MEDSAFE
New Zealand Medicines and Medical Devices Safety Authority

Guideline on the Regulation of Therapeutic Products in New Zealand

Considerations for first-in-human (FIH) and early phase clinical trials

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Contents

1 Purpose

The regulatory requirements for clinical trials in New Zealand are outlined in <link to Guidelines on the Regulation of Therapeutic Products in New Zealand: Clinical trials – regulatory approval and good clinical practice requirements>.

This guidance document outlines considerations for first-in-human (FIH) and early phase clinical trials.

2 Overview of FIH and Early Phase Clinical Trials

Early phase clinical trials can be broadly defined as non-therapeutic, exploratory trials in human participants. They study the human pharmacology, tolerability, and safety of an investigational product and compare how effects seen in non-clinical studies translate into humans.

An FIH trial evaluates an investigational product in humans for the first time. These studies are often undertaken in healthy volunteers but can also include patients with a specific disease.

3 General Considerations

FIH and early phase clinical trials are a key step in medicines development, however they are associated with a greater level of uncertainty (and therefore risk) compared to later phase clinical trials due to the lack of experience with the use of an investigational product in humans.

Clinical trial applications for FIH and early phase clinical trials should include a risk assessment that clearly documents potential risks and how these will be mitigated. Aspects that should be considered as part of the risk assessment include (but are not limited to):

- the quality of the investigational product and active pharmaceutical ingredient
- interpretation and relevance of the non-clinical data
- dosing selection and dose escalation decisions
- clinical trial design and conduct
- trial site facilities, procedures, and staff expertise

Sponsors and investigators wishing to conduct FIH and early phase clinical trials in New Zealand should adhere to the European Medicines Agency (EMA) Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07).

4 Clinical Trial Sites

FIH and early phase clinical trials should take place at clinical trial sites with appropriate facilities, procedures, and staff expertise to mitigate and manage the increased level of risk to study participants. It is expected that clinical trials sites will have significant prior early phase clinical trial experience before conducting FIH trials (for example, multiple phase I trials, at least one of which has

been audited). This is to ensure systems and processes are robust and have been demonstrated to be effective. There should be no unresolved critical and major findings in Good Clinical Practice (GCP), particularly in the area of subject safety. The site should also be notified to Medsafe before a clinical trial application is made.

Further considerations for clinical trial sites are discussed below.

4.1 Facilities

4.1.1 Monitoring and supervision

FIH and early phase clinical trials should take place under controlled conditions (such as inpatient units). Clinical trial units should be set up in a way that allows for close supervision and monitoring of study participants.

All areas of the unit accessible by participants (including wards, bathrooms, recreation areas, etc.) should have alarms that can be used to alert staff to an emergency. These should be regularly tested.

4.1.2 Emergency trolley

Clinical trial units should have access to emergency medicines and equipment for resuscitating and stabilising individuals in an acute medical emergency (such as cardiac or respiratory arrest, anaphylaxis, cytokine release syndrome, convulsions, and hypotension).

An emergency trolley should be easily and rapidly accessible in all areas of the unit occupied by study participants. At a minimum, emergency trolley(s) should be stocked according to current clinical guidelines. The contents should be regularly checked to ensure they remain appropriately stocked and in date.

Continuous monitoring equipment to monitor vital signs such as heart rate and rhythm, blood pressure, oxygen saturation, and temperature should also be available.

4.1.3 Emergency hospital facilities

Clinical trial units not located within a hospital should have procedures in place to transfer participants to hospital with minimal delay in case of a medical emergency. The unit should be able to transfer participants to a hospital that can provide an appropriate level of care in an emergency, with journey time of less than 15 minutes. Relevant hospital and emergency personnel should be aware of the nature of the research being conducted at the clinical trial unit and that participants could be transferred from the unit at any time. The unit should inform the hospital when a participant receives the investigational product in case a transfer is required. An agreed procedure for transferring participants to the hospital should be documented.

For clinical trial units located within a hospital, the unit should have access to hospital emergency response staff who are able to rapidly respond in case of a medical emergency. An agreed procedure for alerting hospital staff should be documented.

4.1.4 Handling and storage of the investigational product

The facilities, equipment, and procedures required for handling and storage of the investigational product will vary depending on the type of trials being conducted at the unit and the nature of the investigational product(s).

Investigational products used in FIH and early clinical trials often require specific preparation at the trial site (eg, oral powder for constitution as a suspension or intravenous formulations requiring dilution steps). There may be a need for flexibility to allow for adjustment of doses as the as safety and pharmacokinetic data becomes available during the trial.

At a minimum, clinical trial units will need basic facilities, equipment, and procedures for the safe storage and handling of the investigational product and maintaining records of its receipt, storage, use, and disposal (for example for trials where the investigational product is pre-packed and labelled by the sponsor ready for administration to individual subjects). There should be a designated storage area for the investigational product that is secure and accessible only to authorised staff. Depending on the activities that need to be carried out at the trial site, additional requirements could include (but are not limited to):

- purpose built or adapted facilities
- temperature and humidity controlled storage areas
- a suitable environment/equipment for the dosage form to be prepared or manufactured[1] (eg, directional air-flow that is controlled for contamination and temperature or laminar flow cabinets for sterile products)
- a rigorous quality control and quality assurance systems
- procedures to comply with GMP
- suitably trained staff with experience preparing special dosage forms of investigational products (eg, pharmacists, technicians).

4.2 Staff expertise

4.2.1 Investigator/Principal investigator

The Investigator/Principal Investigator (PI) should have relevant medical qualifications, training, and clinical experience. Those wishing to undertake FIH trials should have experience running Phase I trials. A relevant post-graduate qualification (eg, post-graduate qualifications in clinical pharmacology or pharmaceutical medicine) is highly desirable.

There should be procedures in place at the clinical trial unit to assess the suitability of the PI. Where gaps are identified there should be appropriate mitigations in place (eg, oversight of an expert advisor).

[1] Note that manufacturing medicines is a licensed activity under the Medicines Act 1981. For clinical trial units wishing to manufacture medicines at the clinical trial site, it will be necessary to obtain the relevant licence(s). In some cases, it may be appropriate to contract a licenced pharmacy or manufacturing licence holder to manufacture a finished product for a clinical trial. It is the responsibility of the investigator to ensure that the pharmacy/manufacturer holds an appropriate licence.

4.2.2 Sub-investigators and other medical staff

Consideration should be given to the early phase clinical trial experience of sub-investigators and their ability to safely provide medical cover in the absence of a PI.

Medical staff trained in advanced life support (ALS) and with experience managing medical emergencies should be present on all dosing days.

4.2.3 Nursing and support staff

The non-medical members of the research team should have appropriate training that allows them to safely execute protocol mandated activities. It is expected that the nursing staff involved in FIH studies have experience in early phase clinical research. All clinical staff should have formal training for managing medical emergencies.

4.3 Procedures

4.3.1 Quality system

Clinical trial units should have procedures in place to cover the full range of activities undertaken at the unit. Procedures should be formally documented as Standard Operating Procedures (SOPs). These SOPs should include procedures for (but not limited to):

- handling common medical emergencies
- handling immediate maintenance of life support in an acute medical emergency including resuscitation and stabilisation of participants
- transferring participants to hospital including handover of relevant medical information
- unblinding in an emergency
- out-of-hours medical cover and contact with the sponsor or investigator
- required qualifications, training, and experience for key roles and responsibilities
- staff training and refresher training to maintain competencies for all key activities
- practical training (including simulation-based training) for handling medical emergencies, to ensure all clinical staff know what to do in such situations
- staffing levels and resourcing requirements
- subject recruitment, including identification, verification of medical history, and monitoring for over-volunteering
- study protocol implementation including dose escalation and stopping rules
- management of the investigational product
- risk assessment and mitigation (independent of the sponsor)

Quality control (QC) activities should be built into all key procedures to ensure standards are maintained, and quality assurance (QA) procedures should detail how these activities are audited.