HealthTech Activator

In collaboration with:

New Zealand Association of Clinical Research

TE TĪTOKI MATAORA MEDTECH RESEARCH TRANSLATOR

NIHI The National Institute for Health Innovation

Example Clinical Investigation Process for a new Diabetes Monitor

A New Zealand medical technology company has developed a new wearable diabetes monitor that they believe may be effective for monitoring insulin levels. The company has identified that there is a gap in the market and it is believed that their product could provide a health benefit to patients.

To determine whether the new monitor can safely and reliably detect and report insulin levels the product will need to be assessed in a series of **clinical investigations** (also called **studies**). Within the clinical investigation context, the medical technology company is referred to as the **Sponsor**.

A medical device investigation may need to demonstrate a clinical outcome, clinical performance, or that the product is usable in the intended environment. For the diabetes monitor, the Sponsor will need to show a measurable clinical difference following the use of their device.

STANDARDS AND NATIONAL REQUIREMENTS

The diabetes monitor has not previously received marketing approval, meaning that it is "**pre-release**". The Sponsor has ensured that they have met the requirements of ISO 14971: **Medical devices – Application of risk management to medical devices** and has risk assessment and risk control processes in place to support the data requirements of, and to justify, a clinical investigation in humans.

Once the activities of ISO 14971 are established and residual risk has been evaluated to be acceptable, the product can be investigated further in a clinical investigation, for which ISO 14155: **Clinical Investigation of medical devices for human subjects – Good Clinical Practice (GCP)** will apply. ISO 14155 addresses GCP for the design, conduct, recording, and reporting of clinical investigations of medical devices carried out on human participants to assess clinical performance or effectiveness and safety.

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In addition to the ISO 14155 standards, national requirements must also be considered. Medsafe is the New Zealand regulatory body. However, Medsafe does not regulate or approve clinical investigations for medical devices in New Zealand. Medsafe requests that it is informed of clinical investigations before they commence (via devices@moh.govt.nz). The Medsafe Part 11 guidelines provide information on regulation *(Guideline on the Regulation of Therapeutic Products in New Zealand. Part 11 – Clinical Trials – regulatory approval and Good Clinical Practice requirements)*.

Medsafe also provides a glossary of terms, some of which are specific for New Zealand. Other glossaries should also be consulted for international terms. Clinical investigations must also meet or exceed the National Ethical Standards for Health and Disability Research and Quality Improvement (NEAC standards).

It is important to be aware of any specific requirements that other regulatory bodies, such as the U.S. Food and Drug Administration (FDA) or European Medicines Agency (EMA) may require for their jurisdiction (such as the FDA's 510K or EU's MDR). Early engagement with regulators is advised for products that are being developed for those markets.

CLINICAL TRIAL DESIGN

When a product is tested on humans for the first time, it is known as a first-in-human clinical investigation. Most first-in-human studies are performed on a small number of volunteers in a **Pilot Stage** clinical investigation.

A Pilot Stage study will evaluate the limitations and advantages of the medical device and is often used to capture preliminary information required for further planning and development of the device and for the next stage of clinical investigation, known as the **Pivotal Stage**. During the Pivotal Stage, confirmatory clinical investigations are conducted to evaluate the devices performance, effectiveness or safety.

The type of device and or how it is used determines its risk classification (Class). The Sponsor must determine the risk class of the device before designing a study. The Medical Devices Risk Classification Rules *(schedule 2)* of the New Zealand Medicines Regulations should be consulted to determine the applicable New Zealand device class.

Class 1 devices are low risk (such as reusable surgical instruments, urine bags, sterile dressings) and can usually be validated by bench testing for safety and performance. **Class 2** devices have a medium risk classification which is split into **Class 2a**: medium-low risk (such as hypodermic needles, suction equipment), and **Class 2b** medium-high risk (ventilators, orthopaedic implants). The diabetes monitor would be a Class 2b device. **Class 3** products are implantable (such as drug-eluting cardiac stents). The highest risk class device is an active implantable medical device (**AIMD**), such as a pacemaker. The risk classification may vary in regulatory regimes outside of New Zealand.

Study volunteers are known as **participants**. Untoward medical occurrences that participants experience during the study are known as **adverse events (AEs)**. Medsafe operates a voluntary scheme for medical device adverse event reporting that Sponsors, users, healthcare professionals and carers can submit reports to. It is recommended that this scheme is used to report serious, unexpected adverse events that occur during the clinical investigation.

A Clinical Investigation Plan (CIP) describes the key information for the study, such as background, rationale, objectives, outcomes design, pre-specified analysis, methodology, monitoring, safety and record-keeping. There are a number of CIP templates available online and examples of completed CIPs can also be found.

USING A CONTRACT RESEARCH ORGANISATION

Unless a Sponsor is experienced in clinical studies, a **Contract Research Organisation (CRO)** who can help them plan and conduct their study should be engaged.

The roles and responsibilities of the CRO and the Sponsor in relation to the study planning and conduct need to be detailed and a contract put in place. Many CROs can offer a full range of the services that are required for the planning and conduct of a study, such as: planning the product development program, writing the CIP and other study documents, providing systems for the capture of data, study management, monitoring, and study reporting. Clinical investigations are complicated and there is a lot of specialist knowledge required to ensure the study meets the standards required to bring a product to market.

As the Sponsor of the new diabetes monitoring device is inexperienced in clinical investigations, they have engaged a CRO who can advise them on how to design their study to meet regulatory and ethical requirements and standards. Either a medical writer or the CRO selected can write the CIP and may put together some or all of the documents required for the ethics submission in New Zealand.

The CRO will also assist the Sponsor in selecting capable and qualified sites to conduct the study and will put contracts in place with the sites. Standardised MedTech Contract Templates are available on the NZACRes website and should be used when engaging New Zealand sites to conduct a clinical investigation.

The CRO has a validated data collection system that will be used to capture the study data, including adverse event and safety data, and a secure document management system (DMS) in which the study documentation and data will be retained. The system is validated and complies with GCP, FDA 21 CFR Part 11 and HIPAA. The DMS will contain essential documents that facilitate the conduct and management of the clinical study and allows for the evaluation of study data integrity, compliance with the applicable regulatory requirements, and the principles and standards of GCP.

The Sponsor has completed the pilot stage which supports entry into the pivotal stage of clinical development. The Sponsor has decided to run an open, randomised, study. A **randomised study** is one where participants are assigned, based on chance, to receive the device or either a comparator device (if a comparator exists) or no device (if the device is novel and no comparator exists). An **open study** is one where the participant and the researchers know which device/if any the participant is using.

Once the draft of the CIP has been written by the CRO, the Sponsor must check it to ensure that it will provide the information required to support the assessment of the device and ensure the data can be used in future regulatory submissions for device registration. The study must be registered on a World Health Organisation (WHO) approved registry, such as clintrials.gov, the Australian New Zealand Clinical Trials Registry (ANZCTR), or European Clinical Trials Database (EudraCT).

The CRO will help the Sponsor identify vendors required during the study, such as laboratory services. The Sponsor has decided to assign the responsibility of vendor selection and management to the CRO.

ESTABLISHING THE TRIAL SITE

At least one site that can perform a pivotal stage clinical investigation will need to be contracted to conduct the study. The CRO will perform a **feasibility assessment** on the site/s being considered and provide the Sponsor with the feasibility information and the list of potential sites. The Sponsor should choose the site/s for the study. The site investigator and their team must be appropriately qualified and experienced to conduct the study.

The clinical investigation will require **ethical approval** from a Health and Disability Ethics Committee (HDEC) before the study can start. The **Coordinating Investigator (CI)**, who is the lead site investigator in New Zealand, will be responsible for submitting the application in conjunction with the Sponsor. The CRO will also help the site prepare the documentation required for the submission. The HDEC provides template documents that should be used for the Participant Information Sheet and Consent forms (PISCF), the Data and Tissue Management Plan, and the Scientific Peer Review. For the planned study, peer review will be required from an independent reviewer.

The Sponsor must ensure that at least ACC-equivalent compensation is available for the participants of the trial. This is usually provided via an insurance policy that indemnifies the participants and those involved in the conduct of the trial.

In New Zealand, each site that will be conducting the study will also perform a **Māori cultural consultation** with a representative from the local iwi. The lead site selected for this study has an established cultural consultation process in place that will fulfil the requirements.

Each site will also need to complete a **locality assessment** to determine whether the study is appropriate for their site. Cultural consultation forms part of the locality assessment as well as being reported on at a national level within the study ethics application.

The ethics, cultural consultation, and locality reviews should all occur in parallel, which saves time during study start-up. The study can't start until all approvals are in place and the site contract is finalised.

Once all approvals and essential documents are in place, a **monitor** will perform the **site initiation visit**. During the site initiation visit, the monitor will ensure that the study team members at the site are appropriately trained on the CIP, the device, and the study procedures, as well as ensure that the correct **essential documents** are contained within the **Investigators Site File (ISF)**. The site can then be opened for participant recruitment.

CONDUCTING THE STUDY

The sites will conduct the study. This means that they will recruit participants into the study, complete the procedures and assessments in accordance with the CIP, establish safety criteria and will record **adverse events**. The site will collect the study data within the **case report form (CRF)** and report adverse events and other safety issues.

During the study, a monitor from the CRO or an independent monitor will perform **monitoring visits** and checks in accordance with the **monitoring plan**. Monitors oversee the progress of a study and ensure that it is conducted, recorded, and reported in accordance with the CIP, standard operating procedures (SOPs), GCP, and applicable standards and local requirements, checking the quality of the data collected and the rights and well-being of the participants are protected.

Once all participants have been recruited, the requirements of the CIP have been completed, and all data has been collected, the site will be prepared for **close-out**. The data quality and completeness will be confirmed, the devices will be **reconciled**, any missing essential documentation from the ISF and TMF will be collected, study supplies will be returned to the CRO or Sponsor and the site will be closed.

At the conclusion of a study, a **clinical investigation report (CIR)** must be written by the Sponsor. A synopsis of the CIR is to be provided to the ethics committee. Participants who chose to be notified of the study results must also be provided with a lay description of the results, this will be done via the site/s that conducted the study to protect the participants' privacy and confidentiality.

If the study data support the confirmatory investigation the data can be used to support a regulatory submission for the diabetes monitor.