out of scope of this SOP. Principal Investigators and Trial Locations should use the NHS capacity and capability process to:

- Highlight any potential issues with the application of proportionality proposed by the Chief Investigator and the Sponsor
- Highlight any potential issues with the risk assessment made by the Chief Investigator and the Sponsor
- Make the Trial Location-level risk assessment

3. PROCEDURE

3.1 Examples of applying proportionality to Clinical Trials

Below are concrete, protocol-level examples of how a Chief Investigator (CI) would apply proportionality when drafting a Clinical Trial protocol. Each example shows what is decided, why it is proportionate, and where it appears in the protocol — exactly the level inspectors expect to see.

Eligibility criteria

- Proportionality applied:
  - The CI limits eligibility criteria to those that are clinically relevant to participant safety and interpretation of the primary endpoint, avoiding unnecessary exclusions
- Example:
  - Rather than excluding participants based on extensive laboratory thresholds with minimal relevance, the protocol restricts exclusions to parameters directly linked to the IMP's known safety profile
- Protocol location:
  - Inclusion and exclusion criteria section

Informed consent process

- Proportionality applied:
  - The CI designs a consent process that is robust but not overly burdensome, reflecting Clinical Trial risk and participant population
- Example:
  - For a low-risk Clinical Trial using a licensed IMP, the protocol allows for remote consent discussions with documented confirmation, while retaining face-to-face consent where clinically indicated
- Protocol location:
  - Ethical considerations / informed consent section

Safety assessments and visit schedule

- Proportionality applied:
  - The CI aligns the frequency and intensity of safety assessments with the known and anticipated risks of the IMP

- Example:
    - The protocol specifies targeted safety assessments at clinically meaningful time points, rather than intensive testing at every visit, where existing data indicate a stable safety profile
- Protocol location:
    - Schedule of assessments

Clinical Trial oversight arrangements

- Proportionality applied:
    - The CI defines appropriate oversight structures based on Clinical Trial risk and complexity
- Example:
    - For short-duration, single-site Clinical Trials with minimal safety risk, the protocol specifies oversight via a Trial Steering Committee (TSC) only, and a Data Monitoring and Ethics Committee (DMEC) is not established
- Protocol location:
    - Clinical Trial governance and oversight section

Data collection and endpoints

- Proportionality applied:
    - The CI limits data collection to Critical-to-Quality data necessary to answer the research question
- Example:
    - The protocol avoids extensive secondary data collection that does not inform safety or primary outcomes, reducing burden on participants and sites while protecting data quality
- Protocol location:
    - Endpoints and data collection sections

IMP handling and pharmacy involvement

- Proportionality applied:
    - The CI specifies IMP handling arrangements that reflect actual risk, avoiding unnecessary complexity
- Example:
    - For a licensed oral IMP with standard storage requirements, the protocol aligns pharmacy processes with routine practice rather than bespoke trial-specific handling steps
- Protocol location:
    - IMP section

Monitoring expectations (high-level)

- Proportionality applied:
    - While detailed monitoring plans sit outside the protocol, the CI avoids implying excessive default monitoring
- Example:

    - The protocol states that monitoring will be conducted using a risk-based approach, without mandating 100% Source Data Verification (SDV), fixed visit frequency, nor in-person monitoring visits
- Protocol location:
    - Quality assurance / monitoring section

Burden on participants and Trial Locations

- Proportionality applied:
    - The CI consciously balances scientific value against participant and Trial Location burden
- Example:
    - The protocol minimises additional clinic visits by aligning Clinical Trial assessments with routine care appointments where feasible
- Protocol location:
    - Participant involvement / Clinical Trial procedures section

3.2 Proportionality assessments during Clinical Trial setup

Task	Responsibility	Activity
1	Chief Investigator	The CI should draft the protocol at a conceptual level. At this stage, the protocol defines: • Scientific objectives and endpoints • Participant population • IMP(s), dose, and design • Core procedures The CI should not yet fix monitoring intensity, oversight committees, or operational controls. This is defining the Clinical Trial proposition.
2	Chief Investigator	The CI should apply proportionality to the protocol and justify this in a 'proportionality justifications' document. See **Section 3.1 Examples of applying proportionality to Clinical Trials** (above) Proportionality justifications should not be documented in the protocol nor the draft CTA Submission Package. The 'proportionality justifications' document should be saved in the TMF. The CI should send the 'proportionality justifications' document, with the draft CTA Submission package, to the sole Sponsor/NHS Co-Sponsor R&D Dept. and CRA as part of **SOP 12.0 Application & Maintenance of a Clinical Trial Authorisation**

3	CRA	Conduct risk assessment as part of **SOP 12.0 Application & Maintenance of a Clinical Trial Authorisation** Risk-assess the proposed application of proportionality with respect to: • Participant safety • Critical-to-Quality data • Clinical Trial and IMP complexity • Trial Location capability and systems • Justification and traceability Share feedback with the Chief Investigator as part of **SOP 12.0 Application & Maintenance of a Clinical Trial Authorisation**
4	Sole Sponsor/NHS Co-Sponsor R&D Dept.	Conduct risk assessment as part of **SOP 12.0 Application & Maintenance of a Clinical Trial Authorisation** Risk-assess the proposed application of proportionality with respect to: • Regulatory compliance and inspection readiness • Sponsor oversight and governance arrangements • Participant safety and safeguarding • Organisational capacity, capability, and assurance • Documentation, justification, and audit trail Share feedback with the Chief Investigator as part of **SOP 12.0 Application & Maintenance of a Clinical Trial Authorisation**
5	Pharmacy representative at the sole Sponsor/NHS Co-Sponsor	Conduct risk assessment as part of **SOP 12.0 Application & Maintenance of a Clinical Trial Authorisation** Risk-assess the proposed application of proportionality with respect to: • IMP safety profile and clinical risk • IMP handling, storage, and accountability controls • Supply chain, labelling, and distribution arrangements • Pharmacy workload, feasibility, and resourcing • Traceability, reconciliation, and compliance assurance Share feedback with the Chief Investigator as part of **SOP 12.0 Application & Maintenance of a Clinical Trial Authorisation**
6	Chief Investigator	Ensure the draft protocol is updated to address feedback from the CRA, Sole Sponsor/NHS Co-Sponsor R&D Dept., and the pharmacy representative as part of **SOP 12.0 Application & Maintenance of a Clinical Trial Authorisation** Where the CI has proposed proportionality measures, and feedback from the CRA, Sole Sponsor/NHS Co-Sponsor R&D Dept., and the pharmacy representative has caused these

		measures to change; the CI should update the 'proportionality justifications' document and save in the TMF.

3.3 Maintenance and re-assessment of proportionality during Clinical Trial delivery

Task	Responsibility	Activity
1	Chief Investigator	Where an Urgent Safety Measure (USM) is required to address an immediate hazard to participants, follow the process described in **SOP 12.0 Application & Maintenance of a Clinical Trial Authorisation** Relevance to proportionality: USMs may require temporary suspension of previously agreed proportionality arrangements.
2	Chief Investigator	Ensure Clinical Trial oversight arrangements continue to operate as intended, and that any material changes to oversight structures (e.g. meeting frequency, remit, or membership) are documented and filed in the TMF. Relevance to proportionality: Oversight arrangements are a key proportionality control.
3	Clinical Research Associate or delegate	Where a Modification to a Clinical Trial is proposed or implemented, review the Modification to determine whether it alters the risk profile of the Clinical Trial. See **SOP 12.0 Application & Maintenance of a Clinical Trial Authorisation** Relevance to proportionality: Modifications may invalidate earlier proportionality decisions. If proportionality arrangements change, ask the CI to update the 'proportionality justifications' document in the TMF.
4	Sole Sponsor/NHS Co-Sponsor R&D Dept.	Where a Modification to a Clinical Trial is proposed or implemented, review the Modification to determine whether it alters the risk profile of the Clinical Trial. See **SOP 12.0 Application & Maintenance of a Clinical Trial Authorisation** Relevance to proportionality: Modifications may invalidate earlier proportionality decisions. If proportionality arrangements change, ask the CI to update the 'proportionality justifications' document in the TMF.
5	Clinical Research	Where factors affecting the Monitoring Plan change (e.g. Modifications, emerging safety signals, significant non-compliance

	Associate or delegate	or trends, changes in Clinical Trial conduct or context, findings from oversight or review activities); amend the Monitoring Plan. Relevance to proportionality: Monitoring intensity and modality are direct applications of proportionality and must be adjusted when risk changes.
6	Chief Investigator	Where there has been no Modification within the preceding twelve months, and no formal oversight group convened within the preceding twelve months; the CI should undertake a periodic review of the Clinical Trial's conduct and context. The recommended trigger is the Development International Birth Date (DIBD), aligning review with the DSUR process. The review should consider Critical-to-Quality factors, including participant safety, data integrity for primary endpoints, recruitment and retention, and any changes to the clinical or regulatory context. Relevance to proportionality: Periodic review tests whether the original proportionality assumptions remain valid in the absence of other governance triggers. If proportionality arrangements change, update the 'proportionality justifications' document in the TMF.
7	Clinical Research Associate	When reviewing the TMF, confirm that proportionality has been actively maintained by verifying that at least one of the following is evidenced within the preceding twelve months: • A Modification with associated risk reassessment, or • Operation of planned Clinical Trial oversight groups, or • Documented periodic review by the CI. Relevance to proportionality: This provides assurance that proportionality decisions have been revisited using a risk-based trigger, rather than left static.
8	Clinical Research Associate	Assess whether proportionality reviews have considered all relevant information, including safety data, deviations, monitoring findings, and emerging clinical context. Record conclusions in accordance with the Monitoring Plan. Relevance to proportionality: Proportionality decisions are only valid if they are based on a complete and current understanding of risk.

4. RELATED TEMPLATES

5. RELATED DOCUMENTS

SOPs

- SOP 9.0 Writing a Trial Protocol
- SOP 12.0 Application & Maintenance of a Clinical Trial Authorisation

Other Documents

ICH GCP E6 (R3)
ICH_E6(R3)_Step4_FinalGuideline_2025_0106.pdf

NIHR Research Governance Guidelines
https://www.nihr.ac.uk/about-us/who-we-are/policies-and-guidelines/research-governance-guidelines

6. CHANGE HISTORY

CHANGE HISTORY			
Date	Version Number	Change details	Approved by
23/04/2026	1.0	Creation	Ann-Marie Murtagh

7. GLOSSARY

Case Report Form (CRF) - A printed, optical or electronic document designed to record all of the protocol-required information for each trial participant, to be reported to the Sponsor.

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.

Critical-to-Quality (CtQ) factors - The attributes of a Clinical Trial that are essential to protect participant safety, ensure the reliability and integrity of Clinical Trial data, and support credible interpretation of the Clinical Trial results.

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

Data Monitoring and Ethics Committee (DMEC) – An independent committee, convened prior to the commencement of a Clinical Trial, that periodically reviews accumulating safety and Clinical Trial data at predefined intervals, or when specified Clinical Trial milestones are met. The DMEC provides independent advice to the Chief Investigator and Sponsor on whether the Clinical Trial should continue, be modified, or be terminated, taking into account participant safety, ethical considerations, and the overall risk–benefit balance.

Development International Birth Date (DIBD) - This is the date that the first CTA for the Clinical Trial was approved.

Development Safety Update Report (DSUR) - A common standard for periodic reporting on drugs under development (including marketed drugs that are under further study).

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.

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.

Investigational Medicinal Product (IMP) – A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a Clinical Trial. This includes products with marketing authorisation when used in a way different from the approved form, for an unapproved indication, or to gain further information about an approved use.

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.

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.

Monitoring Plan - A Sponsor-approved document that sets out how Clinical Trial monitoring will be conducted, managed, and documented, using a risk-based approach to ensure participant safety, data integrity, and compliance with the approved protocol and applicable regulations.

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.

Source Data Verification (SDV) - The process by which Clinical Trial data recorded in the Clinical Trial database or CRF are checked against the original Source Records to confirm that the data are accurate, complete, consistent, and verifiable.

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.

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 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.

Trial Steering Committee (TSC) - An independent oversight body established by the Sponsor to provide overall supervision of the conduct and progress of a Clinical Trial, ensuring that it is carried out in accordance with the approved protocol, applicable regulatory requirements, and accepted standards of GCP.

Urgent Safety Measure (USM) - An urgent safety measure that must be taken to protect Clinical Trial participants against an immediate hazard to their health or safety.