HealthTech Activator

In collaboration with:

New Zealand Association of Clinical Research

Example Clinical Trial Process for a new Psoriasis Treatment

A New Zealand biotechnology company has developed a new pharmaceutical product that they believe may be effective in the treatment of psoriasis. The company has identified that there is a significant need for effective psoriasis treatments and it is believed that their product could provide a health benefit to patients.

To determine whether the new treatment is safe and efficacious, the product will need to be assessed in a series of **clinical trials** (also called **interventional studies**). *The ICH GCP E6 guidelines provide a glossary of common clinical trial terms, as does clinicaltrials.gov.*

The product is novel and has never been tested on humans before. The biotechnology company has sufficient pre-clinical evidence to support a clinical trial in humans and can manufacture their product under Good Manufacturing Practice (GMP).

In New Zealand, an **Investigational New Drug** (IND) filing is not required. However, an IND or its equivalent will be required for the USA, Canada, China, and the European Union (EU). An IND is a request to the **regulatory authority** for approval for a new drug to be administered to humans. Countries that do require an IND or its equivalent do accept data from studies performed in other countries.

To progress the development of their product, the biotechnology company will run a New Zealand-based Phase 1 clinical trial in healthy volunteers to test the safety and dosage of their psoriasis treatment, which is called the **investigational product (IP)**.

CLINICAL TRIAL DESIGN

Clinical Trials should be run in compliance with the GCP guidelines.

> *Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects.*

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In New Zealand, studies must also meet or exceed the National Ethical Standards for Health and Disability Research and Quality Improvement (NEAC standards) and the Medsafe Part 11 guidelines. 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 1572 or CFR 11 requirements) Early engagement with regulators is advised for products that are being developed for those markets.

When a product is tested on humans for the first time, it is known as a first-in-human study. Most first-in-human studies are performed on a small number of healthy volunteers in a **Phase 1** clinical trial. Drugs that are anticipated to potentially have significant toxicity are usually tested in patients rather than healthy volunteers, such as oncology drugs. Within the clinical trial context, the biotechnology company is referred to as the **Sponsor**.

The method of delivery of the IP is important when designing a study. For example, the product may be topical (such as a cream or patch), ingested (such as a pill or liquid that is swallowed), or injectable (such as via injection or infusion).

The Sponsor has pre-clinical evidence to show that the psoriasis IP can be given as an ingestible pill.

A Phase 1 clinical trial tests the safety, side effects, tolerability, and timing of a new treatment (dose-response study). Phase 1 studies do not usually test the efficacy of the product, i.e. the therapeutic benefit. Efficacy will be tested in Phase 2 & 3 trials. Many products will need to be tested to determine the optimal or tolerated dose, known as a SAD/MAD pharmacokinetics (PK) study.

A Phase 1 study will commonly test the new IP via a **single ascending dose (SAD)**. This means that each clinical trial volunteer, known as the **participant**, will receive a single dose of the IP. The first participant/s will receive a very low dose, and the dose will be increased for each subsequent participant or small group (also known as a **cohort**) of participants until the optimal dose is reached. There must be an appropriate time gap between the dosing of each of the participants and the ascending dose groups (this may be hours or days depending on the IP). Phase 1 participants should not all be dosed with the IP at the same time. At least one person in the cohort is dosed in advance of the others, called a **sentinel dosing**. Sufficient time should be given to check for serious side effects from the IP before dosing the next participant.

A **multiple ascending dose (MAD)** study may also need to be performed in Phase 1. A MAD study is one where the participants receive multiple doses of a study drug usually at a set dose.

SAD and MAD investigations are commonly performed at the same time as part 1 (SAD) and part 2 (MAD) of a single protocol. This is often referred to as a Phase 1a and Phase 1b study.

A Clinical Trial **protocol** describes the study's objectives, design, methodology, statistical considerations, and organisation. Protocol Templates are available via TransCelerate or the New Zealand Association of Clinical Research (NZACRes) provides an annotated TransCelerate Protocol template with guidance information (membership required).

USING A CONTRACT RESEARCH ORGANISATION

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

The roles and responsibilities of the CRO and the Sponsor in relation to the trial 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 trial, such as: planning the drug development program, writing the protocol and other study documents, providing systems for the capture of data, study management, monitoring, and study reporting. Clinical trials 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 company of the new psoriasis product is inexperienced in clinical trials, they have engaged a CRO who can advise them on how to design their study to meet New Zealand and international regulatory requirements and standards. The CRO selected will write the protocol and may put together some or all of the documents required for regulatory and ethics submission in New Zealand. The CRO will assist the Sponsor to select sites that are capable and qualified to conduct the study, and help to put the contracts in place with the sites. Standardised contract templates are available on the NZACRes website and should be used when engaging New Zealand sites to conduct a trial.

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 in which the **Trial Master File (TMF)** documentation will be retained. The TMF is a collection of essential documents that facilitates the conduct and management of the clinical trial and allows for the evaluation of trial data integrity, compliance with the applicable regulatory requirements, and the principles and standards of GCP.

The Sponsor has decided to run a randomised, blinded, placebo-controlled SAD/MAD study. A **placebo** is a product that appears to be exactly the same as the IP but doesn't contain any active treatment and can be used as a comparator. A **randomised** trial is one where participants are assigned to receive either the placebo or the IP, based on chance. A **blinded** trial is one where neither the participant nor the investigator knows which treatment the participant is receiving.

Once the draft of the Protocol has been written by the CRO, the Sponsor must check it to ensure that it will provide the information required to support the safety assessment of the IP and ensure the data can be used in future regulatory submissions for marketing approval. 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 sample and IP couriers and laboratory services. The Sponsor has decided to assign the responsibility of vendor selection and management to the CRO.

ESTABLISHING THE TRIAL SITE

At least 1 site that can perform a Phase 1 study 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 Site or the CRO may be assigned responsibility for the production of the documentation required for the ethics and **regulatory** submission. For this study, the Sponsor assigned the responsibility for the ethics submission to the site and the regulatory submission to the CRO.

A Medsafe regulatory submission to the **Standing Committee on Therapeutic Trials (SCOTT)** will need to be submitted by a New Zealand **Applicant** because the IP is a new medicine that has not been approved for use. Because the Sponsor company is based in New Zealand, they will be able to act as the applicant. The CRO will put the documentation together for the submission. The Sponsor will need to ensure that the essential documents required for the submission are prepared, such as the **Investigators Brochure (IB)**, the Protocol, the GMP evidence, and the IP label. *(Appendix 1 of the Guideline on the Regulation of Therapeutic Products in New Zealand. Part 11 – Clinical Trials – regulatory approval and Good Clinical Practice requirements).*

A SAD/MAD trial 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 not be required as the study is being submitted to SCOTT.

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 and is also reported on within the study ethics application.

The regulatory, 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 protocol, the IP, 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 and the IP shipped to the site for participant treatment.

CONDUCTING THE STUDY

The sites will conduct the study. This means that they will recruit participants into the study, treat them according to the protocol and any established safety criteria, and follow-up with the participants for a set period of time following treatment to check for **adverse events (AEs)**. An adverse event is any untoward medical occurrence experienced by a participant during the course of the study which does not necessarily have a causal relationship with the treatment. 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 will perform **monitoring visits** and checks in accordance with the **monitoring plan**. Monitors oversee the progress of a trial, and ensure that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), GCP, and applicable regulatory requirements, ensuring the quality of the data collected and the rights and well-being of the participants are protected.

Once all participants have been recruited and have completed the treatment and follow-up period and all data has been collected, the site will be prepared for **close-out**. The data quality and completeness will be confirmed, the IP 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 study report (CSR)** must be written by the Sponsor. A synopsis of the CSR is to be provided to the ethics and regulatory groups. 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 safety of the psoriasis product, the product may enter the next stage of testing; a **Phase 2** clinical trial/study. In a Phase 2 clinical trial, safety and efficacy are assessed. A Phase 2 trial would be conducted in patients suffering from psoriasis in another randomised, placebo-controlled, blinded trial. The trial would recruit more participants than the Phase 1 trial, and may be conducted at more sites.