UNIVERSITY of LIMERICK

OLLSCOIL LUIMNIGH

Clinical Research Policy

For UL Sponsored Regulated Clinical Trials

Approved by Academic Council 17 May 2017

UNIVERSITY of LIMERICK

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Abbreviations

CRSU	Clinical Research Support Unit
CTIMPs	Clinical Trials of Investigational Medicinal Products
CRB	Clinical Research Board
CTA	Clinical Trial Agreement
GCP	Good Clinical Practice
HRI	Health Research Institute
HPRA	Health Products Regulatory Authority
HSE	Health Service Executive
IMP	Investigational Medicinal Products
PI	Principal Investigator
PAF	Proposal Authorisation Form
QMS	Quality Management System
RAF	Risk Assessment Form
REC	Research Ethics Committee
RSS	Research Support Services
SOP	Standard Operating Procedure
TTO	Technology Transfer Office
UL	University of Limerick
VPR	Vice President Research

2 Definitions

2.1 Sponsor

For Clinical Trials of Investigational Medicinal Products (CTIMPs) the European Commission Directive 2001/20/EC[5] stipulates that a person or organisation must take on the responsibility of Sponsor. Medical Device trials refer to ISO 14155[12] standards where Clinical trials are referred to as Clinical Investigations. For uniformity in procedures and for the purpose of this policy sponsor responsibilities will be defined as per EU Clinical Trials Directive 2001/20/EC and all such studies will be referred to as Clinical Trials.

When UL accepts the role of Sponsor, it is responsible for ensuring suitable arrangements are in place for the initiation, management and financing of clinical trials which requires UL to be the Sponsor.

2.2 Principal Investigator (PI)

A PI must be a UL employee (including a joint appointment between the University and the HSE) and must be a member of the Health Research Institute (HRI) at the University of Limerick (Refer to HRI criteria for membership).

The PI has primary responsibility for the design, implementation, conduct, completion and management of the clinical trial and the PI is accountable to the University as the Sponsor of the research on this basis. The PI must have a valid Good Clinical Practice (GCP) certificate for the duration of the Clinical Trial.

2.3 Health Research Institute (HRI)

The Health Research Institute (HRI), University of Limerick (UL), is a cross- Faculty institute that brings together researchers in UL and its partner institutions to focus on convergent and translational health research. The mission of the HRI is to conduct outstanding transformative research in order to improve the health and well-being of individuals, patients, communities and populations.

2.4 Clinical Research Board (CRB)

Oversight of clinical trial governance, on behalf of the University, will be undertaken by the Clinical Research Board (CRB). This board will support UL in ensuring it meets its responsibilities as Sponsor. The CRB reports directly to the VP Research.

2.5 Regulated Clinical Trials

Regulated clinical trials relates to research on human participants which is governed by the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations, 2004, transposed into Irish law through SI No 190 of 2004. The EU directive regarding medical devices has been transposed into Irish law through SI no253 of 1994, SI no252 of 1994nd SI 304 of 2001 (see section 5). The Health Products Regulatory Authority (HPRA) designated as the Competent Authority (CA) is responsible for the assessment of regulated research which includes clinical trials with medicinal products and clinical investigations of medical devices, conducted in Ireland.

2.6 Non-regulated Clinical Research

Non-regulated clinical research relates to clinical research on human participants which is outside the scope of the Regulations. Non-regulated research may be interventional in design, such as behavioural therapies, exercise strategies, or may be non-interventional trials of medicinal products that are not subject to legislative control (see below).

2.7 Interventional Clinical Research

Interventional clinical research: A study in which human participants are assigned to receive one or more interventions (or no intervention) so that researchers can evaluate the effects of the interventions on health-related outcomes. The assignment of intervention is determined by the study protocol. Participants may receive diagnostic, therapeutic, or other types of interventions.

2.8 Non-interventional (Observational) Clinical Trial

A non-interventional clinical trial is a trial involving use of a medicinal product where the medicine is prescribed in the usual manner, in accordance with the terms of the marketing

authorisation, and not prescribed for research purposes. Treatment is not decided by the trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures are required of the patients for research purposes and epidemiological methods are used for the analysis of collected data. This type of trial is observational in design.

3 Introduction

The University of Limerick (UL) has long been involved in health research with human participants; initial research was about physical activity and its interaction with human health. The establishment of the Faculty of Education & Health Sciences (FEHS) in 2008, incorporating Medicine, Nursing & Midwifery, Psychology and Clinical Therapies, has led to a rapid increase in healthcare research across these disciplines. This growth in health research within EHS departments, as well as health related research conducted by researchers in other Faculties such as Science & Engineering, prompted the establishment of a Health Research Institute (HRI) at UL in 2015, to facilitate an expansion of proactive and planned inter-disciplinary health research.

The aim of the HRI is to develop strong internal and external research collaborations, to advance research that will deliver innovative solutions to disease prevention, healthcare delivery, and the maintenance of healthy individuals. UL's Strategic Plan, Broadening Horizons 2015-19[1] and Research and Innovation Strategic Plan, Excellence and Impact 2020[2], both support this continued growth in healthcare research.

The inclusion of health research as a strategic priority will inevitably result in a greater number of UL-led, health related clinical trials involving human participants.

Certain projects will require regulatory approval from the relevant competent authority, e.g. Health Products Regulatory Authority (HPRA) if they involve clinical trials of investigational medicinal products (CTIMPs) or clinical investigations of a medical device.

In such instances UL may be requested to accept the role of Sponsor.

As Sponsor, UL will be legally obliged to accept overall responsibility for the conduct of the trial or investigation. Sponsor responsibilities and Principal Investigator (PI) responsibilities in the conduct of clinical trials are detailed in the internationally accepted ICH Good Clinical Practice (GCP) standards[3] (see appendix i). These standards are in place to ensure that the safety and rights of research participants are protected at all times.

In order to meet its obligations as Sponsor, and in alignment with UL's policy on Research Integrity[4], UL has developed this policy to provide a framework for the governance of Regulated

Clinical Trials. UL has also established the UL Clinical Research Board (CRB) which has certain delegated responsibilities to oversee clinical trial activities on behalf of the University.

4 Scope

This policy document describes the infrastructure within UL to act as Sponsor for any regulated clinical trial involving human participants. Any such research trial, involving the University acting in a sponsor role, must be managed by a PI who is also a UL employee, including joint appointments between the University and the HSE, and must be a member of the HRI.

This document describes in detail the various stages and mandatory application processes for the PI, which must be adhered to **before** UL will accept the role of Sponsor. The document also outlines the quality assurance and risk mitigation strategies that ensure clinical trials are conducted to the required regulatory standards. This will enable clear research governance that is required to:

- Safeguard human participants in Clinical Trials;
- Protect researchers/investigators (by providing a clear framework to work within);
- Enhance ethical and scientific quality;
- Minimise risk;
- Monitor practice and performance;
- Promote good practice.

This policy document details the responsibilities of UL as Sponsor and the responsibilities of the PI in line with ICH GCP. It is applicable to all clinical trials that fall under the definition of EU Clinical Trials Directive 2001/20/EC[5] and applicable device legislation that requires regulatory approval.

The following section provides background information on the relevant regulation and legislation underpinning clinical trial activity in order to provide a context for this policy.

5 Background - Regulation and Legislation

The clinical trial activities of UL employed researchers is governed by Irish and EU legislation and must be conducted in accordance with the ethical principles that have their origin in the

Declaration of Helsinki[6] and that are consistent with Good Clinical Practice (GCP). UL researchers must also adhere to the 2014 national policy statement, 'Ensuring Research Integrity in Ireland'[7]

GCP was developed by the regulatory authorities of the EU, Japan and the USA as a steering group termed the Tripartite International Conference on Harmonisation (ICH) and provides international assurance that data and reported results of clinical investigations are credible and accurate and that the rights, safety and confidentiality of participants in clinical trials are respected and protected.

The EU Clinical Trial Directive (2001/20/EC), transposed into Irish law as Statutory Instrument (S.I.) 190 of 2004[8], makes compliance with GCP a legal obligation in Ireland for all trials of Investigational Medicinal Products (IMP). Although GCP is not currently obligatory for non-IMP trials, a repeal of Directive 2001/20/EU has been published (16th April 2014)[9]. This repeal proposes a broader concept of "clinical study," including non-interventional studies, be regulated for in the legislation.

The EU directive regarding medical devices has been transposed into Irish law as follows;

- S.I. No. 253 of 1994[9], European Communities (Active Implantable Medical Devices) Regulations, 1994 became mandatory on 1 January 1995.
- S.I. No. 252 of 1994[10], European Communities (Medical Devices) Regulations, 1994 became mandatory on 14 June 1998.
- S.I. No. 304 of 2001[11], European Communities (In-vitro Diagnostic Medical Devices) Regulations, 2001 became mandatory on 7 December 2003.

ISO 14155 (2011)[12] is the standard which addresses good clinical practices for the design, conduct, recording and reporting of clinical trials to assess the safety and performance of medical devices for regulatory purposes.

To ensure that UL researchers operate to the highest standards, regulated clinical trials must apply ISO 14155 (2011)[12] to device-related trials and GCP guidelines to all other regulated studies.

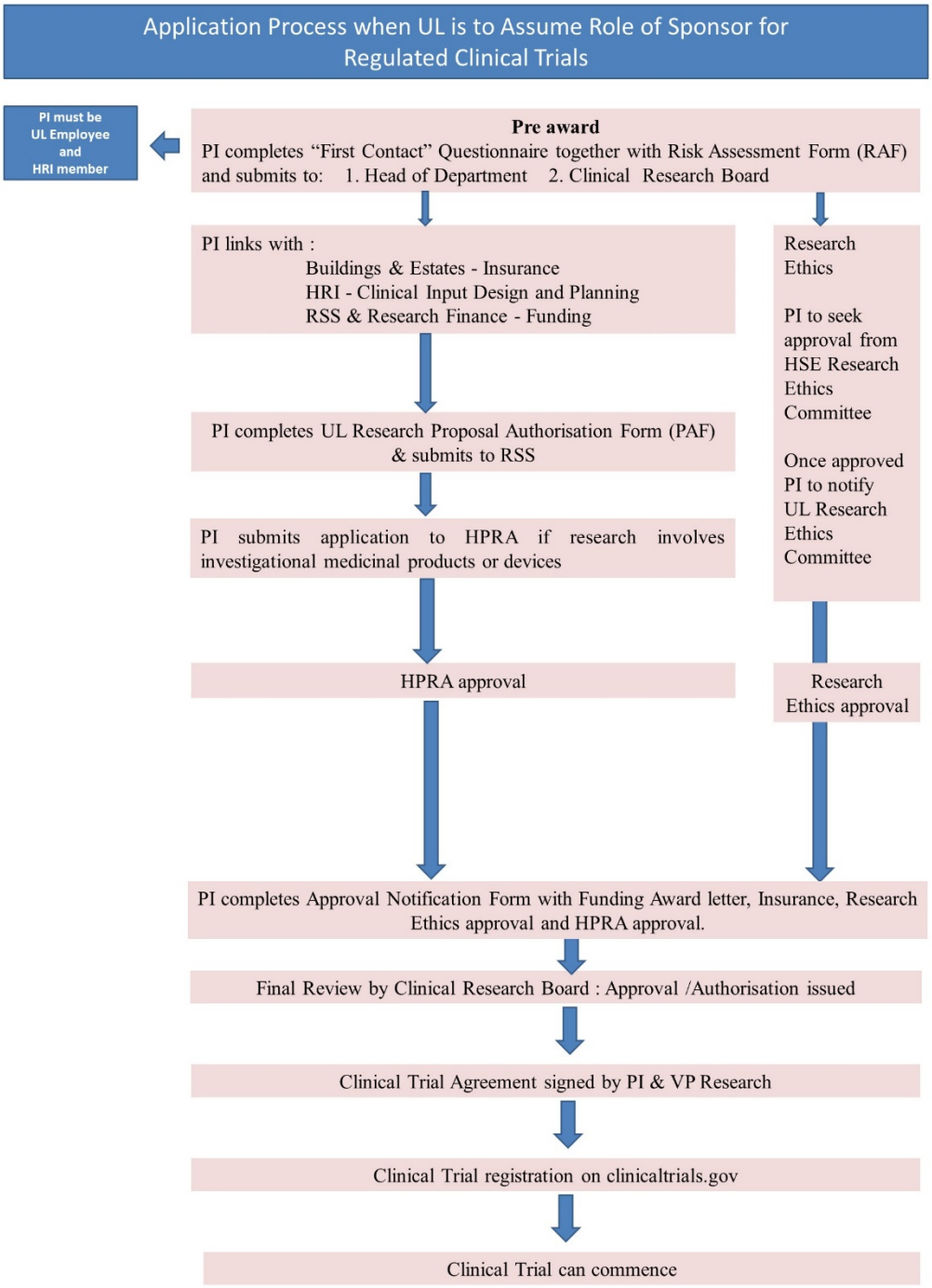
For Clinical Trials of Investigational Medicinal Products (CTIMPs), the European Commission Directive 2001/20/EC[5] stipulates that a person or organisation must take on the responsibility of Sponsor. The Sponsor is defined as: an individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial.

The Sponsor may arrange to delegate any, or all, of their trial-related functions to an individual, company, institution or organisation**.** However, in all such cases, the Sponsor shall retain overall responsibility for ensuring that the conduct of the trials and the final data generated by those trials comply with Directive 2001/20/EC[5] and Directive 2005/28/EC[13].

Similarly ISO 14155[12] defines the responsibilities of the Sponsor, investigators, human ethics committees, regulatory authorities and other bodies in the design, assessment and conduct of clinical investigations involving medical devices**.**

6 UL Governance procedure when assuming Role of Sponsor

Approval for UL to act as a Sponsor is a multi-step process. Initial conditional approval may be issued for the PI to proceed with funding application process but final approval is dependent on completion of all steps as detailed below.


Application Process when UL is to Assume Role of Sponsor for Regulated Clinical Trials
PI must be UL Employee and HRI member
Pre award
PI completes "First Contact" Questionnaire together with Risk Assessment Form (RAF) and submits to: 1. Head of Department 2. Clinical Research Board
PI links with :
Buildings & Estates - Insurance
HRI - Clinical Input Design and Planning
RSS & Research Finance - Funding
PI completes UL Research Proposal Authorisation Form (PAF) & submits to RSS
PI submits application to HPRA if research involves investigational medicinal products or devices
HPRA approval
Research Ethics
PI to seek approval from HSE Research Ethics Committee
Once approved PI to notify UL Research Ethics Committee
Research Ethics approval
PI completes Approval Notification Form with Funding Award letter, Insurance, Research Ethics approval and HPRA approval.
Final Review by Clinical Research Board : Approval /Authorisation issued
Clinical Trial Agreement signed by PI & VP Research
Clinical Trial registration on clinicaltrials.gov
Clinical Trial can commence

6.1 Application and Approval Process

The review and approval for regulated clinical trials for which UL will assume the role of Sponsor is a multi-step process.

Where a Clinical Trial is proposed, the PI must prepare a "first contact" questionnaire which incorporates a Risk Assessment form and insurance checklist. Guidance in relation to clinical risk management is provided in section 8 with insurance requirements outlined in section 9 below.

The PI presents the submission to the pertinent Head of Department (HoD) for review and approval. It is the responsibility of the Head of Department to clearly convey the standards and protocols required for research in that Department and to ensure that adherence to these standards is integral to the staff members of the Department. The PI should also be made aware that all clinical trials where UL is Sponsor will be conducted through the HRI Clinical Research Support Unit (CRSU) - see section 7.4

Once approved by the pertinent HoD, the PI must submit the "first contact" questionnaire and the risk assessment form to the CRB.

The CRB will review the submission, classify the risk based on the RAF details and, if favourable, issue their conditional approval to enable the PI to proceed and engage with the relevant departments to secure the necessary approvals in relation to;

- Insurance
- Funding - Award Agreement signed by VPR

The research ethics application process will be determined if the trial is a single or a multi-centre study, or if it falls under IMP or Device legislation. Likewise an application to the HPRA for regulatory approval will be submitted if the Clinical Trial involves investigational medicinal products or devices which fall under the remit of the regulatory authority. The timing of these applications and associated contractual agreements will be determined on a study by study basis and with the advice of the HRI CRSU.

When the necessary approvals, including ethical committees, insurance, funding and regulatory (where applicable), have been obtained the PI must then complete an Approval Notification Form and submit to the CRB.

The CRB will issue the CTA agreement to the PI for review and agreement.

CRB will then sign off a final approval letter and send approval form to VPR who will sign the CTA and give authorisation for the Clinical Trial to commence. This agreement will also be signed by the Hospital CEO as part of the Research Ethics Committee approval process.

All clinical trials must be registered in the public registry www.clinicaltrials.gov before the first trial participant is recruited.

6.2 Post Approval Process

During the active clinical trial phase, the PI will be required to submit status reports to the CRB on a bi-annual basis - or more frequently if required. Status reports will include updates on overall study recruitment status, safety reports, protocol amendments, major protocol deviations, updates on changes to site personnel, risk assessment status and adherence to financial targets.

7 Governance of Clinical Trials in UL

There are a number of key roles in the governance of Clinical Trials in UL, namely;

UL as Sponsor

Principal Investigator (PI)

Clinical Research Board (CRB)

Health Research Institute (HRI)

7.1 Role of UL as Sponsor

Clinical trials are conducted by a multidisciplinary team of researchers, each with their own roles and responsibilities. The scope of this policy document will focus solely on the responsibilities of UL as the Sponsor and of a PI at UL who, collectively, have overall responsibility for the

clinical trial.

For Clinical Trials of Investigational Medicinal Products (CTIMPs) the European Commission Directive 2001/20/EC[5] stipulates that a person or organisation must take on the responsibility of Sponsor. Medical Device trials refer to ISO 14155[12] standards. For uniformity of procedures, for the purpose of this policy 'sponsor responsibilities' will be defined as per Directive 2001/20/EC[5].

When UL accepts the role of Sponsor, it is responsible for ensuring suitable arrangements are in place for the initiation, management and financing of a clinical trial which has UL as the sponsor. UL may delegate certain responsibilities to the Clinical Research Board (CRB), to the HRI Clinical Research Support Unit (HRI CRSU) management, or to a Principal Investigator, but UL is ultimately responsible for all aspects of the clinical trials and retains overall responsibility for ensuring that the conduct and the final data generated complies with Directive 2001/20/EC[5] and Directive 2005/28/EC[13]**.** This overall responsibility is managed by the VP Research, acting on behalf of UL.

A 'Clinical Trial Agreement,' detailing clinical trial duties and responsibilities will be put in place between UL as Sponsor, the Hospital where the trial will be conducted and the PI. This will be compiled, agreed and signed by all parties **in advance** of clinical trial commencement.

The CRB, acting on behalf of UL in overseeing the conduct of the trial, will be responsible for issuing a standard template agreement and will report directly to the VP Research at UL. The HRI acts as a support for both Sponsor and PI and will advise on research design, quality and regulatory issues.

7.1.1 Sponsor Responsibilities

UL as Sponsor is responsible for ensuring appropriate arrangements are in place for the conduct of the Clinical Trial, namely;

- The PI and other key researchers have the necessary expertise and experience to conduct research as proposed;
- That research teams have attained funding approval and may access sufficient resources to deliver their research as proposed;

- That all clinical trial arrangements comply with applicable national legislation;
- The collection of accurate and high quality data;
- That a suitable UL Research Ethics Committee and/or HSE Research Ethics Committee has approved all clinical trials prior to their commencement;
- That the Principal Investigator obtains written authorisation from the HPRA prior to the commencement of regulated trials;
- That all clinical trials are formally registered on clinicaltrials.gov;
- That agreement has been reached about compensation, in the event of harm to research participants, prior to the commencement of the clinical trial. Refer to section on insurance.
- That suitable management and monitoring systems are in place to ensure the clinical trial is carried out in accordance with the approved protocol (or proposal) and all regulatory requirements;
- That suitable arrangements are in place for the formal recording and reporting of serious adverse events/reactions of any kind;
- Approval of modifications to the design of the clinical trials and processes are in place for obtaining any regulatory approvals and ensuring they are implemented;
- Auditing or inspection by relevant authorities is permitted and facilitated.
- At the conclusion of the clinical trial, the completion of a study report and appropriate dissemination of findings are instigated.

7.2 Role of the Principal Investigator (PI)

The PI has primary responsibility for the design, implementation, conduct, completion and management of the clinical trial and the PI is accountable to the University as the Sponsor of the research on this basis. The PI must have a valid GCP certificate for the duration of the Clinical Trial. GCP training is provided at a number of centres across Ireland and also on-line. GCP certification is issued for a two year period; after that time, refresher GCP training is required.

GCP is an international ethical and scientific quality standard for the design, conduct and recording of research involving humans. Comprised of 13 core principles (appendix X), GCP

applies to all clinical investigations that could affect the safety and well-being of human participants.

According to GCP, a PI is the person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator who is the responsible leader of the team is called the Principal Investigator.

The PI must adhere to all the processes as detailed in Section 6, which include ensuring arrangements are in place for the effective financial management of the study**.** In addition the PI must adhere to policies and procedures at the site where the clinical trial is to be conducted e.g. acute hospital or community-based health settings.

Specific PI responsibilities will be in accordance with those set out in Section 7.2 below and as detailed in the CTA with UL - which will be compiled, agreed and signed by all parties in advance of the commencement of the clinical trial.

7.2.1 PI's Responsibilities

The PI will have suitable experience and expertise in the conduct of clinical trial and is responsible for:

- Undertaking the design, implementation, management, completion and reporting of clinical trials to standards set out in national and international regulations.
- Leading and managing others with delegated responsibility for some of the aspects outlined above as required;
- Ensuring that the clinical trial must comply with all legal and ethical requirements;
- Ensuring arrangements are in place for the effective financial management of the clinical trial. Post award financial management is the responsibility of the UL research finance office.
- Submitting the study to the relevant HSE Ethics Committees for approval a priori. The trial must not commence without written approval being received. A notification letter must also be submitted to UL Faculty's Human Research Ethics Committee.
- Ensuring that substantive changes/amendments to any protocol or proposal are submitted for ethical review and to the Sponsor, through the CRB, for agreement;

- Ensuring that all processes described in Section 6 of this document must be adhered to. Section 6 includes reference to all ethical, regulatory, financial and contractual agreements and approvals that need to be in place before a clinical trial can commence;
- The PI must ensure the necessary Intellectual Property agreements are in place with the sponsor, in line with UL Intellectual Policy;
- The PI must ensure that each member of the research team, including those at collaborating sites, must be qualified with respect to education, training and experience to discharge their role in the clinical trial, and that their qualifications are documented;
- The PI must ensure that potential clinical trial participants are fully informed before deciding whether or not to consent to participate in the clinical trial;
- The research team must give priority and respect to the dignity, rights, safety and well-being of all clinical trial participants at all times;
- When clinical trials involves patients under the care of a doctor, nurse or social worker for the condition to which the research relates, those care professionals must be informed that such patients are being invited to participate and they need to agree to retain overall responsibility for their medical care;
- Participants' care professionals must be given any information directly relevant to the participant's care that arises from the research (unless participants or ethical approval request otherwise);
- The PI must ensure that procedures are in place to ensure collection of accurate and high quality data, and the integrity and confidentiality of data during processing and storage must be maintained at all times, adhering to Data Protection legislation as required;
- The PI must record and formally report significant developments (negative or positive) as the trial proceeds, in relation to the safety of individuals or the scientific direction.
- Reporting on progress and research outcomes must be provided to the Sponsor (through the CRB), to all research funders, and to others with a legitimate interest, in a timely manner and at an acceptable standard;
- Findings must be disseminated promptly and participants be given feedback as necessary, and in a suitable manner
- Arrangements must be made, before the clinical trial commences, to archive all data when research has finished according to accepted research conventions (REF);

- All data and documentation associated with the clinical trial must be available at the request of the CRB, the HPRA and/or other external inspection authorities (where applicable).

7.3 Role of the Clinical Research Board (CRB)

Clinical Trial governance oversight on behalf of the University will be undertaken by the Clinical Research Board (CRB). This Board will support UL to meet its responsibilities as Sponsor. The CRB will report directly to the VP Research.

The membership of the CRB consists of:

- The Director, Health Research Institute (Chair);
- A Nominee of VP Research from Technology Transfer Office;
- The Corporate Secretary or nominee;
- A Nominee of VP Research with clinical research experience ;
- UL's Insurance Administrator;
- A Research Governance Officer.

The Research Governance Officer will provide administration support to the CRB. External Consultancy. Further expertise may be sought by the CRB when necessary

7.3.1 Engagement with the Clinical Research Board (CRB)

- Prior to the submission of any Clinical Trial application where the University is required to be sponsor, the CRB will review the proposed Clinical Trial to assess the extent that it may expose UL to any undue reputational, or other, risk.
- The CRB, through the Research Governance Officer, will issue a draft Clinical Trial Agreement which will be reviewed and agreed by the PI prior to the commencement of the research.
- When the necessary approvals, including ethical committee, insurance, funding and regulatory (where applicable) have been obtained, the CRB will review all relevant documentation for UL-sponsored Clinical Trials and, if suitable, shall recommend to the UL VPR that the CTA may be signed and that the research study may commence. In the event of multicentre trials, multiple CTAs may have to be prepared and signed with various institutes. This review will include an approval process of external vendors, such

as contract research organisations, data management groups, specialist laboratories whose services may also be required to support the conduct of the UL sponsored research, etc.

- During the conduct of the clinical trial the CRB will review all relevant reports and risks and, as necessary, determine if the clinical trial should be halted, amended or terminated.

7.4 Role of the HRI Clinical Research Support Unit (CRSU)

All Clinical Trials where UL is Sponsor will be conducted through the HRI Clinical Research Support Unit (CRSU). Each PI must be a member of the HRI .The CRSU supports HRI members in their conduct of clinical trials, through the support of its research nursing team at several sites, including the UL campus, UL Hospitals sites and Community Health settings.

The role of the HRI in the governance of clinical trials in UL is as a support, to both UL as Sponsor and to the PI in their design and conduct of high quality research that meets all regulatory standards.

7.5 External Consultancy support

Depending on the complexity of the Clinical Trial, the CRB may recommend employing an experienced external consultant to monitor and audit the Clinical Trial. Monitoring and auditing are integral to ensure that clinical trials are conducted, recorded and reported in accordance with the protocol, GCP and meets applicable regulatory requirements. Monitoring is requirement of both ICH GCP[3] and ISO14155[12].

The CRB, following review of the Clinical Trial, will advise the PI should this be required. Provision for such associated costs will need to be included in the budget of any funding application.

8 Risk Management in Clinical Trials

8.1 Overview

All UL- sponsored clinical trials carry potential risks that apply to the University, the Principal Investigator (PI) and/or the funding agency, to society in general, and to a clinical trial participants.

Clinical Research Risk Assessment is a proactive process in which information is collected about a proposed clinical trial to identify clinical risks that may occur.

The purpose of the Clinical Research Risk Management Strategy is to identify all Clinical Research risks and, to the extent it is possible, limit these risks. Success in this endeavour requires a stringent application of processes that are rigorous, reliable, transparent, credible, and quantifiable. It is important that an initial risk assessment of proposed clinical trial takes place by the PI at design stage, to ensure that risks identified are adequately addressed at an early stage and resources required to mitigate these risks are identified and funded.

The risk assessment form has been incorporated in the "first contact" questionnaire and must be completed by the PI as detailed in section 6.1. It will be reviewed by the CRB and risks classified accordingly.

Risk must be continually reassessed during the conduct of the Clinical Trial. This information must be included in the bi-annual reports to the CRB.

8.2 Source of Risk in Clinical Trials

Risks may arise from varied sources in Clinical Trials but are in many cases predictable and can be anticipated. Understanding the origins of such risk is important if they are to be properly and successfully controlled.

Risks should be considered both at a system level and a clinical trial level.

Potential sources of risk may include:

Drug or device trials: The level of risk will typically be higher in interventional research than in observational research – with the risk being highest for phase 1 or 2 clinical trials and less so in phase 4.

Study Population: Risk will vary with the specific research population and level of background comorbidity that is present. It will be higher in clinical trials involving pregnant women, in children or in other vulnerable populations. It is essential that despite the occurrence of increased risks, such patient groups should not become disenfranchised from the benefits of research purely because of the added challenges of conducting such work within these populations.

Nature of the Research: Some research by virtue of its nature may raise concerns or disquiet within specific sections of the community due to background social, cultural, religious or other concerns. Such concerns may persist even though the research is independently evaluated as being scientifically valid and ethically sound. Similarly, research that requires highly personal individual data, such as a detailed sexual history or those examining issues associated with illegal activities such as illicit drug use or which require certificates of confidentiality, all increase potential consequences of any unintended breach of confidentiality. While such inherently high risk research is not impossible to conduct, it is critical that the planning, conduct and reporting of such work directly takes into account and proactively manages these potential concerns and liabilities. Ultimately, it is essential that the institution is provided with the opportunity to consider and balance the potential scientific benefits, ethical considerations and cultural concerns arising from a given protocol, and where necessary to establish any additional monitoring, supervisory or public relations activities it deems necessary for the study to proceed.

Research Team: Risks associated with a specific research team will vary in accordance with the experience, facilities and resources available to the team of investigators both in general terms as well as within the specific proposed area of investigation.

Conflicts of Interest: Conflicts of interest, either real or apparent-especially where financial in nature - may serve to magnify the level of risks within a study. This may occur when the Sponsor is the patent holder of an intervention that is undergoing first-in-human or first-for-indication study under the supervision of that sponsor.

8.3 Quantification of Risk in Clinical Trials

It is notable that all clinical trials are associated with some increased element of risk over routine clinical care. Clinical research can be classified as; extreme, serious, moderate or low risk.

The lists below expands on but does not limit each of these categories.

Extreme risk includes, but is not limited to:

- Research involving genetic treatment or modification
- Observational studies focused on detailed highly personal patient history or illicit activities
- Research on pregnancy (except for purely observation studies)
- Research on children (except for purely observation studies)
- Research on particularly vulnerable participants, such as those unable to personally provide consent so that routine consent in advance of study participation is not feasible
- Research which potentially stigmatises a racial, ethnic or cultural subgroup
- Where a university or members of a research team stand to benefit financially
- Phase 1,2 or 3A Clinical Trial of medicinal product in humans
- Research involving any non-approved implantable medical device
- Any additional consideration which in the judgement of the PI results in an otherwise serious or moderate risk study having a resulting high net risk.

Serious risk includes, but is not limited to,:

- Phase IIIb or Phase IV clinical trials
- Trials of non-medicinal products
- Observational studies with non-routine (relative to specific study population) invasive investigations, other than those with minimal increased risk (e.g. phlebotomy)
- Where direct payment or other inducements are provided to potential participants

Moderate risk includes but is not limited to:

- Any additional consideration that result in a low risk study having a moderate risk

Low risk:

- All other research activities.

Once a Clinical Research trial commences risks need to be continually monitored and assessed.

Residual risks or new risks identified during the conduct of the clinical trials may be classified as follows:

1. Extreme e.g. gross negligence in study conduct, suspected fraud or urgent patient safety issue - such as to require immediate intervention by the CRB escalating to the VPR including possible suspension or termination of protocol and associated action by regulatory authorities.
2. Serious e.g. failure to rectify a repeated minor protocol violation warranting prompt intervention by study staff but not requiring suspension of study.
3. Moderate e.g. minor protocol/SOP violations appropriate for routine reporting to and response by study staff.
4. Low

The PI must be made aware of, and be advised of, the relevant Clinical Trials personnel through the following escalation process, which is based on the residual risk rating:

Residual Risk & Level of Report	Further Information
Extreme **VPR** **Clinical Research Board**	If the residual risk is deemed to be extreme, then immediate action is required. In this case the activity/project should not proceed or if it relates to an existing activity/project then the PI must inform the CRB and the VPR of the matter so that action can be taken immediately to either moderate the risk or close the activity/project.
Serious **Clinical Research Board**	Serious risks require careful on-going management with frequent evaluation of the risk factors by the PI in order to restore them to more acceptable levels of risk. Risks at this level should be reported to the CRB at its bi-annual risk management meetings. In the interim, any escalation of risk should be reported to the VPR immediately.
Moderate **HRI Clinical Operations Manager**	Moderate levels of risk may be acceptable for certain projects and these risks require approval of the HRI Clinical Operations manager prior to commencing the activity/project or to allow the project/activity to continue. Re-assessment of the risk factors should be conducted at regular intervals to assure stakeholders that the risk has not escalated.
Low **PI & Head of Department**	This is the lowest and most tolerable level of risk. Clinical research should carry no higher than tolerable risk without the express approval of the Head of Department/Unit. Re-assessment of the risk factors should be conducted at regular intervals to assure stakeholders that the risk has not escalated.

8.4 Controls to Mitigate the Clinical Trials Risks

Development of a Quality Management System

Quality of clinical trials depends on data integrity and participant protection. To meet regulatory expectations, UL recognises the need for robust Quality Management Systems with specific standards for each clinical trial. Such Quality Management Systems will include: personnel roles and responsibilities, training, policies and procedures, quality assurance and auditing, document management, record retention, reporting and corrective and preventive action.

UL clinical trials will adhere to the individual researcher's departmental- specific QMS, in addition to the QMS of the HRI CRSU for the participant contact element of each clinical trial.

The QMS documentation for the conduct of clinical trials through the HRI CRSU will be structured as follows:

Level 1: Quality Governance Policy Manual
The first level document will provide a general overview of QMS and specify the Quality Policy.

Level 2: Standard Operating Procedures (SOPs)
The second level documents provide more detailed explanation of the QMS elements.
These documents explain how the Quality Policy is to be implemented – i.e., the Who, What, Where and When; these are referred to as SOPs.

Level 3: Work Instructions
The third level documents provide the detailed instructions on implementing the process or procedures to be completed at the clinical site, for example : scope of services, Analytical Plans and Process Documents.

Level 4: Other Instructions
The fourth level documents provide the "How to" in completing specific tasks. These documents include, Forms, Product Specifications, Task Instructions, Industry Standards and Training Records.

9 Insurance Requirements

One of the key components required for any clinical trial is insurance cover. A clinical research insurance checklist has been developed by UL, with its insurance brokers. This checklist has been incorporated in the "first contact" questionnaire and must be completed by the PI (as detailed in section 6.1) so that the CRB, linking with the UL Insurance Administrator, can ensure that there are adequate indemnities in place.

The required indemnity falls within 3 categories:

- Medical Malpractice
- Professional Indemnity and
- Product Liability.

9.1 Medical Malpractice

Where the Clinical Trial is predominantly conducted within a State Claims Agency 'designated entity' then the medical malpractice indemnity for the PI and for all staff working on the study under direction of the PI arises from the State Claims Agency's Clinical Indemnity Scheme (CIS), and is therefore provided by the State.

The HRI/CRSU is in the process of being included as a 'designated entity' for this purpose. This will ensure that personnel working on clinical trials within the HRI/CRSU are similarly protected, by CIS cover, from a medical malpractice perspective. This is subject to government approval via a statutory instrument and, in the interim, the State Claims Agency has agreed to provide medical malpractice coverage to people working at the HRI/CRSU on a case-by-case basis, following pre-approval by the State Claims Agency. This coverage will not extend more broadly to research conducted throughout the University, outside of the HRI/CRSU.

9.2 Professional Indemnity

The UL Professional Indemnity Policy excludes Clinical Trials and medical negligence resulting in claims for bodily injury or mental injury. Medical malpractice indemnity for UL employees conducting clinical trials are not covered by the CIS. The UL Professional Indemnity policy covers financial losses arising from any negligent act, error or omission or professional duty, unintentional breach of trust and/or unintentional breach of confidentiality. UL Professional Indemnity policy excludes any UL sponsored Clinical Trials and also excludes medical negligence which results in claims arising from bodily or mental injury.

In relation to UL-sponsored Clinical Trials, it will be necessary to suitably arrange a specific Clinical Trial Insurance Policy, on a trial-by-trial basis, that is purchased from the project budget.

9.3 Product/Prototype liability

The UL Public/Products Liability Policy specifically extends, to include the Products Liability exposure arising out of manufacture and design of medical devices, probiotic preparations and software, for onward use in Clinical Trials. This liability cover is only for use in Clinical Trials on a small basis, i.e. it will not cover mass production or product for commercial reasons, without it being referred to the Insurer.

10 Review of policy

This policy will be reviewed every two years, or as required so as to incorporate legislative changes, to ensure that it continues to enhance the decision-making and operation of the University.

Appendix

i. References

ii. Principles of ICH GCP

Appendix i

References

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Appendix ii Principles of ICH GCP - summary

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and /or society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
4. The available non-clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. Clinical trials should be scientifically sound and described in a clear, detailed protocol.
6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.
7. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the ethically approved protocol.
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.