

1. Background

Purpose

The Health Research Board (“HRB”) *Strategy 2016 – 2020: Research. Evidence. Action.*¹ launched in January 2016 supports the design, conduct and evaluation of healthcare intervention studies in order to improve health outcomes and health service delivery.

Clinical trials and interventions are an essential step in translating research discoveries and knowledge into new ways of treating patients, delivering care or changing behaviour. Without clinical trials and interventions, there is no evidence whether new medical devices, surgical, physiotherapy, behavioural, or other interventions actually deliver what they claim to deliver, and payers in a healthcare system are without guidance.

Clinical trials and interventions funded through HRB funding schemes are subject to this policy. This policy will form part of our grant general terms and conditions.

The purpose of this policy is to set out the HRB’s requirements for Host Institutions (“HI’s”) before, during and after the conduct of clinical trials to ensure good research governance is adhered to.

Research governance may be defined as the broad range of regulations, principles and standards of good practice that exist to achieve, and continuously improve, research quality both nationally and internationally. Research governance is needed to;

- safeguard participants in health research
- enhance ethical and scientific quality of research
- mitigate risk² and
- avoid research waste.

Definitions and scope

A clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiological procedures, devices, behavioural treatments, process-of-care changes, preventive care, etc.

This policy will cover clinical trials and interventions as defined above, including regulated and non-regulated trials where the HRB is directly funding the trials.

A regulated clinical trial is a clinical trial that falls under the remit of the Competent Authority, in Ireland the Health Product Regulation Authority (HPRA) i.e. they need HPRA approval. These trials typically involve an

¹ <http://www.hrb.ie/publications/hrb-publication/publications//702/>

² This means having an approach to mitigating risks that gives at least the same consideration to the risks that arise if the research does not take place as to those that arise if it does, and the same consideration to the likelihood as to their impact. The risk appetite should favour the research taking place.

Investigational Medicinal Product (IMP) or Medical Device that falls under the IMP regulatory framework (SI 190/2004) which makes compliance with a specific set of Good Clinical Practise 'guidelines' (ICH GCP) and the EU Clinical Trial Regulation EU#536/2014 or the EU Medical Device Regulation 2017/745 a legal requirement for study conduct.

A non-regulated clinical trial is a clinical trial that does not fall within a specific legislative framework.

2. HRB funding for clinical trials and interventions

This policy will cover clinical trials and interventions where the HRB is directly funding the trials through the following HRB schemes only:

- Definitive Interventions and Feasibility Awards (DIFA) and
- Clinical Trial Networks (CTNs); excluding Cancer Trials Ireland (CTI).

Clinical trials funded under the current CTI programme have a separate contract that governs CTI responsibilities for the management and conduct of cancer clinical trials. Similarly, clinical trials conducted in a HRB funded Clinical Research Infrastructure such as the HRB CRFs but not directly funded by the HRB, will have a separate contract that governs their responsibilities for the management and conduct of clinical trials in line with the above policy.

3. HRB Pre Trial Requirements

The Post Award Governance Framework sets out the following requirements.

Approvals and contracts

Approvals are not required when grant applications are submitted for funding review, but in the event that an application is funded, the HI must have the relevant regulatory, ethical and hospital approvals and appropriate governance arrangements in place before a trial can begin.

With the exception of ethical approval, the HRB does not require sight of approval documents when they are obtained.

In the event that the competent authority (i.e. Health Product Regulatory Authority ("HPRA") or a research ethics committee requires amendments that substantially affect the research question, methodology, trial duration or costs to the extent that the project is no longer the same as that approved for funding by the HRB, the HI of the award must notify the HRB.

To ensure that the processing of personal data for the purposes of health research is compliant with General Data Protection Regulation ("GDPR") and the Health Research Regulation 2018, researchers should seek project specific advice from their institutional Data Protection Officer.

If any part of the clinical trial will be subcontracted to a third party, the HI must ensure that they have a formal contract/agreement in place before they start work.

Sponsorship

All clinical trials and interventions under this policy are required to have a formal Sponsor.

The HRB will not act as a Sponsor for clinical trial and interventions.

For clinical trials and interventions under this policy, the Sponsor is defined as the legal entity which has ultimate responsibility for the study and compliance with the regulations, principles and standards of good practice that governs clinical research. The Sponsor takes the responsibility for the initiation, management, financing (or arranging the finance) and reporting of the clinical trial and interventions.

The sponsorship responsibilities for Clinical Trials of Investigational Medicinal Products (CTIMPs) are governed by the EU Clinical Trial Regulation EU#536/2014. The sponsorship responsibilities for Clinical Investigation of a Medical Device are governed by the EU Medical Device Regulation 2017/745. For reference to current legislation please visit the HPRA website.

A Sponsor can be:

- The Principal Investigator's employing institution (*Host Institution - University*)

Or

- One of the employing institutions where the trial is located e.g. a hospital site

The Sponsor for HRB funded trials cannot be an individual or pharmaceutical company. If the Sponsor is a legal entity outside of the Host Institution, the HI must ensure that they have a formal contract in place with the Sponsor and that they are in line with our grant conditions.

Sponsorship oversight should be planned and put in place for the duration of the clinical trial. The level of oversight required during the implementation of the clinical trial should be assessed carefully and commensurate with the clinical trials risk level. All clinical trials and interventions must undergo a risk assessment before an application is submitted to support the Sponsorship decision and oversight arrangements required.

Details of the Sponsor must be provided to the HRB at the time of full application for funding, following a Sponsorship decision.

At application stage, the Sponsor must submit a signed document to the HRB, clearly setting out its responsibilities for the study and any responsibilities delegated to third parties and confirming that the study will be conducted in compliance with Irish and European legislation and guidance and in accordance with the ethical and scientific principles of the Declaration of Helsinki and ICH guidelines, prior to initiation of the clinical trial.

The HRB must be kept informed of any subsequent changes made to the sponsorship arrangements during the lifetime of the award.

Insurance

For all clinical trials, the Sponsor is responsible for ensuring that appropriate insurance or indemnity is in place as per the HRB general terms and conditions to cover liabilities which may arise in relation to the design, management and conduct of the clinical trial.

Trial registration

The HRB believes that making the outputs of HRB-funded research available to the widest possible audience is a fundamental part of its mission. The HRB supports the All Trials Campaign³. Unregistered and unreported

³ <http://www.alltrials.net/>

clinical trials are unethical and can cause harm or at the very least constitute a misuse of public funding. The purpose of clinical trial registration and reporting of progress and results is to counterbalance selective publication and selective reporting of research outcomes, to prevent unnecessary duplication of research effort, to help patients and the public know what trials are planned or ongoing into which they might want to enroll, and to help give research ethics committees, considering approval of new studies a view of similar work and data relevant to the research they are considering.

In line with the *Declaration of Helsinki 2013*⁴ the HRB requires all clinical trials that fall within the scope of this policy are to be registered in a publicly available, free to access, searchable clinical trial or investigation registry or database where available, prior to initiation of the study. Examples of clinical trial or investigation registries include:

- [ClinicalTrials.gov](https://clinicaltrials.gov/),
- [ISRCTN registry](https://www.isrctn.com/),
- [EuCTR registry](https://www.eu-ctr.eu/),
- or on another register listed on the WHO [International Clinical Trials Registry Platform](https://www.who.int/clinical-trials-registry-platform/) (ICTRP).

Secondary data analyses of primary (parent) clinical trials should not be registered as separate clinical trials, but instead should reference the trial registration number of the primary trial.

When registering, the Principal Investigator must;

- Provide summary details of the trial
- Indicate that the trial has been funded by the Health Research Board, citing the relevant grant file reference number
- Include a data sharing plan* [In line with 2017 International Committee of Medical Editors⁵ (ICMJE) clinical trials and interventions that begin enrolling participants on or after 1 January 2019 must include a data sharing plan in the trial's registration]
- Periodically update the listing within the registry, including the main findings from the study or note if the trial is terminated

***Data sharing plan must indicate the following:** *whether individual de-identified participant data (including data dictionaries) will be shared; what data in particular will be shared; whether additional, related documents will be available (e.g., study protocol, statistical analysis plan, etc.); when the data will become available and for how long; where the data will be made available (the Registry of Research Data Repository offers a catalogue of potential data repositories - <https://www.re3data.org/>); by what access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism).*

The HRB will meet the costs of trial registration, and researchers may request such costs as part of the grant application.

4. Post Award Trial Requirements

Conduct

All trials must be conducted in accordance with all applicable legislation, regulations, guidelines and international best practice, including but not limited to, the Declaration of Helsinki, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines (e.g. GCP), EU Directives and General Data Protection Regulation and Health Regulations 2018.

⁴ [Declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects 2013](https://www.who.int/clinical-trials-registry-platform/)

⁵ [http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html](https://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html)

Regulated clinical trials such as a clinical trial of an investigational medicinal product or a clinical investigation must be conducted under the governance of a Clinical Research Facility/Clinical Research Centre (CRF/C), evidence of which must be provided to HRB in the form of a letter from the Director of the facility at the time of application for funding (Collaboration Agreement Form).

Governance

The HRB requires that all clinical trials and interventions have the appropriate governance arrangements in place before a trial can begin.

Arrangements for the management and oversight of clinical trials and interventions will vary according to the nature of the study proposed and should be proportionate to the complexity and associated risks. However, all should include an element of expert advice and monitoring that is entirely independent of the Principal Investigator, research team members and the institutions involved.

Commonly, regulated clinical trials are overseen by three committees⁶:

1. Trial Management Group
2. Trial Steering Committee and
3. Independent Data Monitoring Committee.

The HRB requires that you inform us of the proposed members of the various committees established for your clinical trial and interventions and the terms of reference at the time of making an application for funding. The HRB reserves the right to approve membership and to refuse sanction of appointments of nominated candidates, should it be determined in HRB's absolute opinion that they are inappropriate for the role.

Any change in the composition of the Governance arrangements must be advised in writing to the HRB.

Formal minutes of all meetings of the Governance Committees must be maintained. The HRB reserve the right to obtain these minutes.

Trial Management Group ("TMG")

The role of the TMG is to oversee the day-to-day management and overall conduct and progress of the trial.

The group is expected to include the;

- Principal Investigator(s),
- Trial Manager,
- Statistician and
- Data Manager.

In addition, the group may include other members of the trial team with specific expertise, such as the Database Programmer, Pharmacist, Health Economist and one or two site Principal Investigators.

Group meetings are essential to keep members up to date with the trial and to monitor progress. The frequency of meetings is trial dependent; however, it is recommended that this group would meet frequently during trial set-up and at least quarterly thereafter. A meeting should also be held before a TSC meeting to plan the agenda and required meeting papers.

⁶ https://www.nihr.ac.uk/funding-and-support/documents/funding-for-research-studies/how-to-apply/NETSCC_Project_Oversight_Groups_Guidance.pdf

Trial Steering Committee (“TSC”)

The role of the TSC is to provide oversight of the trial on behalf of the Sponsor, and to ensure that the trial is conducted in accordance with the principles of GCP and relevant regulations and guidelines.

The terms of reference should be agreed, as outlined in the grant application, before the trial starts. It is expected that a TSC includes an Independent Chair, has a majority of independent voting members and includes a public/patient representative. The non-independent members would normally include the Principal Investigator and one or two other site Principal Investigators.

The purpose of the TSC is to:

- Approve the trial protocol before it starts
- Provide advice, through its Chair, to the Sponsor and investigators on all appropriate aspects of the trial’s progress
- To focus on the progress of the trial, adherence to the protocol, participant safety and review any relevant new information regarding the intervention or clinical area that may impact on the trial.
- To ensure appropriate ethical and other approvals are obtained in line with the project plan
- To agree proposals for substantial protocol amendments and provide advice to the sponsor regarding approvals of such amendments

Independent Data Monitoring Committee (“DMC”)

The role of the DMC is to monitor data emerging from the trial, in particular in relation to safety and efficacy, and make recommendations to the TSC regarding any safety issues that should be brought to the attention of participants or any ethical reasons why the trial should not continue. In addition, it considers whether or not any interim analyses are required and would review these data.

The purpose of the DMC is to regularly assess and advise on:

- The data emerging from the trial
- The safety data
- The critical efficacy endpoints
- Whether to recommend to the trial sponsor to continue, modify or stop a trial

All members should be totally independent of the trial. The DMC is usually made up of three to four members and includes an Independent Chair and experts in the field such as clinicians with expertise in the relevant area and expert statisticians. The DMC terms of reference, should be agreed before the start of the trial. This document will outline any stopping rules and the frequency of interim data analyses during the recruitment phase of the trial.

It is expected that nearly all randomised controlled trials (RCTs) will have a DMC; however, for relatively small and/or low risk trials, the TSC may also assume this role. The TSC or the funder and/or sponsor may decide this. Meetings are usually held annually; however, the DMC can meet more frequently if necessary.

Monitoring

The Sponsor is responsible for complying with any requirements for monitoring of adverse events, at any stage of the research as agreed by the TSC.

Publication of results and making clinical trial data accessible

Clinical Trial Protocol and Statistical Data Analysis Plan must be made publicly available before trial recruitment is complete. This is to ensure that researchers and other interested parties can interpret the results of the trial.

The HRB expects HI's to use HRB Open Research (<https://hrbopenresearch.org/>) or other suitable platforms for this purpose. Protocols and analysis plans submitted to HRB Open Research will undergo post-publication peer review. Study protocols published on HRB Open Research may also be incorporated into Registered Reports, where the protocol is published and peer reviewed ahead of data collection and the results are published as a linked research article following study completion.

The results (positive, inconclusive and or negative) from all HRB funded clinical trials must be made publicly available within twelve months of study completion (defined as the last data collection time point for the last participant for the primary outcome measure). These results must be posted to the results section of the clinical trial registry where the trial was originally registered.

The HRB also expects that results of the clinical trial will be submitted for publication in a peer reviewed journal and or through HRB Open Research (<https://hrbopenresearch.org/>). Any peer-reviewed publications that arise from HRB funding must be made freely available in line with our open access policy.

5. Failure to comply

If Host Institutions/Principal Investigators fail to comply with this policy, the HRB will impose appropriate sanctions. These may include;

- suspending awards,
- forfeiting final payments on awards if results are not reported by 12 months after study completion and/or
- not accepting new grant applications from Principal Investigators for all HRB schemes.