Trinity College Dublin: Policy and Procedure for University Sponsorship of Clinical Trials and Studies

Review and Approval:

	Name and Role	Signature	Date
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Further information on Clinical trial Sponsorship at TCD can be found at: Clinical Trial Sponsorship at Trinity - Trinity Research - Trinity College Dublin (tcd.ie)

1. Context

Under EU legislation, clinical trials of investigational medicinal products (CTIMP) or clinical investigations of medical devices require a legal Sponsor to take responsibility for arranging the initiation, management, and financing of the trial. Any legal entity (including a university) that is established in the EEA can function as Sponsor for such trials. The responsibilities of a trial Sponsor are defined in legislation and require extensive management oversight and governance. Clinical Trial Sponsorship by Trinity ("Trinity Sponsorship") allows investigators to apply for grant funding to undertake investigator-led CTs. In addition, some funders require a named sponsor for other interventional or observational trials. Trinity may undertake sponsorship of such trials following review and risk assessment, similar to the process for regulated trials.

2. Purpose of this Policy/Standard Operating Procedure

The purpose of this policy / SOP is to outline how Trinity College Dublin, the University of Dublin (Trinity) carries out the role of legal Sponsor for Clinical Trials of Investigational Medicinal Products (CTIMP), Clinical Investigations of Medical Devices and other interventional and observational trials, where appropriate.

3. Scope of Policy

This policy applies to:

(a) Sponsorship of regulated clinical trials (CT) of investigational medicinal products (IMP) and regulated clinical investigations of medical devices [collectively referred to throughout this policy as "Regulated Clinical Trial(s)"] which are conducted by authorised academic investigators. 'Regulated' indicates that the Trial comes under the Clinical Trials Regulation (CTR) or the Medical Device Regulation (MDR)/In Vitro Medical Device regulation (IVDR).

(b) Sponsorship of interventional trials (where the intervention is not an IMP or medical Device) but where a named sponsor is required by funders or sponsor oversight is deemed necessary by the Head of Clinical Sponsorship Oversight (HCSO) and / or Clinical Research Governance Group (CRGG).

(c) Sponsorship of Observational trials where a named sponsor is required by funders or sponsor oversight is deemed necessary by the Head of Clinical Sponsorship Oversight (HCSO) and / or Clinical Research Governance Group (CRGG).

Trinity will only provide on Clinical Trial Sponsorship where **all 3 criteria** below (a, b and c) are met:

(a) Clinical Trial/study have been approved via the review and application procedure

outlined in Section 7.2 of this Sponsor SOP.

(b) A written agreement to act as Clinical Trial Sponsor has been issued.

(c) The Principal Investigator (PI) is an employee of Trinity or has formal affiliation to Trinity.

A review process, outlined in section 7.2, will be used to determine suitability of each trial/study for Sponsorship and to determine the level of sponsorship oversight required for that trial/study e.g., if pharmacovigilance and monitoring are required, number of monitoring visits, if a sponsor audit is required etc.

The operational costs of trial Sponsorship must be funded by the investigator/ project budget.

Wellcome – HRB Clinical Research Facility at St James's Hospital (SJH-CRF) enable Trinity to sponsor trials/studies by providing operational support of Sponsorship responsibilities/ tasks such as monitoring, pharmacovigilance etc. As part of the Sponsorship application process, applicants need to confirm SJH-CRF resource availability to support the proposed trial/study. Investigators are advised to contact the HCSO and SJH-CRF for assistance with estimating sponsorship task costs *prior to submitting research grant applications*. Such costs may include, but are not limited to, trial monitoring, pharmacovigilance/ device vigilance, regulatory affairs, sponsor audit, data management, archiving.

The scope of services which SJH-CRF supply, to enable to Trinity to fulfil its sponsor responsibilities, is limited to those outlined in Appendix 2. Specific tasks outside this scope of services, such as IMP sourcing, unblinding service, data management may need to be sub-contracted to an external vendor, this needs to be considered at grant application stage to be able to cost effectively for the trial.

As Sponsor, Trinity is responsible for reviewing and approving any third-party vendors who are sub-contracted Sponsor tasks, to ensure quality and compliance with appropriate legislation. Associated costs (e.g., vendor qualification audit) must be paid from the investigators project budget and will be included in the Sponsor-investigator Agreement.

Provision of services by SJH-CRF is subject to:

- SJH-CRF having sufficient human and capital resources available throughout the study.
- Appropriateness of the study to the mission and values of SJH-CRF and its clinical partner.
- Continued existence of SJH-CRF which is externally funded.
- If SJH-CRF are unable to carry out sponsorship tasks (e.g., in the event of not having resources to do so) the Investigator may need to contract external vendors to carry out these tasks. Such vendors must be approved by TCD

Sponsor.

4. Principles

4.1. Why Sponsorship Matters to Trinity

As a university, Trinity has a strong interest in ensuring it can serve as a Clinical Trial Sponsor to enable:

- Clinical research conducted in association with Trinity to be conducted according to the highest international standards for research governance, safety, integrity, and transparency.
- Clinical research conducted in association with Trinity to comply with all applicable legislation including CTR, MDR, IVDR and ICH-Good Clinical Practice (GCP).
- Investigators to competitively pursue funding from Irish and EU sources for experimental medicine and clinical trials/studies.
- Academic clinicians to undertake trials/studies that might not be undertaken by commercial pharmaceutical companies because of a lack of commercial incentives.
- Development of trial activity in the Trinity Cancer Institute.
- Trinity to raise its profile as a centre of research excellence.
- Institutional ownership of intellectual property.

4.2. Legal Obligations of Clinical Trial Sponsors

The Clinical Trial sponsor is the legal entity that takes responsibility for the trial and for ensuring arrangements are in place to initiate and manage the study. Responsibilities include ensuring that appropriate indemnity arrangements are in place for the study participants, as defined in ICH-GCP E6 (CTIMPS) or ISO 14155 (Medical Device Investigations). **Note:** The funder of the study is not necessarily the sponsor, e.g., where commercial companies fund a trial, they may request that Trinity acts as local sponsor for the Irish sites. Similarly, a small medical device manufacturer may request that Trinity acts as sponsor for a medical device investigation.

The duties and responsibilities of a Sponsor for CTIMPs are detailed in ICH-GCP E6 (R2) Section 5.0 ICH: E 6 (R2): Guideline for good clinical practice - Step 5 (europa.eu). For Clinical Investigations of Medical devices, specific requirements are detailed in ISO14155 -Good Clinical Practice for Medical Device Investigations. As there are many similarities between GCP for Medical Devices (ISO14155) and ICH-GCP E6 (for CTs), ICH-GCP E6 will be used as the reference throughout this document.

The Sponsor is legally responsible for ensuring that the conduct of a trial and the final data

it generates comply with all applicable legislation.

4.3. Delegation Framework for Trinity Sponsorship Responsibilities

Sponsor Responsibilities are listed in detail in ICH-GCP E6 (R2) Section 5 ICH: E 6 (R2): Guideline for good clinical practice - Step 5 (europa.eu)

Under legislation, Trinity as a Clinical Trial Sponsor may formally delegate by written agreement, some, or all, of its trial-related Sponsor tasks to an individual (such as the investigator), an institution, or an organisation. However, the ultimate responsibility for the Clinical Trial and any delegated tasks remains with Trinity as Sponsor and they must ensure adequate oversight for any delegated responsibilities.

A delegation agreement will be put in place to indicate the distribution of Sponsorship tasks performed within the University, which will include sponsor tasks carried out by SJH-CRF and any delegation of Sponsorship tasks to other entities or individuals. Where agreed by the HPRA, certain responsibilities for Sponsor medical decisions on the trial may be delegated to the investigator, as PI is often a clinical expert in the therapeutic area.

*Where an agreement, such as a grant collaboration agreement, is in place for a third party to perform Sponsorship tasks, Trinity as Sponsor will still need to perform a vendor review and approval procedure to ensure that delegated tasks are performed to an adequate standard and in compliance with all relevant legislation.

5. Definitions and abbreviation

5.1. Overview of the Regulatory Framework for Clinical Research

Clinical research encompasses all health-related research projects involving human participants (Patients or volunteers), their tissue, bio samples and/ or health data. The regulatory and governance framework for clinical research in Ireland is summarised Figure 1.

CTs involving IMPs or non-CE marked medical devices are governed by European and national legislation and require regulatory assessment and approval by a competent authority (CA). In Ireland, the CA is the Health Products Regulatory Authority (HPRA).

Following the introduction of the Clinical Trials Regulation (CTR) 536/2014, from 31 January 2023 all CTIMPs must be submitted centrally via the EU portal/ Clinical Trials Information system (CTIS). The trial is then assessed by both the National Research Ethics Committees (NREC) and National Regulatory Authorities in each of the countries where the trial will take place. Approval for trials to be conducted in several countries and sites is thus given centrally – i.e., one opinion to cover all sites and countries. Any clinical trial/investigation of an IMP or a medical device falling within the governance of the below legislation requires a legal

Sponsor with responsibilities defined under legislation (refer to figure 1).

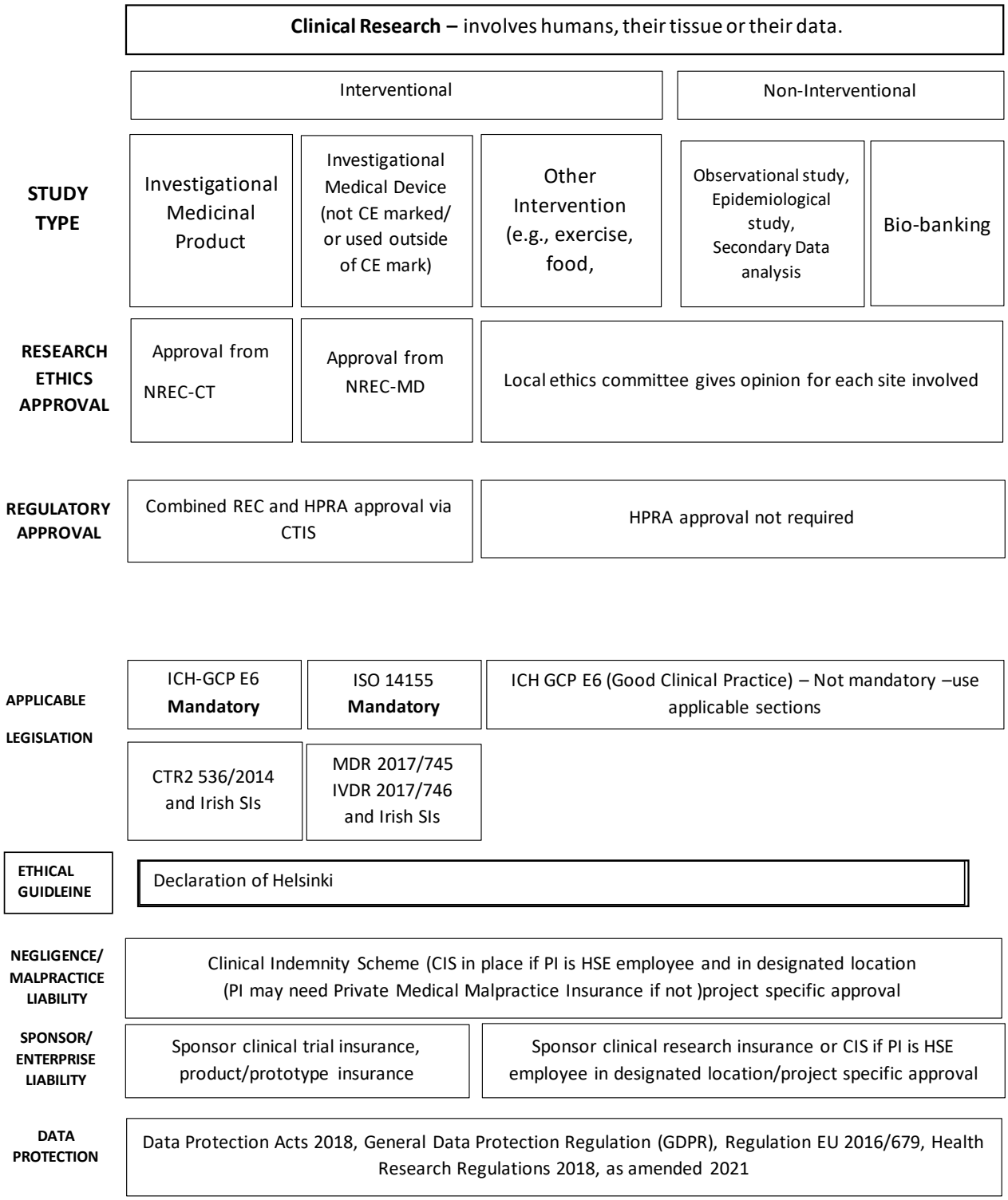


Figure 1 – Regulatory Framework for Clinical Research in Ireland (2023)

5.2. Definitions

Term	Definition
Clinical Trial Information System (CTIS)	CTIS - the online system for the regulatory submission, authorisation and supervision of CTs in the European Union and the European Economic Area. From January 2023 all new clinical trial applications must be submitted via CTIS.
Good Clinical Practice (GCP)	An international ethical and scientific quality standard provided by the International Council for Harmonisation for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of CTs. It serves to protect the rights, integrity and confidentiality of trial subjects.
Funder	The organisation assessing the scientific quality of the research proposed and providing funding to facilitate the conduct of the proposed study, which then requires the Sponsor to takes responsibility before the Trial begins.
Health Products Regulatory Authority (HPRA)	Competent Authority in Ireland for regulating medicines, medical devices and veterinary and cosmetic products. This is the regulatory authority for CTs of IMPs and clinical investigations of medical devices.
Investigational Medicinal Product (IMP)	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including a medicinal product that is already the subject of a marketing authorisation, but— a) is used, formulated or packaged in a way different from the form that is the subject of the authorisation, b) is used for an indication that is not included in the summary of product characteristics under the authorisation for the product, or c) is used to gain further information about the form of the product that is the subject of the authorisation An algorithm for determining whether or not a medicinal product is considered to be an IMP is provided in Appendix 1 of this policy and in cases of uncertainty, the HPRA should be contacted for guidance.
Medical Device (MD) (Definition as per Regulation EU 2017/ 745 MDR)	Any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes: — diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease, — diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability, — investigation, replacement or modification of the anatomy or of a physiological or pathological process or state, — providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations, and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such

	means.
In Vitro Medical Device (IVD) (Definition as per Regulation Eu 2017 /746 IVDR)	'in vitro diagnostic medical device' means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information on one or more of the following: (a) concerning a physiological or pathological process or state. (b) concerning congenital physical or mental impairments. (c) concerning the predisposition to a medical condition or a disease. (d) to determine the safety and compatibility with potential recipients. (e) to predict treatment response or reactions. (f) to define or monitoring therapeutic measures. Specimen receptacles shall also be deemed to be in vitro diagnostic medical devices;
National Research Ethics Committee (NREC)	NRECs are tasked with delivering single national ethics opinions for Clinical trials of Investigational Medicinal Products (CTIMPS) and for Clinical Investigations of Medical Devices.
Principal Investigator (PI)	The authorised health care professional (medical or dental) responsible for the conduct of a clinical trial at a trial site. If a trial is conducted by a team of authorised health care professionals at a trial site, the principal investigator (PI) is the leader responsible for that team. The PI is responsible for the day-to-day running of the study, overseeing the work of the study staff and the safety of study participants. Note -for studies which are not CTIMPS (observational studies, or interventions other than IMP) the PI does not need to be a qualified doctor or dentist but should be a suitably qualified person.
Site	The organisation providing access to the patient's/study subjects and retaining responsibility for the care of the participants to whom they have a duty of care (typically hospital site).

Sponsor	In relation to a clinical trial of an IMP, the individual or organisation that takes responsibility for the initiation and management (or for arranging the initiation and management) of, and the financing (or arranging the financing) for that clinical trial (as per ICH E6 R2) In relation to a clinical investigation of a medical device: the individual or organisation taking responsibility and liability for initiation or implementation of a clinical investigation (as per ISO 14155).
Third Party Vendor	A party that is sub-contracted to provide services to the sponsor to fulfil duties/ tasks required under Sponsorship
Trial Steering Committee	The committee which provides high level oversight and governance of the trial. Ideally, the TSC should include members who are independent of the investigators, their employing organisations, funders and sponsors. The TSC should monitor trial progress and conduct and advise on scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the Data Monitoring Committee (DMC) or equivalent and ultimately carries the responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy.
Data Safety Monitoring Board/Data Monitoring Committee	A committee that may be established by the sponsor to assess at intervals, the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial. The role may be carried out by a medical monitor in some cases. For low -risk studies it is not necessary to establish such a committee e.g., Observational studies or low risk interventions without invasive test procedures.

Study Types	
Clinical Investigation (Medical Device)	would be considered as non-regulated interventional research studies. Refer to section 6.1 for further information. Further guidance on the distinction between regulated and non-regulated medical device studies is available from the HPRA: http://www.hpra.ie/homepage/medical-devices/regulatory-information/Clinical-investigations. Device Investigations where no commercial application / development is intended may fall under Section 82 rather than section 62 of the MDR / It is advised to contact Sponsor QRM, TCD HCSO and, if necessary, HPRA to discuss this.

Clinical Study (as per Clinical Trial Regulation 536/2014)	'Clinical study' means any investigation in relation to humans intended: (a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products; (b) to identify any adverse reactions to one or more medicinal products; or (c) to study the absorption, distribution, metabolism and excretion of one or more medicinal products; with the objective of ascertaining the safety and/or efficacy of those medicinal products;
Clinical Trial (as per Clinical Trial Regulation 536/2014) May also be known as a Clinical Trial of an Investigational Medicinal Product (CTIMP)	Clinical trial' means a clinical study which fulfils any of the following conditions: (a) the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned. (b) the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study. or (c) diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects. 27.5.2014 EN Official Journal of the European Union L 158/11 (1) OJ C 253, 3.9.2013, p. 10.
Investigational Medicinal Product (IMP)	Investigational medicinal product means a medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial.
	Further guidance on the definition of a regulated clinical trial is available in EudraLex, Volume 10, Guidance Documents Applying to Clinical Trials, Questions and Answers, available on the website of the European Commission. In particular, the decision tree provided in the guidance is useful – a copy is included in Appendix 1 of this policy)
Low Intervention Clinical Trial	'Low-intervention clinical trial' means a clinical trial which fulfils all of the following conditions: (a) the investigational medicinal products, excluding placebos, are authorised; (b) according to the protocol of the clinical trial, (i) the investigational medicinal products are used in accordance with the terms of the marketing authorisation; or (ii) the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned; and (c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned;
Non-Interventional (defined by CTR 536/202014)	Non-interventional study' means a clinical study other than a clinical trial

Interventional Study	A clinical study in which participants are assigned to receive an intervention so that researchers can evaluate the effects of the intervention on biomedical or health related outcomes. This intervention could be of any type including, an investigational medicinal product, a prototype medical device, a nutritional supplement, a physiotherapy program or, as in Health Services Research, it could be the way in which services are configured or delivered. The trial could mandate that all the subjects receive the intervention of interest (a single arm trial) or that some subjects are randomly assigned to the intervention(s) of interest and others to a comparator – often a placebo- arm. *Note that among the scientific community Interventional studies are often referred to as 'clinical trials', however under the Clinical Trial regulation (and when speaking to regulators e.g., HPRA, the term term "Clinical Trial" in a more restricted sense, in that they only apply it to trials of an Investigational Medicine Product only. Clinicians/scientists who do not regularly interact with the regulatory authorities m a y be confused by this this distinction. For the purposes of clarity Trinity Sponsor office will use the term 'regulated Clinical Trial' and 'regulated Clinical Investigation 'to indicate trials/ Investigations that fall under the remit of the regulatory authorities via legislation (MDR/IVDR and CTR)*
Regulated trial/ investigation	Interventional study (either a clinical trial of an IMP or a clinical investigation of a medical device) falling under the jurisdiction, by legislation (MDR/IVDR/CTR) of the regulatory authorities.

5.3. Abbreviations

CA	Competent Authority
CE	Conformité Européen (European Conformity)
CIS	Clinical Indemnity Scheme
CRGG	Clinical Research Governance Group
CT	Clinical Trials
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTR	Clinical Trials Regulation 536/2014
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union

GCP	Good Clinical Practice
HCSO	Head of Clinical Sponsorship Oversight
HPRA	Health Products Regulatory Authority
HRB	Health Research Board
HRR	Health Research Review form
HSE	Health Service Executive
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP	Investigational Medicinal Product
IVDR	Invitro Medical Device Regulation
MDR	Medical Device Regulation
NREC	National Research Ethics Committees
PI	Principal Investigator
QMS	Quality Management System
RDO	Research Development Office, Trinity College Dublin
REAMS	Research Ethics and Management System
SJH-CRF	Wellcome – HRB Clinical Research Facility at St James's Hospital
SOP	Standard Operating Procedure
SQRM	Sponsor Quality and Regulatory Affair Manager
SUSAR	Suspected unexpected serious adverse reaction
Trinity	Trinity College Dublin, the University of Dublin

6. Policy

6.1. Governance of Sponsorship by Trinity

Within Trinity, Clinical Trial Sponsorship is overseen by the Dean of Research and managed by the HCSO. Operational support of Sponsorship is provided by the SJH-CRF and by the Sponsor Quality and Regulatory Affairs manager (SQRM). The model for governance of Sponsorship within Trinity is as follows (illustrated in Figure 2):

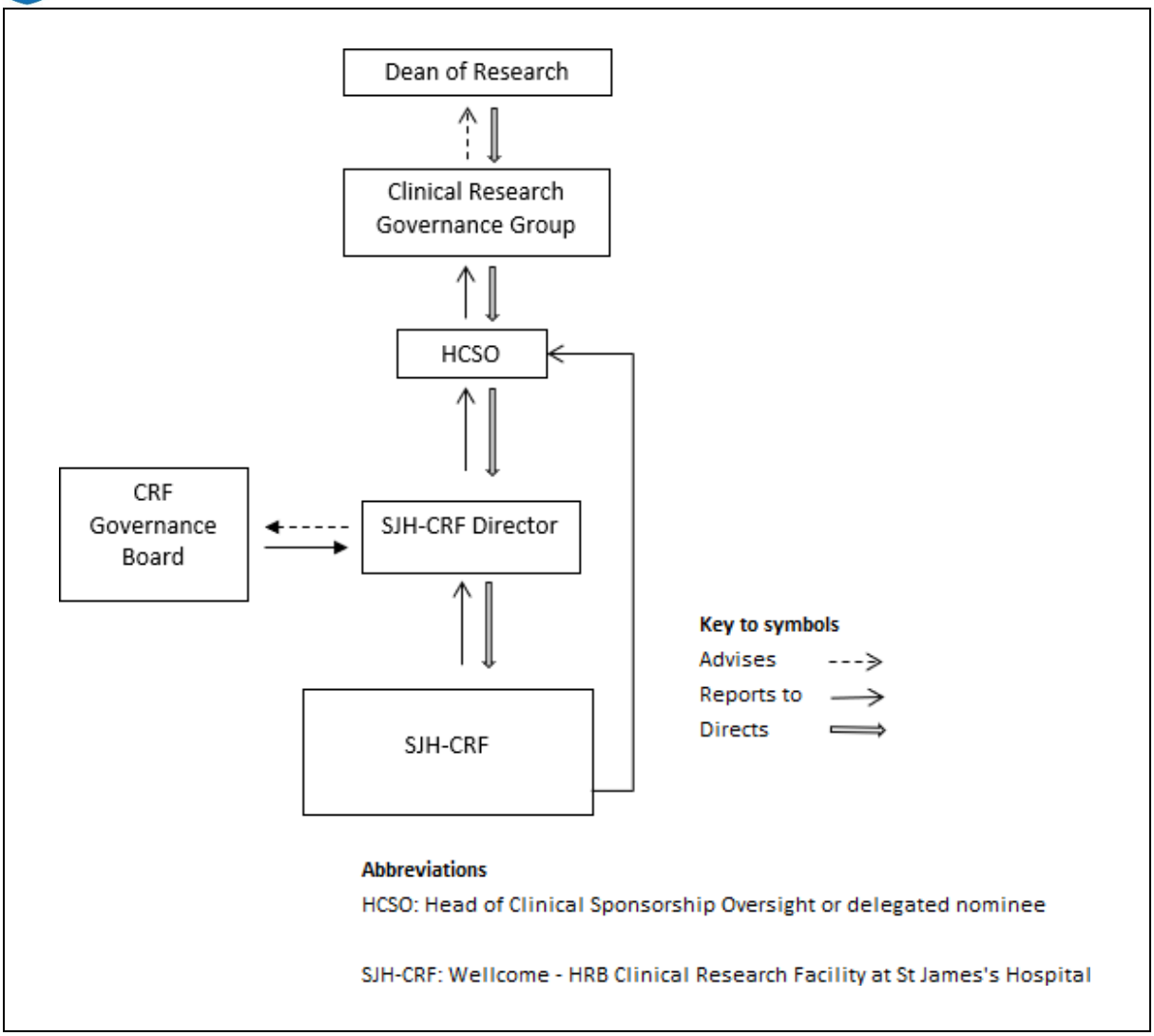
- The Dean of Research is responsible for Clinical Trial Sponsorship on behalf of Trinity.
- The HCSO is responsible for operational oversight of Trinity Sponsorship, assisted by the Sponsor QRM.

- A Clinical Research Governance Group (CRGG) has been established in Trinity to advise the Dean of Research on trial Sponsorship decisions and to review risks associated with Sponsorship. Core membership of this group is: Dean of Health Research, Director of SJH-CRF, HCSO, and a legal expert from Research Contracts and Consultancy office (RCCO). Subject matter experts from within TCD or external subject matter experts may be invited to join the CRGG for review of trials in specialized areas e.g. Paediatrics. This will be agreed by HCSO and Dean of Research (or designee) in advance of the meeting. This group will make a recommendation to the Dean of Research on sponsoring trials/studies or not. Dean of Research will give the final decision on sponsorship.
- A hierarchy of approval for different study/ trial types, based on risk, is as follow:

Type of study/trial	Approver
Observational – Single or multi-site in Ireland	HCSO
Observational- Includes sites outside Ireland	HCSO
Interventional -Non-Regulated – Single or Multi site, Ireland	HCSO
Interventional- Non-Regulated, Includes sites outside Ireland	CRGG and DOR
Regulated IMP or Medical Device – Single or Multi site Ireland	CRGG and DOR
Regulated IMP or Medical Device – Includes Sites outside Ireland	CRGG and DOR

- A written clinical trial agreement (including delegation of agreed Sponsor tasks to PI) will be put in place between Trinity, the trial site, and the PI.
- Distribution of Sponsor tasks within Trinity and to third parties will be described in a delegation agreement.
- The scope of services provided by the SJH-CRF to a Trinity sponsored trial will be agreed between HCSO or designee and SJH-CRF Director or designee. This will be documented.
- A trial steering committee and data and safety monitoring board may be established where appropriate, to ensure adequate review and o safety oversight of the trial.

Figure 2 – Governance Model for Clinical Trial Sponsorship in Trinity



6.2. Insurance

6.2.1. Sponsor

Trinity as Sponsor must ensure that there is appropriate insurance cover in place for:

- the study participants
- those involved in conducting the research
- Trinity.

Trinity has a CTs insurance policy in place. There are some exemptions and limitations to the scope of research covered under the policy. Insurance cover for the trial and any prototype or novel product will need to be confirmed as part of the application review process and the PI may be asked to provide additional funding to extend cover where necessary. HCSO will liaise with Trinity Estates & Facilities on clinical trial sponsorship for multinational as required trials

to ensure cover is possible.

6.2.2. PI and site staff:

Medical practitioners practicing in public hospitals in Ireland are covered by the national Clinical Indemnity Scheme (CIS), which is administrated by the State Claims Agency. This is essentially a state insurance scheme covering clinical practitioners working in public hospitals. The scheme compensates patients who may have been harmed in a public hospital. All hospital sites will be required to confirm medical malpractice/ negligence cover is in place and extends to CTs before the study start.

While the scheme covers medical negligence that may occur during the course of a trial, it doesn't cover incidents arising from the trial itself, a product used in the trial (IMP, Device, Food supplement etc), or poor trial design. CIS cover extends to the PI and the staff working on the study under the direction of the PI.

6.3. Withdrawal of Sponsorship

Trinity may withdraw Sponsorship of a trial at its discretion, where information provided on the original application changes without prior notification to the HCSO and approval of the Dean of Research. This includes, but is not limited to:

- PI
- Site deficiencies
- Inadequate Funding
- Trial design
- Risk based review
- Risk Benefit analysis.

HCSO may suspend sponsorship (suspend the trial) or withdraw sponsorship (terminate the trial) if she/he has serious concerns regarding participant safety or data integrity. safety or HCSO will consult the CRGG and DOR re any withdrawal of sponsorship.

7. Responsibility and implementation

7.1. Roles and Responsibilities for Sponsorship in Trinity

7.1.1. Wellcome –HRB Clinical Research Facility at St James's Hospital (SJH-CRF)

The SJH-CRF was developed with the aid of a funding award made to the Trinity School of Medicine by Wellcome and the HRB and has been operated by Trinity since 2013. The SJH-CRF is situated in St. James's Hospital and is jointly governed by St James's Hospital and Trinity.

The SJH-CRF quality team enable TCD to carry out Sponsor responsibilities by providing operation support for functions including Trial Monitoring, Pharmacovigilance, Regulatory Affairs. A detailed matrix for execution of Sponsor-related tasks is provided in Appendix 2. This demonstrates what tasks that can be provided by Trinity and identifies functions that need to be outsourced by the PI and their team to external vendors.

The SJH-CRF can provide operational support for regulatory and ethics submissions, trial monitoring, pharmacovigilance, site initiation, research nursing support, project management advice, a regulated trial site, lab, pharmacy services and assistance with selection of third-party vendors for IMP sourcing and data management.

7.1.2. Investigators

The investigator is expected to take responsibility for the protocol, trial organisation, data management, reporting functions, IMP sourcing, statistics, and medical expertise. These activities will need to be performed in full accordance with ICH E6 (GCP) and relevant European and National legislation. On a case-by-case basis Trinity may delegate some of all sponsorship tasks to the PI. This will be clearly outlined in the contract and agreements. Trinity will have overall responsibility and oversight of these tasks.

The PI must be a Trinity employee (or affiliated employee) at the time of sponsorship. The PI is responsible for the design, implementation, conduct, management, oversight, and completion of the clinical trial. See ICH-GCP E6 R2 Section 4 for a full list of PI responsibilities. The PI is accountable to Trinity (as Sponsor) in relation to the trial.

The investigator is required to submit a request for sponsorship to Trinity before submitting a grant application (See Sponsorship request form – prefunding.) Investigators complete this form electronically at: Clinical Trial Sponsorship at Trinity - Trinity Research - Trinity College Dublin (tcd.ie). This enables feasibility review of Sponsorship and adequate costing of Sponsor tasks **prior** to the grant application and allows agreement in principle for Sponsorship of the trial/study.

If funding is granted, a full application for Trinity Sponsorship application can be made via the Health Research Review Form (HRR). Review of the application will include (but is not limited to) accurate costing, risk assessment and risk mitigation, protocol development, resource identification, third party vendors and an implementation plan. It is the investigators responsibility to be forthcoming with this information and to update the sponsor re any changes.

The PI is responsible for the day-to-day running of the study and the safety of the study participants. This includes, but is not limited to, responsibility for overseeing the study budget, overseeing the work of study staff, ensuring that the study is conducted rigorously and on time and that all necessary legislation is complied with. The PI must have training and certification in ICH-GCP E6 for the duration of the trial. PI responsibilities are listed in detail in ICH-GCP E6 (R2) Section 4.0 ICH: E 6 (R2): Guideline for good clinical practice - Step 5

(europa.eu).

7.1.3. Head of Clinical Sponsorship Oversight (HCSO)

The HCSO is employed by Trinity to maintain operational oversight and coordination of Trinity Sponsorship. The HCSO provides, at application stage, assistance to PIs in, establishing regulatory requirements, risk review and mitigation, assistance in trial costing and study set-up plan. In Addition, the HSCO advises on resources required and works with RDO to determine budget required. Throughout the trial, the HCSO is responsible for maintaining oversight of operational conduct and ensuring that the trial is conducted in compliance with the agreed protocol and applicable legislation, that safety reporting is conducted in compliance with legislative requirements, that risk-benefit review is performed as per agreed protocol, reviews monitoring reports, reviews major protocol deviations and GCP breaches and ensures these are followed up appropriately. HCSO is assisted in these responsibilities by SQRM.

7.1.4. Research Development Office, Trinity Research (RDO)

RDO assists investigators applying for funding to support their studies. All investigators are encouraged to contact the RDO for assistance with grant applications at the earliest stage. RDO will direct PI to Sponsor office and or SJH-CRF for assistance in costing sponsorship activities, and work with the Sponsor Office/SJH-CRF to determine the necessary budget.

7.1.5. Estates and Facilities

Estates and Facilities is responsible for ensuring that adequate insurance is maintained by Trinity to cover its obligations as Clinical Trial Sponsor. This includes indemnification of the trial and trial protocol and where applicable, ensuring that prototype or product liability is in place. Questions on the Sponsorship application form (pre-funding) and the Health Research Registration form (HRR) enable Sponsor to inform Estates and Facilities of relevant information re the trial/Study.

7.1.6. Research Contracts and Consultancy Office, Trinity Research and Innovation

The Contracts Office is responsible for ensuring that adequate agreements and contracts are in place to meet the responsibilities of Trinity as Sponsor, such as the clinical trial agreement with the trial sites and investigator and any sub-contracted activities.

7.2. Application Procedure for Investigators Seeking Sponsorship

This section outlines the application procedure for Sponsorship.

7.2.1. Request for Clinical Trial Sponsorship - Pre-funding award:

For any Funding application which requires a named sponsor the investigator will request sponsorship by completing and submitting the Sponsorship Request form. The application process is as follows (illustrated in Figure 3):

a) PI submits request for sponsorship electronically before finalising funding application.

HCSO may request supporting documentation from PI, such as the Grant application itself, budget, or a protocol summary if available.

b) HCSO will review the sponsorship request form using criteria outlined in this section and in Section 7.3 and check that the budget provides for provision of sponsor services, appropriate to the type of trial. HCSO will involve SJH-CRF to advise re budget for sponsor services as appropriate.

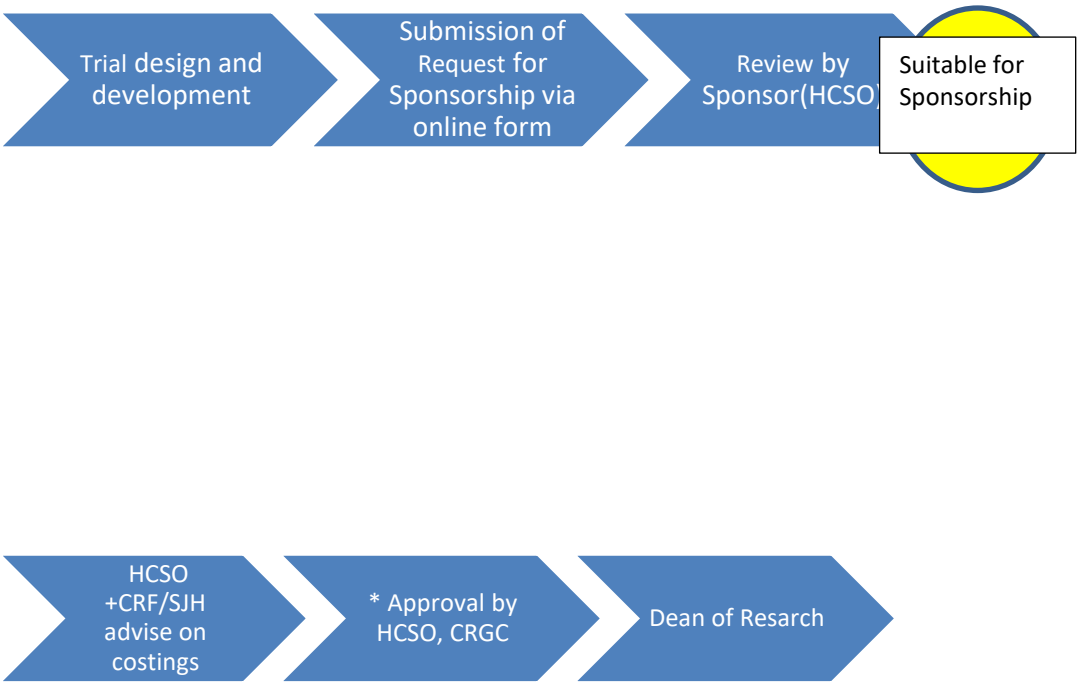
c) If HCSO considers that the trial is suitable for Trinity Sponsorship, HCSO will approve the trial for Trinity Sponsorship in principle. HCSO may ask CRGG for input at this pre-funding stage if appropriate. Sponsorship in principle is conditional and dependent on items such as adequate funding, protocol review by Trinity, a risk- benefit review, a Trial Steering Committee and Data Monitoring Committee appointed, (if appropriate) and formal approval process as outlined below.

d) Key Assessment Criteria for Sponsorship

Several areas will be taken into consideration when assessing a study for suitability for Sponsorship. These include but are not limited to:

- Known trial risks and benefits
- Scientific or clinical justification
- Investigator (and team) experience in clinical research
- Project feasibility
- Strategic alignment with Trinity's goals
- Adequate funding and resourcing for Sponsorship.

Figure 3: Process for Application to Trinity for Sponsorship



7.2.2. Following Grant Funding Approval

If Funding is granted the PI will complete a Health Research Registration Form via RPAMS ***(HRR Form).*** This is part of the Contract office procedures for setting up an account for the trial/Study

a) Contracts office staff forward all HRR forms to the HCSO for review. This triggers a detailed protocol review, sponsorship plan and accurate costing by HCSO with the assistance of SJH-CRF as required.

b) Where third party vendors are required for a study, vendor quotes and selection process will be initiated. This may include a prequalification audit by the Sponsor to ensure that the supplier is compliant with relevant legislation and quality standards.

c) HCSO may approve the trial (See hierarchy of approval, section 6.1) or when required request a meeting of CRCG to will discuss the trial. If trial is approved by CRGG, the Dean of Research issues formal decision on Trinity Sponsorship to PI. Note that Sponsorship may be conditional, e.g. on setting up an independent data monitoring committee, etc.

Research Contracts and Consultancy prepare and finalise contracts, a trial specific steering committee and data and safety monitoring board will be established by the PI and Sponsor. The trial set-up process commences as per the Sponsor and SJH-CRF Standard Operation Procedure (SOP) and Quality Management Systems (QMS).

7.2.3. Inadvertent Non-Compliance: Risk Mitigation via REAMs

A potential risk exists whereby investigators may not be aware that a proposed trial falls under the Clinical Trial or Medical Device Regulations and thus Sponsor is not contacted re such trials. To mitigate this risk a question has been added to the Research Ethics and Management System (REAMS) which is designed to capture such trials and avoid inadvertent non- compliance. The question asks if this interventional trial in humans involves a medicine or a medical device. If applicant answers, 'yes' REAMSs prompts applicant to contact HCSO to request a 'letter of compliance'.

HCSO will review the project to determine if the interventional trial comes under the remit of Medical Device Regulations OR the Clinical Trial regulation. If it does not come under the MDR or CTR the HCSO will send the PI an email or letter indicating this. REAMS refers to this as a 'letter of compliance' from HCSO. This document must be uploaded to REAMS as part of the application before REC will consider the submission.

If the proposed trial falls under the MDR or CTR the regulatory approval pathway will be via the National Research Ethics Committee and HPRA for Medical Devices, and via the Clinical trial Information system (CTIS) for Clinical trial of Investigational Medicinal Products, not via the TCD RECs HCSO /Sponsor staff will engage directly with the PI to discuss the proposed regulated CTIMP / Clinical Investigation and PI has the resources to conduct such a trial.

7.3. Risk Assessment and Management

All clinical research involves potential risk to the research subject, PI, Sponsor and funder. Trinity will implement a risk assessment and management plan to ensure that risks associated with Trinity Sponsored trials are appropriately mitigated. This requires stringent application review and trial management processes that are rigorous, reliable, transparent, quantifiable, and auditable.

7.3.1. Types of Risk Associated with Clinical Research

In patient focused research risks may arise from a variety of sources but these are usually predictable. Understanding the origins of research risk is important if such risks are to be properly assessed and managed. Potential sources of risk include but are not limited to:

- **Phase of trial/ available clinical data** – the level of risk will depend on how much is known about the IMP or the device, for example there is less information available on potential risks associated with a phase I or first-in-human study than a phase IV trial or a trial using a marketed product.
- **Nature of intervention** – the type of medical device (example, class III surgically implanted device versus class I device) or pharmacological properties of the IMP will have a significant impact on the risk level of the trial.
- **Study population** – the level of risk varies with specific research population and levels of comorbidity. For example, it will often be higher in studies involving pregnant women and young children or people with chronic diseases such as diabetes.
- **Study Procedures** – the study procedures and trial design will impact on the level of risk. Non-routine clinical procedures will provide a source of additional risk as will study design, such as complex randomisation or blinding procedures.
- **Research team** – where the expertise and experience of the team members and the resources they have at their disposal affects the risk of a study.
- **Conflicts of interest** – may be a risk factor, for example, if the investigator leading the study has a vested interest in the study demonstrating efficacy.
- **Data Protection** – a data privacy impact assessment will be required as part of study design to ensure that risks are identified and measures, including training, are adequate to ensure data privacy.

7.3.2. Assessment of Risk

All applications for Trinity sponsorship will undergo a risk assessment. This assesses the level of risk (high, medium, low), considers the probability of a risk being realised and includes the controls to mitigate the risk. The Sponsorship Risk Assessment form should

be completed by the PI and the HCSO or designee and will be submitted with the application for sponsorship.

7.3.3. Risk Management Plan

Risk management does not eliminate risk, but it can reduce risk and reduce the impact of risks. A risk management plan will be implemented to minimise risks for the life cycle of a trial. This will be based on the trial protocol review and Sponsorship Risk Assessment Form. Risks will be reported, and issue escalated as per the SJH-CRF and Trinity Sponsor SOPs and QMS.

7.3.4. Quality Management System (QMS)

A robust QMS with specific standards for each clinical trial is important to meet regulatory expectations and to assess and mitigate against risk. Quality of CTs depends on data integrity and participant protection. The QMS will include but is not limited to personnel roles and responsibilities, training, policies and procedures, quality assurance and auditing, document management, record retention, risk assessment and management, reporting and corrective and preventive action. Change control. Trinity sponsored CTs will adhere to the QMS of the SJH- CRF and Trinity Sponsor SOPs.

8. Related documents/ References:

- Sponsorship Request form Pre-funding Clinical Trial Sponsorship at Trinity - Trinity Research - Trinity College Dublin (tcd.ie).
- Health Research Registration Form (HRR) Post funding award
- SPN-FM –PI Risk Assessment for TCD Sponsored Trials
- SPN-FM – Sponsor Risk Assessment for TCD Sponsored Trials

9. Document/version Control for New Policies

Version	Summary of Changes
Version 1.0	New Document
Version 2.0	Format change and finalised by the CRF working group
Version 3.0	• Amended to account for ICH-GCP E6 (E6) revision 2 addendum • Amended to reflect new role in the CRF to implement Sponsorship services (SPQM) • Format and content changed to align with status of document as a Trinity Policy • Reviewer (RDO, Contracts Office, SPQM) comments incorporated. • Application procedure split into two phases (pre- and post- grant approval) • Addition of a CRGG to assist in sponsorship oversight

Version 4.0	• Amended QRAM to SPQM • CRF working group updates included • Amended Investigator Responsibilities • Definitions included for Trial Steering committee and Data and safety monitoring board • CRF abbreviation updated to SJH-CRF • Scope of the policy updated to reflect institutional changes • Regulatory framework updated to reflect changes and updates to regulatory framework • The Governance Model for Sponsorship in Trinity has been updated to reflect institutional changes • The roles and responsibilities for Sponsorship in Trinity has been updated • The application procedure for Investigators seeing sponsorship has been updated and the study registration form included in the appendix • The risk assessment and management sections have been updated as the information can be found in the quality management system and will be assessed on a case-by-case basis. • Withdrawal of Sponsorship has been updated to include additional information and clarification • Appendix 3 Job description has been removed to reflect institutional changes • Investigator Responsibilities have been updated to include additional clarifications
V5.0	Update to reflect new legislation including: • Clinical Trials Regulation EU2014/ (CTR) • Medical Device Regulation EU 2017/ 745 (MDR) • Invitro Medical Device Regulation EU/2017/ 746 (IVDR) • Include mention of sponsorship of Non-Regulated Interventional Trials • Remove Forms from Appendices and provide links instead
V5.1	Following the Research Committee Meeting on 12 September 2023, section 7.3 was added re the risk of inadvertent non-compliance and mitigation of this risk using REAMs system. Minor corrections to Figure Page 14 and sections 6.2.3 and 6.2.4 -remove mention of RDO assisting investigator with Sponsor cost budget.
V5.2	Updated to harmonise with the College policy template. No content was altered except title of section, reference to section and organisation of section.
V5.2	Approved by University Council, 14 February 2024

Document Control for Revised Policies

10.1 Date of initial approval: 26 April 2016

10.2 Date revised policy approved: 14 February 2024

10.3 Date policy effective from: 14 February 2024

10.4 Date of next review: 2028/2029

Appendix 1: Decision tree to establish a whether a study is a "clinical trial"

From Regulation (EU) No 536/2014 Questions & Answers – document January 2022 Annex 1

This algorithm and its endnotes will help you answer the question on whether a given investigation on humans is a clinical trial governed by the Regulation EU No 536/2014. Please start in column A and follow the instructions.

Additional information is provided in the notes at the end of the table. If you have doubts about the answer to any of the questions, contact the national contact point(s) of the Member State(s) Concerned.

Column A	Column B	Column C	Column D	Column E
Is a medicinal product being investigated? *(1)* **If** you answer no to I of the questions in column A below, the investigation **does not** fall within the scope of Regulation EU No 536/2014 If you answer yes to the question, below go to column B.	What effects of the medicinal product are you looking for? If you answer no to all the questions in column B below, the investigation does not fall within the scope of Regulation EU No 536/2014 If you answer yes to any of the questions below go to column C	**Why are you looking for those effects?** If you answer no to all the questions in column C below, the investigation does not fall within the scope of Regulation EU No 536/2014 If you answer yes to any of the questions below go to column D - the investigation is a clinical study as described in article 2(2)(1) of Regulation EU No 536/2014.	**How are you looking for those effects?** If you answer NO to all the questions in column D below, the clinical study is a non-- interventional study that does not fall within the scope of Regulation EU No 536/2014 If you answer yes to any of the questions below go to column E the study is a clinical trial according to Regulation EU No 536/2014	**Is your clinical trial a low-intervention clinical trial?** If your answer NO to any of the questions below in column E, the trial is a clinical trial within the scope of Regulation EU No 536/2014 but is NOT a low-intervention clinical trial as defined in Regulation EU No 536/2014. If you answer YES to ALL of the questions below, the trial is a low- intervention clinical trial. A specific set of risk-adaptations can be applied.

A. Is the investigated substance or product either presented as a medicinal product or does it function as such, in accordance with point 2 of article 1 of Directive 2001/83/EC? *(2*	8. Is the aim of the investigation on the medicinal product: 8.1. To discover or verify/compare its clinical effects? 8.2. To discover or verify/compare its pharmacological effects, e.g., pharmacodynamics? 8.3. To identify or verify/compare its adverse reactions? 8.4. To study or verify/compare its pharmacokinetics, e.g., absorption, distribution, metabolism or excretion?	C. Is the objective of the investigation on a medicinal product: C.1. To ascertain or verify/compare the efficacy of the medicine? *(3)(4)* C.2. To ascertain or verify/compare the safety of the medicine?	D.1. Is the assignment of any patient involved in the study to a particular therapeutic strategy decided in advance by a clinical trial protocol *(5),* and does the assignment not fall within normal clinical practice in the Member State(s) Concerned? *(6)* D.2. Is the decision to prescribe a particular medicinal product clearly taken together with the decision to include the patient in the study? D.3. Are diagnostic or monitoring procedures applied to the patients included in the study, other than those which are applied in normal clinical practice in any of the Member State(s) concerned? *(6)*	E.1. Is this a study of one or more medicinal products, which all have a marketing authorisation in the Member State(s) concerned? E.2. Does the protocol of the clinical trial specify that (i) the investigational medicinal products are used in accordance with the terms of the marketing authorisation; or (ii) the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned; E.3.Do the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice (b) in any member state concerned? **("Yes" to this answer means that the additional procedures do not pose more than minimal risk or** burden; "No" means that the additional procedures **do pose more than minimal risk or burden)**

(1) Please refer to Q&A "Is the definition of 'medicinal product' relevant for the scope of the Clinical Trials Regulation?" and Q&A "Can a study be considered as clinical trial within the scope of Regulation (EU) No 536/2014 if it starts after administration/exposure of the investigational medicinal product has finished?

(2) The following substances are not considered to be medicines

- Human whole blood, blood cells, or plasma (this does not include derivatives of human whole blood, human blood cells and human plasma that involve a manufacturing process)
- Food products, including dietary supplements
- Cosmetic products (Regulation on cosmetic products EU no 1223/2009, article 2.1.a.)
- Medical device (Medical Device Regulation EU no 2017/745, article 1.2 and 2.1)

The qualification of borderline products is a national competence. When there is an uncertainty on the status of a given product, this needs to be clarified with the national competent authorities.

(3) Efficacy is the concept of demonstrating scientifically whether and to what extent a medicine is capable of diagnosing, preventing or treating a disease and derives from EU pharmaceutical legislation.

(4) This includes studies on "drug utilisation" of medicinal products used in normal clinical practice and trials on "palatability" intended to assess the suitability of a formulation for a particular population.

(5) Assignment of patients to a treatment group by randomisation planned by a clinical trial protocol cannot be considered as current practice

(6) Please refer to Q&A "What is not considered as "normal clinical practice?" and the guidance for Risk proportionate approaches in clinical trials: 2017_04_25_risk_proportionate_approaches_in_ct_0.pdf

(europa.eu)

(7) In case of doubt whether an intervention poses only minimal burden or risk to participants, please contact the concerned national competent authorities.

Appendix 2: Detailed Delegation of Sponsorship Tasks – Scope of Services

PI	Principal Investigator	CO	Contracts Office, Trinity Research and Innovation
Sponsor	Head of Clinical Sponsorship Oversight (HCSO) + Sponsor Quality and Regulatory Affairs Manager (SQRM)	DOR	Dean of Research
		E&F	Estates and Facilities
SJH-CRF	Clinical Research Facility		
Third Party	Third party service provider may be required - funding provided by PI/ study		

TASK	PI	SJH-CRF	Sponsor	CO	E&F	Third Party	DOR
Implementing and maintaining quality assurance and quality control systems with written SOPs in compliance with protocol, GCP and regulatory requirements		x	x				
Review study specific SOPS	x	x	x				
Quality control system for data handling		x				x	
Sponsor Audit (May not be necessary for every Trial)			x				
Review of audit			x				
Escalation of non-compliance	x	x	x				x
Securing agreements to ensure direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring, auditing and inspection				x			
Obtain agreement (written) from investigator to comply with GCP, applicable regulatory requirements and approved protocol and to permit monitoring, audit and inspection.				x			
Study related contracts put in place				x			
Ensuring appropriate written agreements are in place for all sub-contracted responsibilities				x			
Define, establish, and allocate all trial-related duties and functions	x	x	x				
Maintain delegation log	x	x					
Provision of suitably qualified medical personnel	x						
Selection of investigator(s)/institution(s).	x		x				

The PI and Sponsor should utilise qualified individuals (e.g., biostatisticians, clinical pharmacologists, and physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and CRFs and planning the analyses to analysing and preparing interim and final clinical trial reports.	x	x	x			x	

Task	PI	SJH- CRF	SPONSOR	CO	E&F	Third party	DOR
Selection of investigator(s)/institution(s).	x		x				x
Provision of protocol and an up-to-date Investigator's Brochure to investigator/institution.	x						
Preparation, approval and submission of EC application and amendments	x	x					
Response to EC questions	x	x					
Retain copy of EC approval documents		x					
Preparation, approval and submission of CA/ HPRA applications and amendments	x	x	x				
Response to CA/ HPRA questions	x	x	x				
Retain copy of CA/ HPRA approval documents	x	x					
Investigator's brochure and changes or annual updates	x						
Manufacture, labelling and packaging (if required) and changes to manufacture						x	
Obtaining importation/ manufacturing licences	x					x	
Obtaining/ contracting QP release documents	x	x					
Retaining copies of importation/ manufacturing/ export licences		x					
Randomisation code generation and quality control	x	x				x	
Unblinding procedure	x	x				x	
IMP stability testing and IMP sample retention						x	
Product distribution to investigator						x	
Control of receipt of IMP		x					
Storage and handling instructions for IMP		x					
Accountability log for IMP		x					
Recall procedures for IMP		x				x	
Destruction of unused IMP		x				x	

Records for IMP: shipment, receipt, storage, disposition, return and destruction		x					
Selection and qualifications of study staff	x	x					
SOP for monitoring		x	x				
Preparation and review of monitoring plan		x	x				
Preparation and Review of monitor reports		x	x				

TASK	PI	SJH- CRF	Sponsor	CO	E&F	Third Party	DOR
Escalation of significant issues			x				x
Review of protocol deviations and GCP breaches		x	x				x
The Sponsor may consider an independent data-monitoring committee to assess the progress of a clinical trial, including the safety data and the critical efficacy.			x				x
Ongoing safety evaluation	x		x				x
Notification of ongoing safety measures to CA/ HPRA, ethics committee and PI	x	x					
Implementation of urgent safety measures	x		x				
Submission of safety updates to CA/ HPRA	x	x					
Unblinding and medical cover	x						
Staff training	x	x					
Maintain trial master file		x					
Case report form creation, review and approval	x	x				x	
System suitability check		x					
SOP for electronic data processing system	x	x				x	
Data entry, review and processing	x	x					
Maintain a security system that prevents unauthorized access to the data						x	
Data backup						x	
Safeguard of blinding during data processing		x				x	
Documented list of individuals with permission to make data changes		x					
Statistical analysis	x					x	
Quality control check of trial master file		x	x				

Clinical study report submission to CA/ HPRA	x	x	x				
Archiving of trial documents	x	x					
Provision of insurance and indemnity to cover the PI and institution against claims arising from the trial including malpractice and negligence	x				x		
Provision of treatment costs for trial subjects in the event of trial related injuries					x		