

Process Evaluation of Functional Food Clinical Trials in New Zealand

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Abstract

Consumer demand for scientifically backed products has led to a surge of demand for functional food products and ingredients. Due to rising healthcare costs and greater desires to control their health, consumers are increasingly turning to functional foods as a cheaper, more natural substitute to medicines. A more educated consumer-base and the regulations surrounding nutritional-content claims leads functional food products to require evidence through clinical studies. However, clinical trials have largely existed within the pharmaceutical space, so operational knowledge is mostly siloed within that industry.

The main objective of this thesis research is therefore to understand how to begin functional food clinical trials by reviewing the regulations and standards for conducting clinical trials, determining evaluation criteria for clinical trial processes, and discovering clinical operation processes; including employing a qualitative methodology to analyse themes and processes from 8 interviews. This methodology uses an adapted Context Input Process Product evaluation framework to determine the evaluation criteria.

The main findings of this research show that clinical trial and operations processes involved in functional food testing generally follow Good Clinical Practice, but the exact pathway depends on the desired outcome, thereby influencing the preceding processes. Collaborations play an important role at all stages of the clinical trial process and were explored incorporating both industry and academic perspectives. Importantly, the findings of this thesis differ from others in the pharmaceutical, or functional food literature by including insight into the participants' values, which were shown to impact how researchers collaborate and share knowledge. The primary themes were clinical operations expertise, reliance on international markets, and the importance of regulatory compliance. The process analysis yielded four main categories of processes: Planning, Executing, Closing Out and Accessing the Market. These are structured in a process map that may guide beginners to the clinical trial space.

This thesis research is the first of its kind in New Zealand, and as such its contributions are seen largely as bringing together information and expertise that was previously passed on through professional practice. In doing so, this thesis and its findings form a general guide for industry use in establishing a clinical trial program or to inform early clinical trial strategy.

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Table of Abbreviations

ANZCTR	Australia and New Zealand Clinical Trial Registry
CDM	Clinical Data Management
CIPP	Context, Input, Process and Product
CRF/eCRF	Case Report Form, electronic Case Report Form
CRI	Crown Research Institute
CRO	Contract Research Organisation
EBP	Evidence-based Practice
EFSA	European Food Standards Authority
ePRO	Electronic Patient Reported Outcomes
FSANZ	Food Standards Australia New Zealand
GCP	Good Clinical Practice
HDEC	New Zealand's Health and Disability Ethics Committee
HVN	High-Value Nutrition Ko Ngā Kai Whai Painga
ICH	International Committee on Harmonisation
IRB/ERB	Institutional Review Boards/Ethical Review Board
MBioEnt	Master of Bioscience Enterprise
MCHRI	Monash Centre for Health Research and Implementation
NDA	Dietetic Products, Nutrition and Allergies
NEAC	National Ethics Advisory Committee
RCT	Randomised Controlled Trial
SAE	Serious Adverse Events
UAHPEC	The University of Auckland Human Participants Ethics Committee
UoA	The University of Auckland

1 Introduction

New Zealand's natural health products sector is growing with many companies already entering the global market. There are strong incentives for New Zealand to promote natural health products as evident by the High-Value Nutrition Ko Ngā Kai Whai Painga (HVN) program; one of 11 National Science Challenges established in 2014 and funded through the Ministry of Business Innovation and Enterprise. A subsection of the natural health product sector is that of functional food ingredients, which will be the focus of this thesis research.

1.1 Functional food ingredients

According to Food Standards Australia New Zealand (FSANZ)¹, functional foods are defined as *“...similar in appearance to conventional foods and intended to be consumed as part of a normal diet but modified to serve physiological roles beyond the provision of simple nutrient requirements”*. As such, the functional food industry's regulatory environment sits between food and medicine. The general approach is food ascendant, where products must meet food safety standards, but any additional claims must bear scientific evidence such as labelling, nutrition content or clinical trials. From a consumer perspective, functional foods are generally viewed as cheaper, more natural alternatives to medicines.² In a 2018 Business Communications Company report, the global functional food market is expected to reach USD\$110.9B by 2023. Current trends include baby boomers and millennials, with both groups citing increased healthcare costs and a greater desire to control their health leading to increased engagement in the functional food market.²

1.2 The importance of clinical trials for functional food ingredients

The push for clinical food trials has arisen from the demands of a more educated consumer. With more companies entering the functional food and beverage market, competition is high. The modern consumer looks for more scientific information and wants an added perceived benefit over a competitor product. Another avenue of differentiation functional food companies use is in labelling and nutritional claims. However, marketing nutritional claims fall under the regulatory framework where the product is sold rather than where the company is based, so the requirements differ depending on the region concerned.

Consumers are creating the demand for scientifically backed products but may not necessarily understand the data behind them. Brands can fill educational gaps through marketing the science and teaching the customers about the products, which can enhance consumer trust and brand

loyalty.³ Regulatory agencies do not require clinical trials to prove safety and efficacy for functional food ingredients, but the positive results can aid building product legitimacy in the market. Furthermore, this research exists within the greater context of clinical operations for functional food trials and is designed to connect to real-world outcomes. Thus, uncovering the links between marketing, operations and scientific evidence plays into clinical trial design.

As part of establishing the scope of this research, the concept of good clinical practise (GCP) will be reviewed concerning requirements for conducting clinical trials established by EFSA (European Food Safety Association), ICH (International Committee on Harmonisation) Guidance and other local bodies. Additionally, there will be a review of the New Zealand and Australian Food Standards Code Section 1.27. Current New Zealand standards are developed for investigational pharmaceutical products and food standards but lack definitive guidance for functional food products. The review focuses primarily on GCP due to the operational aspects of the research and future implementation.

1.3 Clinical research

In New Zealand and according to guidelines for GCP by ICH, a comprehensive definition of a clinical research trial is as follows:

“Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy.”⁴

Clinical trials answer specific research questions in the context of pharmaceutical development; they answer a series of questions regarding dosage, safety, and efficacy. Clinical studies follow GCP guidelines as set out in ICH-GCP and Medsafe (Part 11), which ensure participants' rights and safety when conducting a trial. A clinical trial is a regulatory requirement when getting a pharmaceutical to market and is necessary for new and approved pharmaceuticals. However, whether an investigational product falls under the classification depends on if it is designed for a therapeutic purpose.⁵ Medsafe (Part 11) only applies to medicines or foods with *therapeutic* purposes in relation to treatment and prevention of disease so beyond the scope of this thesis and will not be considered further here.

1.3.1 A brief word on the current clinical trial paradigm

In the pharmaceutical industry, clinical trials follow a testing process that starts with preclinical studies in animals, cell lines or computer models. Phases 1, 2, 3 and 4 build upon the preclinical data by evaluating dose-tolerability, safety, and efficacy. The need for such a lengthy and expensive development process comes from regulations originating from the Food and Drug Agency and the ICH. Instead of targeting therapeutic indications as seen in pharmaceutical trials, clinical trials for food ingredients are oriented towards health claims, which enhance consumer perception of the product and add value to the final product.⁵ However, while beyond the scope of this thesis, given the current global pandemic, it is important to mention here the likely ongoing implication that the pandemic will have in terms of the conduct of clinical trials. The COVID-19 pandemic has disrupted the traditional centralised model and provided an opportunity for researchers to move to a decentralised trial model. In doing so, trials that are no longer reliant on physical sites or specialised staff can be operated at a lower cost making trials more accessible to smaller companies without the required infrastructure. The growing acceptance of decentralised trials prompted Anagenix to consider commencing a clinical trial programme thus promote this thesis.

Decentralised trials came to the fore in the early 2010s but were viewed as less rigorous than centralised trials. The COVID-19 pandemic is forcing clinical trial operators to consider alternative options for patients and staff, that reduce COVID exposure risk. Virtualisation is becoming increasingly more common, and both patients and sponsors report satisfaction with telehealth services.⁶ Decentralisation offers reduced workload, travel times and administrative burden compared to paper-based trials by distributing tasks such as data entry to the patients or directly via smart monitoring devices. For example, one study saw a reduction of data verification queries by 86%⁷. Remote data collection through ePROs, validated questionnaires and or electronic diaries aims to mitigate risks associated with participant compliance and the manual transfer of physical datasheets to an electronic format. One issue is known as the “parking lot effect” and happens when a study participant forgets to fill out weeks of paperwork on time so tries to recall and update the paperwork in the parking lot before meeting with the site staff. For many people, remembering what they had for dinner a week prior can be difficult, let alone how they felt or precise details of food items and serving sizes.⁸ One study showed that participants underreported study data (e.g. questionnaires) by 25%.⁹ After implementing electronic diaries, another study saw an increased compliance at 94% compared to 11% compliance for paper diaries.⁸ Another phenomenon affecting data validity is White Coat Hypertension or White Coat syndrome, which results in elevated blood pressure observed in a clinic compared to the home

setting. This “white coat” effect would therefore be minimised should participants be able to conduct self-testing remotely. Overall, integrating remote monitoring devices may assist in accurate, efficient, and cost-effective data collection for a clinical study.¹⁰

A spectrum exists between fully decentralised and fully centralised trials, largely dependent on the disease state of trial participants and clinical endpoints being measured.⁶ Pharmaceutical clinical trial investigators conducting trials during the COVID-19 pandemic needed to adapt trial designs and protocols quickly to account for physical distancing restrictions and isolation orders to complete ongoing studies. Consequently, the pandemic provided an opportunity to test decentralised trial tools. Participant interactions decreased from January 2020 to April 2020 of the COVID-19 pandemic but clinical trial sites maintained triple the virtual interactions from May 2020 to Dec 2020. Such a sustained increase of interaction demonstrates participants’ and investigators’ uptake of remote health technologies. However, with any new technological paradigm shift, risks exist. Challenges in adopting these new technologies are data quality, participant safety, regulatory compliance, and internal management. Clinical trial sponsors are worried about the reliability and validity of novel electronic Patient Reported Outcomes (ePRO) technology and how it meets regulatory standards. Participants vary in their access to technology so designing participant centric trials will be an important factor in mitigating these concerns. Successful industry adoption of decentralised trials depends on participants, investigators, and sites. Managers’ ability to driving internal change will determine the fastidiousness of decentralised trials in the future.⁶

1.4 Purpose of the Study

Functional food ingredient companies are facing increasing pressure from consumers to sell scientifically validated products. Anagenix is one such New Zealand company; it doesn’t currently have the internal capabilities to conduct trials itself and while it has outsourced clinical trials previously, outsourcing trials to Contract Research Organisations (CROs), third-party enterprises that provide drug development and commercialisation services on behalf of pharmaceutical companies, is costly. Furthermore, the company’s desire to plan and manage clinical trials comes during the COVID-19 pandemic. COVID-19 restrictions continue to disrupt clinical trials, so Anagenix aims to conduct decentralised trials to mitigate risks to participants and study staff. Therefore, the question this research aims to solve is **how a company like Anagenix can conduct functional food clinical trials in New Zealand.**

This thesis addresses existing gaps in the pharmaceutical, functional food ingredient and operations literature, and fits within clinical operations, a field underexplored due to its pragmatic

nature. Typically, clinical operations and procedures are passed down within a company and through professional organisations. New Zealanders were shown to be better at exchanging professional expertise internally through meeting with colleagues and meetings.¹¹ Demonstrating that most industry knowledge is kept within the industry and passed down to others selected to be a part of it.

The following literature review covers the definition of a functional food ingredient, the market, and why clinical trials are important in the functional food ingredients industry. The review introduces health claims and how claims can impact the clinical study design. The New Zealand ethics framework for clinical studies is discussed and followed by an introduction of the Privacy Act 2020 with other relevant data management legislation. Reviewing this wide body of mostly technical literature sets the stage for later discussing clinical trial processes and providing a base on which to evaluate these processes.

2 Literature Review

2.1 Food, health, and nutrition claims

As discussed earlier (see **Section 1.4**), with the increasing competition between functional food companies, health claims are becoming increasingly important to differentiate products. Each country regulates food safety and food labelling claims differently. However, while the New Zealand regulations are most relevant to companies selling and manufacturing locally, the European health claims framework is included here as they provide comprehensive legislative and scientific guidance that outlines stringent criteria for clinical trial design, and are often used to guide local, New Zealand decision making.

2.1.1 Food Standards Australia and New Zealand (FSANZ)

The Food Standards of Australia and New Zealand (FSANZ) are responsible for the regulatory framework for making and regulating health claims in the two countries. Standard 1.27 defines health and nutrition content claims and describes the conditions and circumstances for making health claims and is described below in **Table 1**.

Table 1- Standard 1.27 (FSANZ) ¹²

1.2.7- Outline	<p>This Standard:</p> <p>(a) sets out:</p> <p>(i) the claims that may be made on labels or in advertisements about the nutritional content of food (described as ‘nutrition content claims’); and</p> <p>(ii) the claims that may be made on labels or in advertisements about the relationship between a food or a property of a food, and a *health effect (described as ‘health claims’); and</p> <p>(b) describes the conditions under which such claims may be made; and</p> <p>(c) describes the circumstances in which endorsements may be provided on labels or in advertisements.</p>
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According to FSANZ, a health claim is “a claim which states, suggests or implies that a food or a property of food has, or may have, a health effect”.¹² Health claims that refer to disease or biomarkers associated with diseases are considered high-level health claims. A nutrient content claim focuses on the presence or absence of, for example, dietary fibre, energy, minerals, protein, or carbohydrates.^{12, 12} FSANZ presents over 200 pre-approved health claims, with one common example being Vitamin D contributes to normal cell division. These claims can be found in FSANZ Food Standards Schedule 4. However, with new product development being a common commercialisation strategy, it is more likely for a company to apply for new health claims. Applying for a new health claim (both general and high-level) requires evidence for a causal relationship and can be self-substantiated through a systematic review of the food-health relationship.¹³

The systematic review part of the health claim application starts by defining the food, properties, health effect(s) and the intended health relationship of the food, evaluating the evidence and overall decision.¹³ The systematic review then identifies the relevant existing studies and analyses the methodological quality of each study and the studies as a group. The review can include evidence of any study type but must assess bias, quality and whether there was sufficient statistical power to test the hypothesis.¹³ The food-health relationship is also compared against the comprehensiveness of evidence in humans, that is, “A food-health relationship cannot be established from animal and in-vitro studies alone. Studies in humans are essential”.¹ After submission, the High-Level Health Claims Committee considers the evidence presented and provides a recommendation for approval or rejection.¹⁴ Understanding the process by which health claims are lodged and assessed contributes importantly to functional food clinical trial design.

2.1.2 European Food Safety Authority (EFSA)

EFSA was established in 2002 as an independent European agency that provides scientific advice on food safety.¹⁵ Articles 13.1, 13.5 and 14 of European commission regulations form the basis of EFSA’s Scientific Opinion. Like FSANZ, EFSA evaluates claim applications based on the evidential presence of a cause-and-effect relationship between the food and health state.¹⁶ The basis of an EFSA health claim addresses the questions: “Is the food/constituent sufficiently defined and characterised?”, “Is the Claimed effect sufficiently defined, and is it a beneficial physiological effect?” and “Have pertinent human studies been presented to substantiate the claim?”.¹⁶ EFSA identifies narrow criteria for what studies can be used to substantiate a health claim, and the Dietetic Products, Nutrition and Allergies (NDA) Panel evaluates these claims.¹⁶

EFSA presents scientific requirements for cardiovascular health and antioxidants, immune function, and weight management.

As with FSANZ, human studies are vital in substantiating a claim, so the NDA panel emphasises studies using the food/constituent in a consistent formulation across studies in the claim (e.g., syrup, powder, whole food product). As far as showing a “beneficial effect”, each claim category adheres to its own scientific guidance as set out by EFSA but overall, a claim’s effect must be *“testable and measurable by generally accepted methods”*.¹⁶ A claim is more likely to be successful if it incorporates primary outcomes showing a biological change, stable and specific ingredient formulation, dose-response, and efficacy in multiple, real-world end-products.¹⁷ According to the contract research organisation Atlantia Clinical Trials, 3-5 good quality studies can provide sufficient evidence to secure a positive opinion from EFSA.¹⁷

2.2 Study Design

Consumer-driven demand for clinically verified food products has resulted in the functional food ingredients industry using clinical trials as a commercial strategy. Due to the regulatory, legislative, and commercial stakes generally associated with the clinical trial process, preparing the research protocol to meet scientific requirements is crucial to discuss early in the process.

2.2.1 Research protocols

Randomised clinical trials (RCTs) are studies in which participants are randomly assigned to a control or intervention and provide the best evidence for or against an investigational product. RCTs evaluate safety, efficacy, and effectiveness. ICH-GCP section 6.4 guidelines require a description of the study design, blinding procedure, and randomisation methods. The common RCT types employed are parallel and crossover trials, which evaluate one intervention against a control. Parallel trials concurrently track outcomes in randomised groups. In contrast, crossover studies separate participants into groups and, partway through the study, there is a washout period and participants are reassigned to the alternate intervention/control. Crossing over participants mitigates statistical risk and allows participants to act as their control in addition to the investigational product they receive. Crossover studies require fewer participants and can help mitigate confounding factors but are limited by their increased study length and types of suitable interventions (e.g., crossover studies are not possible in the context of weight-loss).¹⁸

Table 2 (below) outlines and describes the ICH-GCP guidelines for designing and describing a clinical trial.

Table 2-ICH-GCP Section 6.4, Study Design ⁴

Guideline	Description
6.4.1	A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.
6.4.2	A description of the type/design of trial to be conducted (e.g., double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures, and stages.
6.4.3	A description of the measures taken to minimise/avoid bias, including: (a) Randomisation. (b) Blinding.
6.4.4	A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).
6.4.5	The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.
6.4.6	A description of the “stopping rules” or “discontinuation criteria” for individual subjects, parts of trial and entire trial.
6.4.7	Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.
6.4.8	Maintenance of trial treatment randomisation codes and procedures for breaking codes.
6.4.9	The identification of any data to be recorded directly on the Case Report Forms (CRFs) (i.e., no prior written or electronic record of data), and to be considered to be source data.

Clearly defined and measurable study objectives and endpoints are critical aspects of clinical trial design. The primary objectives define the most relevant research questions and help frame the initial study design. The objective should include the outcome, the intervention, the control, study population, study duration, and the endpoint. Additional measures can be included in secondary study objectives and can address issues that arise from the primary objective or complement the primary objective findings. Any goal or surrogate endpoints are typically used to track the disease state to the intervention or control and provide clear evidence for when the study stops and when an intervention is proven efficacious.¹⁸

During the initial protocol design, it is essential to consider the ability for an intervention to be generalised to the broader participant population.¹⁶ EFSA factors in generalizability to ensure the intervention is effective.¹⁶ In this case, efficacy differs from effectiveness in that effectiveness is measured in the broader participant population, whereas efficacy looks at how well the intervention works in the clinical trial.¹⁸ Inclusion and exclusion criteria should also be carefully considered as they will affect statistical analysis by influencing the data collected and participants recruited.¹⁸ The participant population demographics must also follow ethical guidance in that vulnerable populations need to be treated differently, and statistical anomalies can either be more easily accounted for or adjusted.¹⁸

Recruitment is one of the essential steps in the clinical trial process. Without proper recruitment practices or participants, the study loses feasibility and may not commence. In traditional clinical trials where sites are dependent on a physical location and recruitment relies on the outer population, part of the feasibility strategy is for sites to cater to the local population, ensuring that investigators can get enough participants for the study.¹⁹

2.3 Regulatory Compliance

A clinical trial must fit within the larger regulatory environment. Each country is different but ultimately will follow ICH-GCP guidelines combined with local regulations. Section 2.3 of the thesis covers the New Zealand ethical framework relevant to conducting local functional food trials.

2.3.1 Ethics

Ethics forms the basis of clinical research conduct - with three foundational documents: Nuremberg Codes, Belmont report²⁰ and Declaration of Helsinki²¹ outlining the researcher-participant relationship. The GCP principles arose from the Nuremberg trials in response to human experimentation on victims during the holocaust, and which led to the creation of the Nuremberg Code.²² The Code highlights the importance of voluntary consent of research participants and set the foundation for clinical research in the 20th century. The Belmont report established the basic bioethical principles of justice, beneficence, and respect, that ethics bodies across the world have adopted. The Declaration of Helsinki introduced now-prevalent concepts like informed consent, privacy and confidentiality, and research ethics committees. Despite these three documents not being codified into law, they have profoundly impacted the field of clinical research and heavily influence New Zealand's Health and Disability Ethics Committee (HDEC).²³

HDEC reviews health and disability research to ensure it “*meets or exceeds established ethical standards*”.²³ HDEC accepts and approves clinical trials in New Zealand nationwide according to

their set ethical standards. HDEC reviews are separated into “full reviews” and “expedited reviews”. The full reviews are mandatory for medicines as defined in the Medicines Act 1984, class II medical devices, participants who are not able to provide informed consent to participate, or participants who have limited capacity to give such consent.²³

Section 11 of the New Zealand Public Health and Disability Act 2000 established HDEC to “*secure the benefits of health and disability research.*”²³ The governing document for national standards is the National Ethical Standards for Health and Disability Research and Quality Improvement²³, the fundamental principles of which are as follows:

Bioethics Principles ²³

- Beneficence
- Non-maleficence
- Respect for people
- Justice

Te Ara Tika Principles

- Tika
- Manaakitanga
- Whakapapa
- Mana

New Zealand ethical standards emphasise Māori inclusion, as evident in the Te Ara Tika Principles and Standards 3.1-3.6c. All research in New Zealand must understand how it impacts Māori populations through a prospective consultation process.²³ The recommended approach is to engage with Māori stakeholders early during clinical protocol design to mitigate risks regarding ethics, data quality and research objectives. Māori involvement in research follows a tiered system with the more Māori individuals and data are necessary to data collection, the more involvement from Māori researchers and integration of Māori principles is expected. The basic level of Māori involvement expects valid justification for Māori exclusion, researchers to understand how their research reflects the principles of the Treaty of Waitangi and that local Māori consultation shows that the research design is appropriate for Māori.²³ Māori perspectives are important for New Zealand research regardless of if the results are disseminated to a Māori audience or data is from Māori participants. While not strictly notable in the New Zealand context due to adopting the Te

Ara Tika principles above, the “FAIR and CARE” principles for indigenous data governance provide international guidance for managing data from indigenous perspectives.²⁴

In contrast to the national ethical body, local ethical bodies approve trials that pose minimal risk to the participants. An example of a local ethical body is the University of Auckland Human Participants Ethics Committee (UAHPEC). Referred to as Institutional Review Boards (IRBs) or Ethical Review Board (ERB) ICH-GCP, local and international guidelines govern requirements for these boards.

ICH E6 (R2) defines an Institutional Review Board (IRB) as:

“An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing a continuing review of trial protocol and amendments and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.”

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IRBs are critical in the establishment and functioning of a clinical trial because they act as an independent third-party that maintains the safety, rights, and well-being of the trial participants. An IRB reviews a clinical trial proposal and determines whether a trial can proceed by examining essential documents related to study protocols, informed consent, participant compensation and investigator qualifications. The board should be composed of “*at least five members*”, one with expertise outside the sciences and one who acts independently from the institution and trial site.²⁶

2.3.2 Informed Consent

Informed consent is a crucial aspect of recruitment and retention in clinical trial operations and a vital regulatory step to ensure participants are sufficiently informed to make educated decisions about participation. Processes and documentation should be adapted to include lay summaries and understandable language. Additionally, individuals cannot be paid to participate in the study but rather are compensated for their time. Principles regarding informed consent stem from the ethical principles described above and are represented in ICH-GCP Section 3, National Ethics Advisory Committee (NEAC) Section 7 standards, and other agencies documentation internationally. Vital elements of informed consent include clear communication to potential study participants of the research purpose, research design, potential conflicts of interest and any harms or foreseeable side effects. NCEA standards treat consent as a dynamic, informed, and voluntary process, thereby integrating bioethical and Te Ara Tika principles.²³

2.4 Confidentiality and Privacy

Confidentiality and privacy are prevalent issues in clinical research and health information technology. In New Zealand, ICH-GCP section 4, the Health (Retention of Health Information) Regulations 1996, Health Information Privacy Code 2020 and the new Privacy Act 2020 contribute to the research privacy framework.²⁷⁻³⁰ The privacy commission creates resources on the privacy act, privacy rights and responsibilities regarding privacy.²⁷

New Zealand's legal framework treats privacy as an issue linked to people. Deidentified information, public information, and personal information all come from individuals.³¹ The health information privacy code and privacy act "*promote and protect individual privacy*"³¹. Any company operating in New Zealand must comply with the Act and limit cross-border information sharing. The new Privacy Act (2020) emphasises accountability towards vulnerable populations and preventing breaches, and obligations should a breach occur. The rest of this section covers newly emerging concepts in research regarding privacy and confidentiality.

2.4.1 Data Minimisation

Data minimisation means that researchers should collect only the information needed to conduct the research. However, researchers may, either inadvertently, unethically, or with ethical approval, ask for more information than necessary for the actual research. Data minimisation also researchers to examine which data is necessary to achieve study objectives, where it will come from and what to do with it. Data minimisation may pose challenges for exploratory studies in which it is not yet know what data will need be needed.³¹ Data minimisation also ties into use limitation, which means, in relation to research, the researcher should provide only information for the purposes it was collected. In New Zealand, 13 Privacy Principles come from the Privacy Act 2020 and summarised by the Privacy Commission. Of relevance to data minimisation are the following:

- Collect only the information you need (Principle 1)
- Collect information directly from the person concerned (Principle 2)
- Retain information only if you need it (Principle 9)
- Use the information only for the purposes you collected it (Principle 10)

2.4.2 Transparency and Fairness

The importance of informed consent arises in transparency and fairness so participants can fully understand how and why their data is used. Early participant engagement assists in mitigating issues that may arise with transparency and fairness in research.³¹ As such:

- Tell people why you need information and what you will do with it (Principle 3)
- Be fair and respectful when collecting information (Principle 4)

2.4.3 Data Sharing

Reidentification using electronic datasets is becoming increasingly more common, so lawful information disclosure is paramount when collecting personal data. In one case, the Australian Department of Health released individuals' de-identified medical records on the data.gov.au website in interest of public health research.³² Before releasing the data, the unique identifiers were anonymised, and the data was encrypted. Four months later, University of Melbourne researchers discovered ways to decrypt the data and recover personal identifying information.³² The breach demonstrates the importance of proper data disclosure.

Proper anonymous or deidentified disclosure and disclosure with prior authorisation are acceptable. Disclosure is also acceptable when a participant's safety is concerned, such as in the case of a Serious Unexpected Adverse Event. Any and all such potential disclosures must be declared during the ethical approval process.

Data sharing overseas is a slightly separate matter. The Crown has international information agreements in place with countries with similar privacy laws to ours. The added benefit these agreements have for organisations conducting clinical trials is that participants will not need to be notified that their data is being sent overseas (which is a legal requirement otherwise). This data sharing must be disclosed during the ethical approval process, and follow the following Privacy Principles:

- Only disclose information with a lawful basis (Principle 11)
- Only disclose information overseas if it will be protected (Principle 12)

It is relevant to note that cloud storage is not inherently disclosure, but if Amazon Web Services (AWS), for example, further analyses the information stored for their purposes, then it becomes disclosure.³¹ Furthermore, Privacy Principles 5-8 govern data storage, access, correction, and accuracy which correspond to data management practices. These practices will be discussed in the next section.

2.4.4 Clinical Data Management and Documentation

Clinical data management (CDM) is a broad topic. Critical documentation associated with CDM in New Zealand include the Privacy Act 2020, Health (Retention of Health Information) Regulations of 1996, ICH-GCP Section 5.5 guidelines and the HISO 10064:2017 Health

Information Governance Guidelines. In September 2021, HDEC introduced requirements for new ethics applications to include a data management plan. That data management plan is a practical embodiment of the privacy concepts mentioned in the last section. The introduction of this plan will be one of the topics of this thesis research.

2.5 Overview and Scope of Research Thesis

To answer the primary and secondary research questions posed (see **Sections 2.5.1 and 2.5.2**, below), I first looked at past examples from the MBioEnt program then explored examples from outside the program, notably Master of Clinical Research programs in the United States. As interviews would be necessary to acquire the untaught experiences of those accustomed to running clinical studies, I investigated literature review styles, methodologies, and data analysis methods; key sources included Dunn³³ and Krishanasamy³⁴ from the MBioEnt program and Hatfield³⁵ and Schroedter³⁶ from the Master of Science in Clinical Research Management program at The University of North Texas Health Science Center at Fort Worth. The methodologies differ between Dunn³³ and Krishanasamy³⁴. Dunn's³³ methodology relied on a qualitative interpretivist approach and designed semi-structured interviews to inform a dyadic case study. Krishanasamy³⁴ employed a similar methodology that first identified relevant theory and collected data through semi-structured interviews. However, in contrast to Dunn³³, Krishanasamy³⁴ used thematic analysis to link codes and themes. Each of these approaches fit their specific research's purpose but are based on the social sciences rather than health sciences.^{33, 34}

Hatfield³⁵ and Schroedter³⁶ used quantitative methods to satisfy the Master of Clinical Research requirements at the University of North Texas Fort Worth. The theses' organisational structures were the most like that of the literature base; however, their methodologies lacked a discernible theoretical basis. Through exploration of the methodological sources such as SageMethods and google scholar, it is apparent that this research would need to draw from methodologies, theories, and methods from a broad source of domains due to its interdisciplinary nature. The researchers³⁵⁻³⁷ discussed their chosen methods but failed to clarify the rationale for the research design, which negatively impacted the theses'³⁵⁻³⁷ replicability and credibility. Theory of change and program theory were considered but were determined not to be effective for the present research thesis. Theory of change would be useful if the research tracked efficiency or organisational change overtime. Such research would need to observe long-term effects of a specific process and how the organisation responded to those changes. Program theory is common in evaluation methodologies as it creates a logic model for the evaluators to assess the

evaluated. While some aspects of program theory can be found in **Sections 2.7**, and **2.8**, a fully developed program theory would be out of scope for this research.

Upon closer inspection of the keywords and formatting in the theses of Hatfield, and Schroedter, key terms such as “evaluating” and “identifying barriers” are steps in the evaluation process. Hatfield³⁵ and Schroedter³⁶ narrowly focused on one step of the evaluation process, which hinders their research design and its capacity for implementation. These researchers used a short but broad scope in their evaluation research of the practical aspects of their projects. In contrast, I utilised a narrow but long scope that encompassed study start-up and the steps up to achieving a health claim to address the following research questions. In doing so, I aim to provide a “roadmap” for New Zealand industry to embark on clinical trials of functional food products/ingredients.

2.5.1 Primary Research Question

- How can a New Zealand functional food ingredients company establish a clinical trial programme?

2.5.2 Secondary Research Question

- What are the relevant regulations and guidelines for conducting functional food trials in New Zealand?

This research aims to answer these questions by:

- 1) Exploring clinical study operations pertaining to functional food ingredients (*Research Aim 1*).
- 2) Determining evaluation criteria for clinical operation processes in a functional food ingredient company based on standards identified in the literature review (*Research Aim 2*).

2.6 Rationale

Research and development within the functional food industry relies heavily on skills and capacities learned in academic settings. In contrast, the pharmaceutical industry takes a large responsibility in training their staff in-house, which inadvertently creates a disconnect between skills learned in university and the skills needed to perform clinical trials. The changing landscape of functional food clinical trials requires an influx of new knowledge and understanding, and companies that rely on functional food studies for a value-added benefit to their products exist outside the existing talent pool. Therefore, there is a gap in the clinical operations’ academic

literature, reflecting the lack of available resources or understanding in procedures for conducting clinical trials in an underdeveloped regulatory environment. The literature gap widens when looking at the New Zealand context and presents an exciting space to begin research. This thesis contributes to filling this gap by providing a starting point for companies outside the pharmaceutical space to begin clinical trials in New Zealand for functional food ingredients/products. Therefore, I hypothesised knowledge transfer would emerge as a theme during data collection and analysis.

To structure the interviews, and analyse the data I obtained, I used an adapted version of Stufflebeam's³⁸ educational framework where the emphasis was put on problem identification, needs assessment and educational strategies. Rather than rely on a full evaluation analysis at the end, analysis took the form of workflow analysis, in what would be considered the educational strategy. The methodological choices in this thesis are unconventional and unique to this study's circumstances so are not without limitation. However, evidence supporting the chosen methodologies is discussed in the following sections.

2.7 Evaluation Theory

Evaluation is a form of disciplined enquiry that focuses on an object (evaluand) and its value. The value comprises intrinsic and extrinsic qualities, which allows the person performing the evaluation (evaluator) to rate the value based on predetermined standards and criteria, e.g., applicability.³⁹ Evaluation precipitated as an academic discipline in the mid-20th century to satisfy organisational needs, business education, and governmental policy. Evaluation has slowly gained broader acceptance in clinical education, public health, and medicine due to Evaluation's ability to draw from both qualitative and quantitative data.⁴⁰⁻⁴⁴ The medical domain employs Evaluation Theory through clinical trials, clinical education, program development and evidence-based medicine. This research draws theory from educational, clinical, and developmental contexts, from industry, regulatory, participatory, and academic sources.⁴⁵

Program Evaluation Theory is a subset of Evaluation Theory that focuses on implementing change in an organisation and improving or assessing programs. Program Evaluation Theory applies to this thesis research because it uses an inductive approach to standards and exhibits a flexible program theory. Program Evaluation forms the basis of education, medicine, sociology, and psychology. It is a field influenced by theory and feeds into theory by collecting empirical evidence and outlining methods for that data collection and analysis.⁴⁰ Program Evaluation inhabits multiple domains, but this present research draws from theory in the education, medical education, and health service domains. The three domains separated early in their theoretical

history but continue to influence each other in practice. First, I will present within the domain of health services where prominent theorists include Kern, Calley, Timmreck, Golden and McGaghie⁴⁵, whereas the prominent theorists in the educational domain include Alkin, Stufflebeam, Weiss, Smith, Guba, and Lincoln.⁴⁴ This thesis' research methodology utilises theoretical approaches from both domains.

2.7.1 Medical Education/Health Services: Six-Step Framework for Curriculum Development

Kern's⁴⁵ six-step curriculum development framework has origins in the existing medical education domain, which was based on Evaluative Theory from Calley, and McGaghie. The framework fills a methodological gap in medical education by integrating stakeholder (i.e., Student, participant) perspectives. Kern⁴⁵ outlines a six-step approach that forms the structure of the research methodology.

- Problem identification and general needs assessment
- Targeted needs assessment
- Goals and objectives
- Educational strategies
- Implementation
- Evaluation and feedback

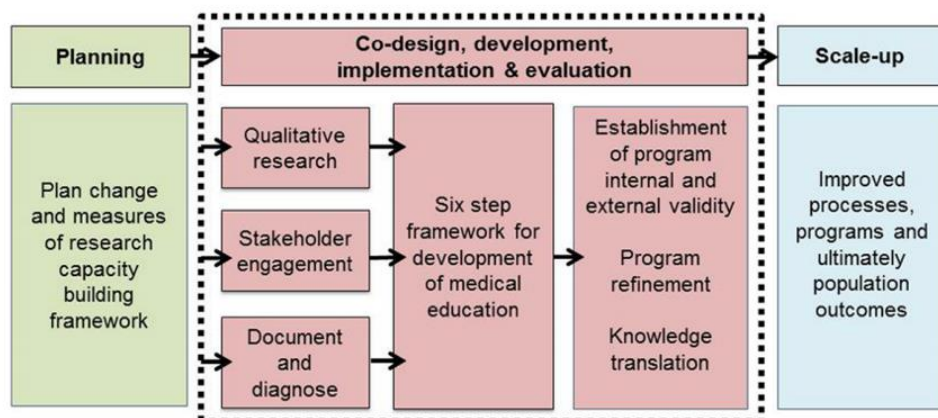


Figure 1-Six-Step Medical Curriculum Framework

Misso et al.⁴⁶ adapted Kern's⁴⁵ framework for developing a new research capacity building program at the Monash Centre for Health Research and Implementation (MCHRI) that the organisation can use to evaluate and fill their expertise. The mixed-methods study used the six steps to understand and implement a novel program with improved processes and outcomes. Essential data collection methods include cross-sectional online surveys, semi-structured interviews, document review and observation. The methods integrated qualitative approaches to understand better evidence-based practise (EBP), which allowed the researchers to gather depth, breadth, and additional insights that traditional quantitative approaches would not give. Overall, the findings allowed the MCHRI to build internal skillsets, address gaps in clinical practice and build multidisciplinary teams.^{45, 46}

The issue with this domain of evaluation is that it is outcome focused. The framework is suited for situations where management is involved from the program's inception to its primary outcome being met. A framework like this requires a lot of time and feedback from all company levels during the planning, development, and scale-up phases. This framework also assumes a formative evaluative approach, so the planning stage may undergo many iterations before moving on to the development and implementation phases. For this thesis, the only steps that would fall under the scope of the primary research question and specific aims are targeted needs assessment, and goals and objectives. Educational strategies would need to be heavily altered to fit an organisational system like a business or clinical research centre. So, while the medical domain provides a relevant theoretical basis, using such a framework is impractical for summative process evaluation research.

2.7.2 Education Domain: CIPP Model

Educational Evaluation began in 1950 by Ralph Tyler with his assessments for student achievements, curriculum development, and teaching assessments. Governmental organisations, agencies and programs later used his work in education. Educational Evaluation differs from other types of Evaluation in that there was a clear set of stakeholders contributing to the evaluation framework: students, parents, schools, and the public. Teachers acted as evaluators, and students, programs, and achievements as the evaluands.⁴⁷ A new framework emerged in the 1960s that was designed to provide decision making information to education administrators. Daniel Stufflebeam developed the Context, Input, Process, Product (CIPP) model to create three steps: *"delineating of questions to be answered and information to be obtained"*, *"Obtaining relevant information"*, and *"providing the information for decision making"*.⁴⁷ The CIPP model can be oriented to evaluate specific evaluands such as processes, efficiency, sustainability, and transportability. The model's flexibility is its greatest asset, but for the sake of brevity, only one type of evaluation will be explored in detail, Process Evaluation. **Figure 2** is adapted from Stufflebeam⁴⁰ and designed to demonstrate the inclusion of the data collection methods used in the present thesis.

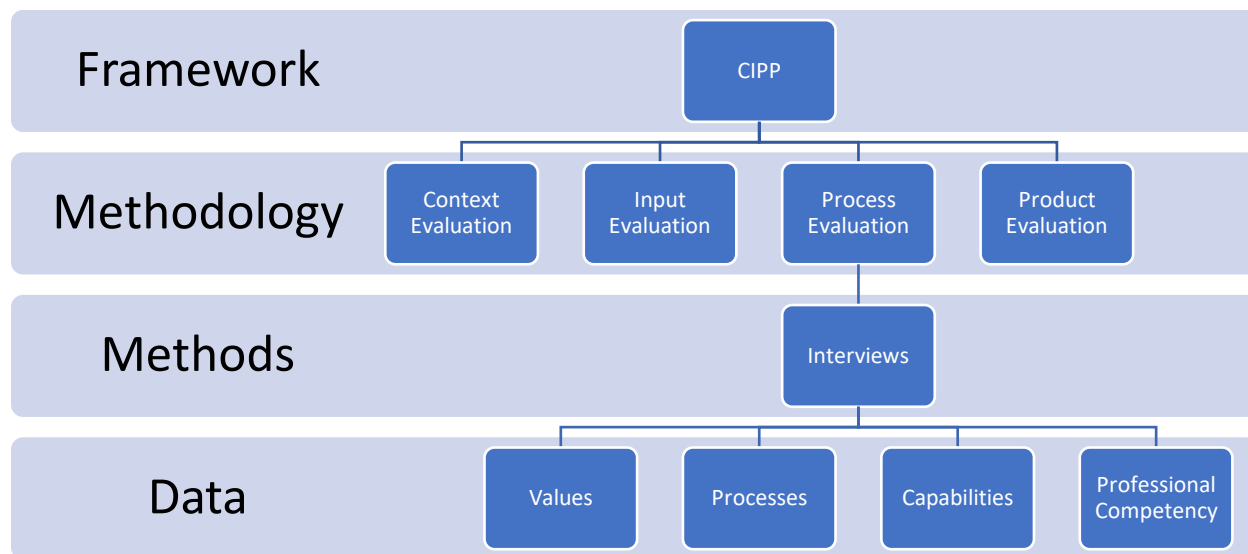


Figure 2-CIPP Methodology Hierarchy

2.8 Process Evaluation

Process Evaluation “*monitors, documents and assesses program activities.*”³⁸ Due to time and resource constraints, the CIPP model was adapted to answer the primary research questions and specific aims of the present thesis. Evaluation research involving clinical trials is varied depending on the type and desired outcomes. For this reason, methodologies relating to clinical operations were inconsistent within the literature, resulting in this research’s methodologies being adapted to its primary outcomes. An organisation should engage in Process Evaluation while a program is operating and show accessibility, efficiency, how well the program is being implemented, and what changes should be made early in the program’s lifespan.⁴⁸

An interpretivist framework is better suited to identify specific meanings within contexts or values. The relationship between the participant and researcher is more participative than in a positivist paradigm, which will allow the researcher to gather information directly from the individuals performing the processes or work tasks.⁴⁹ While Process Evaluation can effectively employ qualitative and quantitative methods, only qualitative methods were used in the present study for the sake of time.

3 Methods

The following methods were used to explore the procedures, workflows, and requirements for functional food ingredients studies in New Zealand. Thematic analysis and process analysis were utilised to enhance and specify themes derived from the literature review and determine evaluation criteria for the processes discovered through process analysis, which were then used to inform the industry “roadmap”.

1. Literature review
 - a. Find criteria and standards for feasibility
2. Semi-structured Interviews
 - a. Study Research staff
 - b. Relevant industry experts

These methods are described in detail below.

3.1 Sampling Techniques

This research used purposive sampling techniques that can give information-rich responses from verified sources. The sampling began with the help of my supervisors and participants were approached based on the perceived expertise within the New Zealand functional food ingredients industry. One major limitation with sampling and recruitment is that there are few New Zealand experts in this area, and many maintain multiple roles between industry and academia. One person cannot speak to everyone in the industry, so the findings are biased by the experts’ availability and the wider context of Auckland being in COVID-related lockdown for most of the interview period.

3.2 Interviews

The interview was designed to be semi-structured to elicit broader findings and cover potential researcher biases. Interviewees were contacted through the academic and industry supervisors and followed up by the researcher. Potential participants were sent Participant Information Sheets and Consent forms outlining the purpose of the research and how their information was used. The Participant Information Sheets and Consent Forms were templates approved by UAHPEC. Blanket coursework ethics was obtained for SCIENT 794B (Protocol No: 022768 (exp. 16-Apr-2022)). Ethics covered meetings/interviews with people with specialist knowledge. The participants were not sent a list of questions beforehand as this was semi structured and I wanted a realistic reaction rather than a formulated, written one. The interviews (video calls) lasted an hour in duration and typically followed the format of Introductions, gathering details of Professional

Experience then, depending on the interviewee's expertise, more information was sought regarding, clinical trial management, data management, Māori consultation and ethics, budgeting, and health claims. The questions were tailored based on their expertise and interviewees were probed further depending on their knowledge about the subject. To conclude the interviews, I asked, "How would you recommend a company to begin a clinical trial programme?" and "Is there anything I left out that should be included or is there anything else you'd like to add?" to cover blind spots that may have been missed. Interviews were recorded and transcribed using Google Meets and Otter.ai, respectively. The audio obtained was processed by the Otter.ai software then manually reviewed for accuracy. The transcripts were adjusted to remove as much identifying information as possible and for conciseness in some cases. The quotes used in this research were anonymised and further amended for clarity.

3.3 Analysis

To better understand the types coding techniques, I reviewed Saldaña's⁵⁰ Coding Manual for Qualitative Research. This manual provides information on descriptive coding, prescriptive coding, magnitude coding, in vivo coding, and process coding. I used a combination of these techniques in my data analysis to incorporate different perspectives on the same data. Prescriptive and descriptive coding were used during the first coding cycle. Quickly labelling the data allowed me to become familiar with it before diving deeper into process and magnitude coding. Process coding identifies actions within a text by tagging it with "-ing". For example, if someone mentioned they sent a sample to a lab, then the code could be "Sending away a sample", "analysing a sample" or "collaborating with laboratory agencies" depending on the rest of the context and how specific the code is. Magnitude coding marked whether a text selection was positive or negative. I used this technique to mine for Values within the data by searching for phrases such as "I think...", "It's important that...", "I/he/she/they should..." and determining the adjective and whether it had a negative or positive connotation.

Thematic analysis and process analysis were used to address the primary and secondary research aims. The methodology behind thematic analysis was adapted from Stufflebeam as previously discussed (see **Section 2.7.2**) but it was unclear from the original literature how to analyse the data gained from the CIPP framework. I investigated further resources that could provide coding guidance in CIPP and identified the evaluation checklist⁵¹ summarised in **Table 3** below. This checklist provided ample scaffolding for a coding scheme, and I further adapted the categories into prescriptive codes that would be more relevant for the clinical trial setting. More details on the changes and rationale behind the code categorisation can be found in **Chapter 4**.

Table 3- Original evaluation criteria list ⁵¹

Societal Values	Criteria Inherent in the Definition of Evaluation	Ground-Level Criteria	Technical Requirements	Duties of Personnel	CIPP Evaluation Model Criteria	Institutional Values
Equity	Merit	Idiosyncratic Criteria	Codes	Professional Competence	Defensible Purpose	Mission
Effectiveness	Worth		Standards			Goals
Conservation				Job Performance	Needs	Priorities
Excellence					Supportable Plan	
Citizenship					Responsible Implementation	
Freedom						
Lawfulness					Laudable Outcomes	
National Defence						

4 Results & Discussion

I conducted eight interviews with New Zealand professionals with varying levels of exposure to clinical research and from different disciplines. **Table 4** lists the participants and their roles, qualifications, and experience with clinical trials. Out of the eight participants, six have PhD degrees, and two have master's degrees. Four maintain university affiliation while four are affiliated with industry. Within the industry subgroup, two participants were in the functional food industry and one within the pharmaceutical industry. Participant 2 gained clinical research experience while working for a Crown Research Institute (CRI). His focus was mostly on animal models and on a few occasions, he collaborated with international universities on human trials in the functional food space. Overall, I reached out to fourteen individuals and interviewed eight. Reasons for the six declined requests included family emergencies, issues gaining departmental approval to participate in this research and perceived lack of experience about the topic by the potential participant. Those six who declined represented the areas of Māori consultation, and a CRI perspective on food clinical trials.

Table 4-Participant Attributes

Interviewee	Affiliation	Role	Highest Qualification	Clinical experience
Participant 1	University	Researcher, PI	PhD	5 years
Participant 2	CRI then Industry	Researcher, PI	PhD	Many animal studies and 2 human studies.
Participant 3	University	Researcher, Technician	PhD	6 years as a technician
Participant 4	University	Researcher, Technician	PhD	None, her expertise was data management
Participant 5	University	Researcher, PI, HVN	PhD	Many human studies
Participant 6	Industry- Functional Food	Senior Manager	PhD	20 years of research strategy
Participant 7	Industry- Functional Food	Manager	Masters	5 years of regulatory and commercialisation
Participant 8	Industry- Pharma	Manager	Masters	20 years of Clinical Operations

Codes were created from the interview transcripts and fit into 5 major categories: **Clinical Trial Management, Evaluation Criteria, Processes, Science Commercialisation and Values**. The CIPP methodology prescriptively assigned a coding structure for the **Evaluation Criteria** and **Processes**. When deciding how to create and assign codes I first reviewed the CIPP framework

for information about data analysis where I identified a list of categories (**Table 3**).⁵¹ Societal Values, Criteria Inherent in the Definition of Evaluation, Criteria Inherent in the CIPP Evaluation Model, Institutional Values, Technical Requirements, Duties of Personnel, and Idiosyncratic Criteria. I combined Societal and Institutional Values into **Values** as a prescriptive code. However, none of the examples from the checklist⁵¹ were used as prescriptive codes because the checklist was oriented towards the education domain. The institutional values of Mission, Goals and Priorities were later merged into the results and discussion as “a sense of purpose” rather than a specific code or result. The **Technical Requirements** remained relatively the same, as a code to include standards, guidelines, and legislations. Duties of Personnel became **Professional Competency** and classified under **Evaluation Criteria**. Idiosyncratic Criteria has been described as a “throwaway” category of sorts, that *“cannot be specified in advance, must be negotiated, should be defined in conservable operational detail”*⁵¹, so I decided not to tie this category to anything specific and that Idiosyncratic Criteria would represent novel, descriptive codes discovered through the coding process e.g., **Science Commercialisation**. The Criteria Inherent in the Definition of Evaluation were disregarded during the coding process because aspects of “merit” and “worth” were to be extrapolated from the **Values** data and magnitude coding. It’s relevant to note that single passage may be assigned to multiple codes depending on the richness of the data.⁵⁰ This method is called double-coding and was done to fully capture complex information and draw links between codes that may not seem to be connected. **Table 5** contains a full list of child codes from the two parent codes, **Evaluation Criteria** and **Values**. The table is included as a preface to the subsequent sections and to show the organisational scheme behind the codes. While some child codes are listed, they’re not discussed due to insufficient data from the interviews conducted. For example, Access to a **GMP facility** is noted under **Capabilities and Capacities**, but it was only mentioned once despite needing a **GMP facility** being corroborated in the literature review. For the **Values**, the codes were further subcategorised into organisational and individual values. These categories weren’t codes but assist in organising the results within this thesis. A full list of codes can be found in **Appendix A**

Table 5-Evaluation Criteria Codes

Evaluation Criteria	
Capabilities/Capacities	<ul style="list-style-type: none"> • Researchers • Technicians • Access to GMP facility • An academic partner • Proper storage/logistics • Network of suppliers, analysers, people
Professional Competency	<ul style="list-style-type: none"> • Research • GCP trained • Clinical operations • Higher degree • Clinical trial experience • Digital skills
Program Needs	<ul style="list-style-type: none"> • Funding • Technology for data collection, storage, and analysis. • Regulatory compliance
Technical Requirements	<ul style="list-style-type: none"> • FSANZ/EFSA Standards • ICH-GCP • HDEC • Other reg agencies • Audit
Outcomes	<ul style="list-style-type: none"> • Consumer data for branding • Scientific evidence for health claims • A product that sells internationally
Values	
Positive	Negative
<ul style="list-style-type: none"> • “Good Science” • Benefit to the wider community • Effective communication • Experience • Financial motivation • Honesty • Independence • Digital skills 	<ul style="list-style-type: none"> • Financial motivation • Low risk appetite • Nutraceutical scepticism • Outdated • Ivory tower

4.1 CIPP Evaluation

CIPP framework evaluates programs based on Context, Inputs, Products, and Processes. The decision-making process is driven by concepts of worth and merit that feed into purpose. An element of the framework is considered worthy based on organizational, societal, or individual values e.g., equity. The Program Needs are informed by **Professional Competencies**, **Technical Requirements**, and **Capabilities and Capacities**. The **Attitudes** and **Values** of the employees and program stakeholders contribute to the program's purpose. The purpose then informs concepts of merit or worth which are used to determine which program elements are of benefit to the business. Overall, this framework accounts for many aspects of program development and assists leadership with strategic decision-making. The rest of **Section 4.1** discusses the different evaluation categories. **Table 5** includes descriptive and prescriptive codes modified from in Stufflebeam's evaluation checklist (**Table 3**).⁵¹

4.1.1 Capabilities and Capacities

Capabilities and Capacities is a code that generally refers to equipment, expertise, and operational capabilities for establishing a clinical trial program. The following section lists the most important codes and their supporting data. Quotes were amended for clarity and all names that appear in the quotes have been anonymised.

- **Researchers**

"I'd say for organisations who do want to be testing functional food products the first thing is to get in touch with researchers who do know what they're doing in the first place. I think that's the most important [thing]. It's all well and good to want to do something but doing it well is a whole different kettle of fish." - **Participant 1**

"I'm a nutritionist, a clinical nutritionist, a dietician, and a gastro physiologist...It seemed quite natural to move into metabolic health because that's the reason why over nutrition and absorption is implicated in metabolic disease."—**Participant 1**

"I'm a molecular biologist by training. I have my Bachelors of honours in genetics, and then I worked for a few years at Massey University and then at [company name redacted], and then I started my PhD at the University of Auckland."—**Participant 4**

"I'm a process engineer so I studied [my doctorate in] process engineering at the technical uni in Hamburg. And I was focusing and majoring in biotechnology, so I was just doing most things in

terms of fermentations enzymes, you know, things with less impact, environmental impact, and chemical engineering normally.”—Participant 6

Researchers are the individuals responsible for the overarching commercial and scientific strategy that accompanies a trial. All the researchers interviewed possessed higher degrees with strong laboratory experience. The transcripts identified **Researchers** with practical experience, a key component for a company starting functional food trials. Academic networks play a role in disseminating knowledge, and expertise across New Zealand. The participants come from varied disciplines within the life sciences, genetics, nutrition, and biotechnology. Participants 1 and 4 gained clinical trial experience through their PhD programs in clinical operations and data management, respectively. In contrast, Participant 6 moved to a series of management roles after completing his PhD where he gained experience. While it wasn't clear if a career in clinical research was deliberate, Participants' 1, 4 and 6 experiences resulted in strategic research positions but their entry into the field came across as a coincidence rather than a directed pathway. I therefore suggest that while experienced researchers are necessary, a career entry pipeline doesn't necessarily exist which may impact the availability of expertise in New Zealand.

“Quite often you might have a biotech started by scientists who are really good at the science but aren't necessarily across all the different operational aspects.”—Participant 8

However, Participant 8 states that having research experience doesn't translate to clinical operations acumen. So even though the pipeline incorporates scientific academic sources, there's little input from industry's required competencies until the individual joins a Clinical Research Organisation

- **Technicians**

“Get a really good ClinOps person, a clinical operator...someone who's really experienced, who's done this a lot. Because there is a lot of skill to clinically managing a study, [and] managing your vendor.” – Participant 8

“I have been involved in a number of studies from cross sectional observational, cohort study, to short term acute response study, to longer term interventional study. So, I have been involved in grant applications and study design writing protocols, arranging the studies activities including writing SOPs. And managing the whole study process to writing up the thesis after data analysis.”—Participant 3

Technicians are distinguished from **Researchers** by their hands-on role in managing the study. **Technicians** are primarily responsible for executing the internal processes of the clinical trial program and interacting with participants. Typically, this role is held by students completing master's and PhD degrees, and the study most likely contribute to the research portion of their theses. In such cases, the student acts as the **Technician**, the student's supervisor as the **Researcher** and the product's company as the sponsor. The importance of clinical trial experience is repeated throughout the interviews but was succinctly captured by Participant 8 in the above quote. It's not clear on how someone gains the necessary experience other than by managing studies. Participant 3 outlines the aspects of clinical operations she completed during her thesis. This ties to the overarching purpose of the research of how to conduct clinical trials. This concept will be explored more under **Professional Competency**.

- **Access to GMP Facility**

"I think I'm finding a very good facility, a qualified facility in compliance with all the requirements, as well as the, you know, in terms of ethical requirements and also the GCP clinical practice." –

Participant 3

GMP refers to Good Manufacturing Practices and is followed alongside GCP practices. Using a GMP facility ensures the investigational products are produced in a standardised way that won't introduce extra variables to the study.

- **An Academic Partner**

The interviews revealed the symbiotic dynamic between academia and industry that will be touched on, but largely remains out of scope of this thesis due to the separate body of organisational literature that accompanies it. However, it's relevant to note the universities provide the research, expertise, and staff necessary to conduct trials. In one specific case discussed in the interviews, the university was working on scientific research that was of interest to industry. At the University of Auckland, researchers have access to data management professionals, Māori Consultation teams and ethics advice. These processes are challenging for a company to navigate without prior experience. By partnering with academia, the university receives funds to complete the study while the company receives data, publications, and access to resources otherwise unavailable to them.

"I mean we always have an academic partner right. Otherwise, we don't get the ethics, we don't get the publication, so we don't get the students." - **Participant 3**

Participant 3 notes the importance a relationship with academia plays in the functional food space. New Zealand's functional food research network includes the University of Auckland's Human Nutrition Unit, the Riddet Institute, and the University of Otago as the main academic centres. In some cases, **international** collaboration is required when suitable partners aren't found locally.

"[University from the UK] have a huge history of clinical trials I think they've run something like 70 or 80, published clinical trials, basically that's what they do so they had huge experience they had everything completely sorted and set up and it was a really nice, easy. [Especially] for me as I've not really run a clinical trial before. I've done lots of in vitro/in vivo stuff but never clinical so that was a nice easy."—Participant 2

There's a lot of expertise to be gained through international collaboration. International collaboration can be academic and/or commercial and exist between New Zealand and any region. The above example demonstrates how valuable international academic partnerships can be for an organisation to gain **Clinical Trial Experience**.

- **Proper Storage/Logistics**

"We see frequently that at university, research groups budget for this million-dollar...mass spectrometer or a really great microscope that generates a terabyte of data per experiment, but most often, they do not foresee what implications that has for the storage. If that's 20 terabytes, it could [take] a fortnight [to process] especially if the microscope is not attached to something that can handle that sort of data."—Participant 5

4.1.2 Professional Competency

Professional competency is a subcategory to **Capabilities and Capacities**. The skills and expertise the staff bring are just as crucial in running a study as the equipment used. This section differs from the previous by outlining professional attributes and experiences. While these attributes can vary widely in terms of scientific field, the codes below contribute to the professional skills necessary to run a clinical trial program.

- **Research**

"I think we have a bit of the different expertise within the unit... We've got individuals with a nutrition background so heavily nutrition based. We've got [name withheld] who is a research fellow and...a food scientist. So that's where product development aspects come into play. I have a

gastrophysiology background. So, I think in terms of expertise, we're quite well rounded at the [location]" –Participant 1

In contrast to **Researchers** mentioned in the previous section, Research refers to the systematic investigation of experience in an academic setting. Many different backgrounds are valued in the functional food setting due to the variety of products. Some trials may include variables that require scientific advice for postprandial glycaemia, HbA1c or thermogenesis. The researchers then use scientific enquiry to inform product development, which is when the different experiences become valuable to the sponsor.

- **Higher Degree**

"I have been involved in a number of studies from cross-sectional observational cohort studies to short term acute response studies, to longer term interventional study. So, I have been involved in grant applications and study design writing protocols, arranging the studies activities including writing SOPs. And managing the whole study process to writing up the thesis...That was the structure of my PhD programme." –Participant 3

"I'm a nutritionist, a clinical nutritionist, a dietician and a gastro physiologist, so that's what I did my PhD in." –Participant 1

"I'm a molecular biologist by training. I have my Bachelors of honours in genetics, and then I worked for a few years at Massey University and then at [company name redacted], and then I started my PhD at the University of Auckland." –Participant 4

Another attribute linked to research and researchers is the possession of a higher degree. A PhD was observed to be a standard qualification in the field. In the case of Participant 3, the **Researcher** gains Clinical trial experience through their **higher degree** with the help of **academic** and industry partners.

- **GCP trained**

"Good Clinical Practice. You don't want to run a study and then not have the data collected in a manner that is amenable to some statistical analyses." – Participant 1

"...GCP stuff we do anyway, for clinical trials. We try and practice as far as you can with food trials, they're not pharmacological trials, they're not drug trials. So, it's, some of the things are relevant. But there are some things in food trials that make it quite difficult."—Participant 5

GCP refers to the set of practices laid out by the ICH-GCP and addressed earlier in Chapter 1 of this thesis. The New Zealand Medicine's act requires GCP to be followed to ensure standardisation of clinical procedures. GCP training can take place online or in person.

- **Digital skills**

“So, we try to support some digital skills and tools, training at the University [of Auckland]. This is not something that our centre is paid for, but we think is, it is important to do...”—

Participant 4

Technological aptitude is becoming more important for researchers as trials move from paper to digital media. The modern researcher needs to know about data privacy, format standardisation, confidentiality, data sharing and data minimisation as discussed earlier. With data being the core output of scientific research, securing it becomes a risk mitigation strategy itself. This code comes mostly from Participant 4's transcript and reflects her role as a data expert. Digital skills become more important now that data management plans are mandated by HDEC. Before gaining ethical approval, a researcher will need to explain:

“How and where are you going to store your data? How long are you going to keep it? How are you going to share it with others?”—Participant 4

Additional concerns can arise when there are changes in the protocol partway through the trial: *“...you have said that you will keep your data on university server, but you want to use cloud storage, so that is in conflict with what you said in your ethics so you either have to get an amendment or in the future... use a more umbrella term for these things so that you comply with ethics.”—Participant 4*

4.1.3 Program Needs

Within the context of this research, **Program Needs** refers to overarching needs to allow the program to function. While **Capabilities** and **Professional Competency** could be classified as **Program Needs**, the sections were subcategorised to align better with additional categories from the CIPP framework.

- **Funding**

“We need the funding to run the studies. Although we're academic work within the University, a lot of the studies that have been conducted with the unit have been with [company name redacted]

and with Plant and Food Research. We've always had industry links with a lot of the clinical studies.”- Participant 1

“We're too small of a country and, and the research funding pool is too small, we need to be really collaborating.”—Participant 5

“There are certain people to look after the budgeting issues, including our research proposal manager”—Participant 3

It wasn't unexpected that a key program need would be **funding**. However, how the **funding** is managed, and the funding sources can both vary. If an academic unit is conducting the study, then the funding is a combination of grants, university funds and industry partnerships. Gaining funds through partnerships is expected in the New Zealand context due to the small funding pool as indicated by Participant 5 above.

- **Regulatory Compliance**

“...Initially, I just do the preunderstanding piece and just try to figure out... what's the regulatory landscape? how difficult is that going to be for us? And what do we already have available in terms of our documentation that we can use to help with customers registrations?”—Participant 7

Regulatory compliance is a continuous process in clinical trial operations. Compliance is sought before the trial starts, during recruitment, execution and even after publication. The requirements vary at each stage, but the first step is to do background research. The processes relating to clinical trials is discussed further in **Section 4.3**.

4.1.4 Technical Requirements

The technical requirements were mainly gathered using secondary resources during the literature review however they were heavily discussed during the interviews, with the literature review providing the base knowledge to engage on these topics. It's worth noting that **other regulatory agencies** appeared independently in the data collected but was not as fully explored due to being out of scope of the New Zealand context.

- **FSANZ/EFSA Standards**
- **ICH-GCP**
- **HDEC**

- **Other reg agencies**
- **Audit**

“So, everything has an audit trail. So, when a regulator comes to inspect, they can trace every single point right to where it was originally collected from the original source... so everything in it has this audit trail.” – Participant 8

“[T]here are certain standards to meet as a clinical facility and also maintain a clinical lab. ...I know like [location] go through an audit every year to make sure that we comply with the standards.” –Participant 3

An unexpected finding from the primary data compared to the secondary data was the mention of a clinical trial **audit**. The **audit** is performed by a qualified third-party auditor and can happen at any time. **Data management** practices play an important role in the audit process because all data needs to be traceable from source data with changes being noted in the record (i.e., researcher must comply with their predetermined (and approved) Data Management Plan.

4.1.5 Outcomes

- **Consumer data for branding**
- **Scientific evidence for health claims**
- **A product that sells internationally**

“[Outcomes] are somewhat loose. If you're doing this trial for improvement of your marketing branding position, and then you put challenge back from the scientific evidence into the communication and marketing team. And so, this is there's companies that are really really good at this, and some other companies are not because how do you wrap up something like quite stark clinical trial outcome that gives you a statistical likelihood of, you know, your bone density is higher?” –Participant 6

An unexpected observation found in the transcripts was the presence of three distinct **outcomes**. This research is geared primarily towards the processes, but the CIPP framework also accounts for outcomes and in this case merits special mention. Through the interviews, it became clear that consumer data for branding and data for scientific evidence later to be used in health claims present different strategic approaches, and either outcome should be chosen before designing a clinical study. Depending on the market of entry, the scientific evidence can change. For example, the European Union has strict entry requirements, governed by EFSA (see **Section 2.1.2**), for

products making nutrition and content claims much more so than it does for the same nutritional content claim. Whereas there are ways to incorporate consumer data from clinical trials into marketing outside of nutrition content claims, it depends on the company's overall strategy, budget, and goals as to which would be best for their product.

“But when you move to the pharma industry, then the goal is very different and it's really more about bringing a product to market I know that the Crown Research Institute they were trying to bring in products to markets as well, but it's because in the nutraceutical industry, it's a lot less regulated than the medicinal pharma industry. So that's that slightly different.”—Participant 8

“Well, [Company]'s exporting...I think it was 80% export, maybe even more now. And you know, it has certain highlights and there's certainly a huge amount going into China, then Asia, then Australia, US, not so much Europe these days.”—Participant 6

The clinical outcomes for functional food trials are contrasted to pharma in that pharmaceuticals are designed to achieve an indication for a specific disease state and face much higher regulatory burden than functional foods. However, this higher regulatory burden is rewarded with increased financial gain compared to the nutraceutical industry. In the pharmaceutical industry, there isn't a product unless it's approved to go through the regulatory approval whereas in the nutraceutical industry a product can still go to market as a food or supplement without achieving health claims or conducting a clinical trial.

4.2 Values

Principles, attributes, or qualities generally understood to be important or good contribute to evaluation by informing the institutional mission, goals, and priorities. **Values** assist an organisation to define its function, prioritise its activities.⁵¹

4.2.1 Positive Values

This section mentions the most relevant codes that were further subdivided in two. A full list of values can be found in **Appendix A**. The following list of values was created as descriptive or in vivo codes from the primary data. Magnitude coding was used to mark a positive or negative attribute by looking at phrases such as “I think...”, “It's important that...”, “need”, “easy”, and “helpful”. Positive codes were further grouped based on whether they applied more to an individual or organisation.

Individual

The individual values overlap with **Professional Competencies** discussed earlier and apply to what individuals value from each other and the program. **Good Science** was a frequently observed value and is a loaded concept that covers what the **Researcher** thinks of himself/herself (touching on integrity), the outcomes and the methodology. Below is evidence for this code.

- **Good science**

“[You] get much tighter [data when] you get rid of all the interpersonal differences.”—Participant 2

The above quote shows that good science can refer to objectivity and a commitment to proper statistical modelling. Participant 8 reiterates the importance of Research in her usage of Good Science.

When further asked about the choice to include a trial that may or may not contribute to a health claim or marketing data, Participant 2 gave the following answer:

“You don’t have to run any clinical trials to sell the product. [We did it because it’s] good science right? and I like to think that on some days I’m a good scientist. I just wanted to know that the [pharmacokinetic] data was so overwhelmingly positive”. —Participant 2

This quote suggests that good science is tied to being a good scientist/researcher. There was no mention on how the trial related to the overall strategy, budget, or planning. Participant 2 was driven by a sense of duty for complete scientific data that could give confidence for a successful product.

“Do the preclinical work, get your science, the mechanism of action...a particular disease indication...and then once you’ve got that good science, maybe even your Nature publication.”—

Participant 8

- **Benefit to the wider community**
- **Equity**

“We need to make sure that our intervention...would benefit the wider community, and it can be generalised to a wider population not just limited to certain ethnic groups, or certain area of people.”—Participant 3

Benefit to the wider community and **Equity** relate to the purpose of work that the clinical study staff perform. The former conveys a sense of duty and research impact whereas equity refers to how participants are treated during the trial.

Organisational

The organisational values provide examples of what organisations already conducting clinical studies can leverage when creating their program.

- **Safety**
- **Reputation**
- **Perseverance**
- **Scientific Rigour**
- **Openness to Industry**

“It wouldn't be up to me then to commercialise it, but the people that you are partnering with the research, they are then given this, you know, wonderful resource to go away and continue the commercialisation. It's not HVN's role to take [the investigational product] to that level, but that the idea that you are partnering with industry, means that it gives [the researchers] the ability to go away and fully commercialise it.”—Participant 5

“The knowledge transfer is not one sided from science to industry but also both sides because my experience told me that the scientists can't work alone... we would need to meet the longer projections of industry, interest, including the cost. If it should be cheap enough to scale up in the future.”—Participant 3

Scientists' attitudes toward industry involvement are mixed as shown from quotes above. **Openness to Industry** is positioned in opposition to **Ivory Tower** and negative **Financial Motivation** (see **Section 4.2.2.**). Participants 3 and 5, both **Researchers**, admit that the work they do cannot exist in isolation. Research originates in academic settings (usually through a **Researcher's** special interest or a student's need for a thesis), so industry partnership ensures the tangible commercial output to satisfy HVN funding guidelines.

- **Nutraceutical Skepticism**
- **Experience**
- **Ivory Tower**

“We are internal to Auckland University in that we only help Auckland University researchers, and the only the times when we touch on, or collaborate with industries is when they have a collaboration going on with a researcher... I only mainly work with Crown Research Institutes in the context of High Value Nutrition, but I do not work that much with industry.”—Participant 4

The only evidence supporting **Ivory Tower** code is from Participant 4. It’s difficult to draw a definitive conclusion from a single quote, however looking at other participant’s transcripts reveals a strong connection between researchers, universities and CRIs. Such consistent connections suggest functional food clinical trial expertise and interdisciplinary collaboration exist situated within academia rather than industry.

- **Multiculturalism**

“Most of the distributors we've dealt with have been able to communicate in English, although sometimes a bit broken, but I mean the general ideas and the meaning does get translated across.... So, I don't think there has been any like major language issues that I've encountered personally. From the regulatory point of view, a lot of the documents have been translated into English. I'm lucky I can read Chinese so for like the Chinese market or Taiwan...A lot of the information is pretty standard.”—Participant 7

Because New Zealand is an English-speaking country, businesses can easily communicate with others around the world as a lingua franca. However, the above quote shows the value in a multilingual workplace.

- **Financial Motivation**

“You can take this to the normal we are making a metabolic health claim or a cardiovascular health claim on the bottle. We will spend another US\$5 million on this to chase it...or you go the other way. You go to social media you go to people...to find what’s really valuable for them.”—Participant 6

“We take a founding stake in this you get some capital from the market; you take your energy and your insights, and you go and run and make amazing things. Well, strangely that hadn't happened. And that's very very sad when you see that, that the opportunity is not understood in the framework of the company.”—Participant 6

In this context, financial motivation is seen as a positive trait because it creates value for shareholders and value for New Zealand industries. There is a flipside from the scientists’ perspective of financial motivation seen as “*tainting science*”, as discussed in **section 4.2.2** but

Participant 6 discusses the willingness to pursue functional food trials but acknowledges the strategic considerations necessary to execute it. Financial motivation in this instance doesn't mean greed but suggests a cognisance of costs, and its requirement for desired outcomes.

4.2.2 Negative Values

Negative values were determined based on different language towards a trait or activity. If something was deemed “hard”, “difficult”, “challenging” or otherwise insinuated to be “wrong” rather than “good”, it was marked as a negative value. There are few negative values because in all other cases they were just being deemed not positive rather than negative *per se*. For example, rather than make “inexperience” or “lack of experience” a negative code, **Experience** was classified as positive because the binary coding scheme infers the opposite to be true, thus avoiding redundancy.

- **Financial Motivation**

“We [researchers] were quite keen to not have any industry involvement.”—Participant 2

Financial motivation was deemed both positive and negative, but it depended on where it was applied to receive the positive or negative attribute. Generally, scientists viewed financial motivation negatively whereas industry professionals viewed it positively. Scientists thought that finances biased results and introduced external interests that could threaten the quality of the data. This value shows a key gap in the academic and industrial relationship. Previously it was stated that facilities need industrial partnerships so at an organizational level sharing finances is favoured but at the individual level scientists may not feel comfortable with their project having “strings attached”.

- **Outdated**

“I think it's still gonna be around [the Natural Health Products] Bill and trying to get that through and just getting harder regulations you have for dietary supplements... [New Zealand is] very outdated and not on par with any other international regulatory body. Like for example, the TGA in Australia, EFSA in Europe, they're the gold standard in terms of regulatory bodies and product registrations.”—Participant 7

This code very narrowly refers to New Zealand's regulatory system as it relates to functional foods and supplements. Some members of industry felt that New Zealand is not keeping pace with the rest of the world, especially compared to key markets in Asia, Europe, and the United States. Therefore, there is frustration with organizations attempting to harmonize their products across

different regions and it became evident that a flexible and multicultural work environment is necessary to succeed in those markets. When asked about where the regulatory market in New Zealand is going, Participant 7 responded with the above quote.

- **Low Risk Appetite**

“In theory [applying for health claims is] well-defined but in practice is actually up to the regulators in the committees of the regulators and then you provide evidence and you put your first two trials and they look at it and saying this is very nice, indicative evidence but not enough...No board approving your finances on clinical trials is wanting to indulge this. Because either you can tell me it cost you exactly \$3 million, or euros or USD whatever.”—Participant 6

Therefore, low risk appetite in this context refers to investors, board members or other directors’ attitudes towards funding.

4.3 Process Map

The process map (shown in **Figures 3-5**) is the primary analytical outcome developed during this thesis research and helps visualize and organize the processes involved in starting a clinical program for functional foods in New Zealand. The processes were derived from the transcripts using process coding techniques and the process map created in Microsoft Visio [Visio in Microsoft 365, Microsoft Corporation]. **Figures 3, 4 and 5** were developed from the primary data collected during interviews and therefore from my original work. I scanned the transcripts for actions that the participants described then created the codes. After reviewing each participant’s transcript for actions, I compared across interviews and grouped similar actions together. The number of times an action was mentioned had no relevance to its inclusion. Because the participant pool was small and varied, I reasoned that because a process was mentioned once, it could be important from that participant’s perspective and may be relatively unknown to other participants. I compared participant transcripts to determine the chronological order of the map.

The process map focuses on the steps between understanding the market and identifying the research gaps up until the point at which a health claim is lodged. These processes are mostly internal but there are important external steps or subprocesses that feed into the main linear map; This will be discussed further in Chapter 5. The process map ends at FSANZ registration because any post regulatory work would be considered outside of this thesis, and it is also possible these processes can loop back to previous processes if certain conditions are not met.

4.3.1 Clinical Trial Planning

The planning stage (**Figure 3**) starts with a company identifying a need for a clinical trial. This could come from company strategy, new product development or as a partnership with a university, for example for a research thesis. The first step is understanding the market, identifying emerging research gaps, and understanding the regulations for the functional food under investigation. These three processes are interrelated and somewhat cyclical as the market informs the viability of the science, and the regulations determine the profitability and product development timeline. So, while **Figure 3** shows them as modular, these processes are much more interconnected in practice. Benchmarks include a literature review of animal and human studies, and a market report. After an investigational product has been loosely developed and a hypothesis formed, the clinical operations team performs a feasibility “study”. The purpose of the feasibility study is to ensure the potential trial will be able to recruit enough participants, manage the investigational product, and properly operationalize the study (tying in the Program Needs from **Section 4.1.3**). If the trial is deemed feasible, budget preparations begin, if not, then the team re-evaluates the research, market, and regulations. The budget is intended for external and internal audiences so while it is started before designing the study, the budget is not finalized until the study is approved by the sponsor.

Study design is a core part of the planning stage because the study protocol needs to reflect the desired outcomes. So, whether a trial is meant to gather data to be used in health claims, or marketing data the outcomes need to be decided early in the design process. Concomitantly, the team designs the product in terms of the format, formulation, or delivery method. A health claim is granted only to the exact formulation employed in the clinical trials e.g., problems may arise if a liquid delivery format was used in the trial, but a new untested powder format wants to make the same claim. Once the protocol and investigational product have been finalized, approval is sought from a funding agency. The High Value Nutrition Ko Ngā Kai Whai Painga (HVN) National Science Challenge, funded via the Ministry of Business, Innovation and Enterprise, currently acts as a governmental funding channel for functional food clinical trials in New Zealand but is not the only source of funding. HVN facilitates most of the functional food studies in New Zealand with the aim to increase high value food exports from NZ and is active until mid-2024 (HVN Challenge mission: *“to grow the science excellence and knowledge New Zealand needs to create and deliver food to the world that people choose to stay healthy and well”*). HVN commonly acts as a study co-sponsor so getting HVN approval is a common step for universities and companies conducting trials within this programme.

The final steps of the planning process are applying for ethical approval and prospective (i.e., prior to recruitment) registration of the trial to the Australia and New Zealand Clinical Trial Registry (ANZCTR). The HDEC application process starts with seeking Māori consultation for the study protocol and can include creation of a data management plan, recruitment plan, and advertisement materials. Applying for ethical approval wasn't further deconstructed because the subprocesses weren't mentioned in the transcripts explicitly, but rather found in secondary HDEC resources.

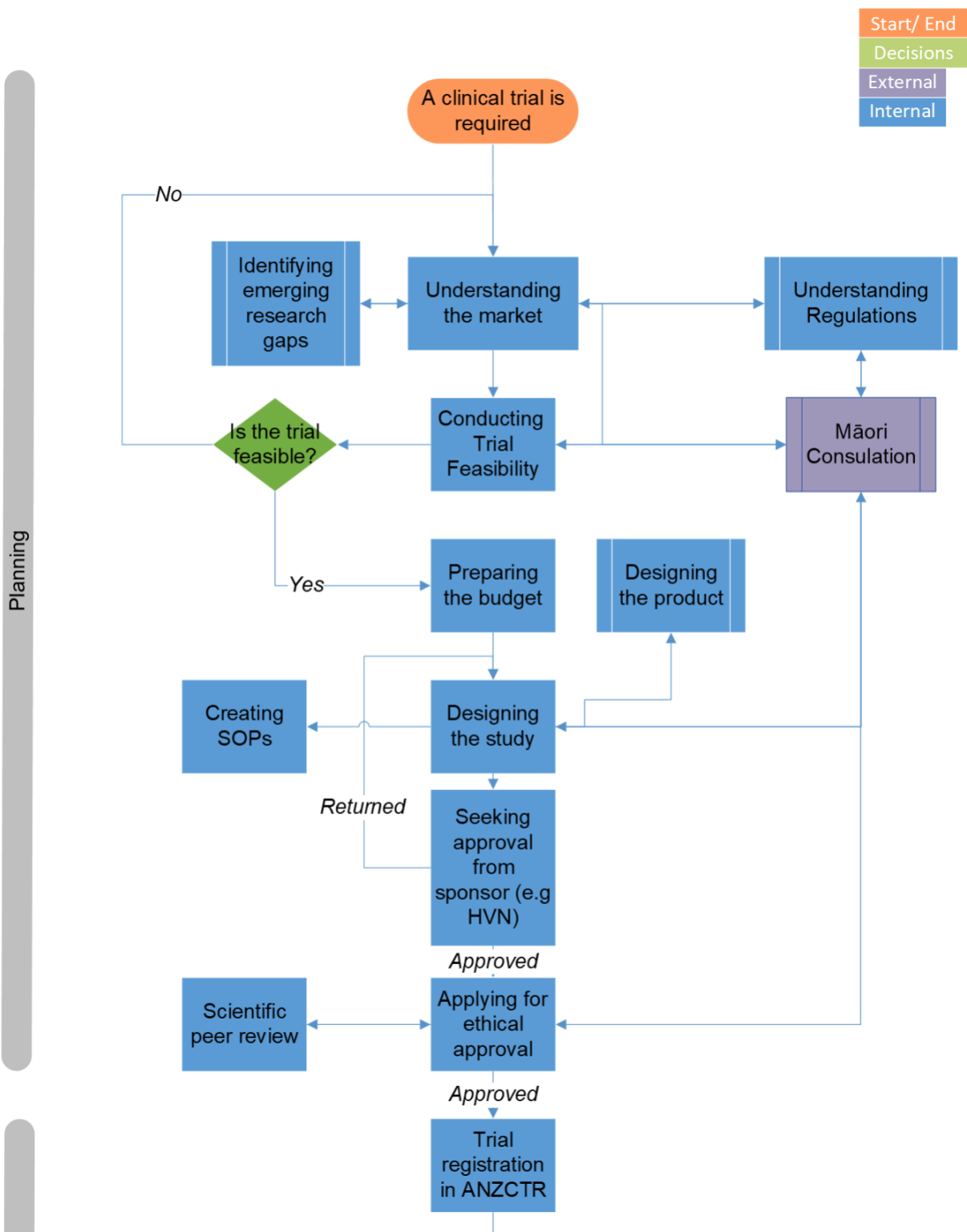


Figure 3- Process Flowchart; Planning

4.3.2 Executing and Closing Out

After the trial is registered and approval gained from HDEC, participant recruitment can begin and the Executing and Closing Out processes begin (**Figure 4**). The recruitment step varies depending on the type of study being conducted and its duration (i.e., a single visit study versus a residential trial). The participant population also influences how long recruitment takes (i.e., how strict are the inclusion and exclusion criteria). During the recruitment process informed consent is administered and participants are screened for eligibility. Once informed consent is obtained, the participant is randomized and placed into an intervention group. According to **Figure 4**, engaging with participants, collecting data, and managing data happened subsequently however it is more likely that these processes occur simultaneously. Technicians ensure participant compliance by seeing or speaking to participants over the phone and answering any questions they may have about the study; however, the Principal Investigator has overall responsibility for the appropriate conduct of all aspects of the trial.

Another key aspect of clinical operations during the data collection process is data standardization and monitoring for serious adverse events (SAEs). It's mandatory that clinical studies report SAEs to HDEC and for the Principal Investigator to determine if the event is linked to the trial. Depending on the outcome (as shown in **Figure 4**) SAEs linked to the investigational product can result in its termination.

Managing data is an oversimplified label for the numerous tasks that fit under that umbrella. Data management can include standardization, data cleaning, updating databases, or sending samples for analysis. Collaborating with testing service agencies sometimes puts extra strain on study staff due to logistics, delays, or tissue sample handling, so it is important to work closely with testing agencies (such as AgResearch and the Malaghan Institute). Ultimately, the execution phase ends once the data has been analysed and the study has been published.

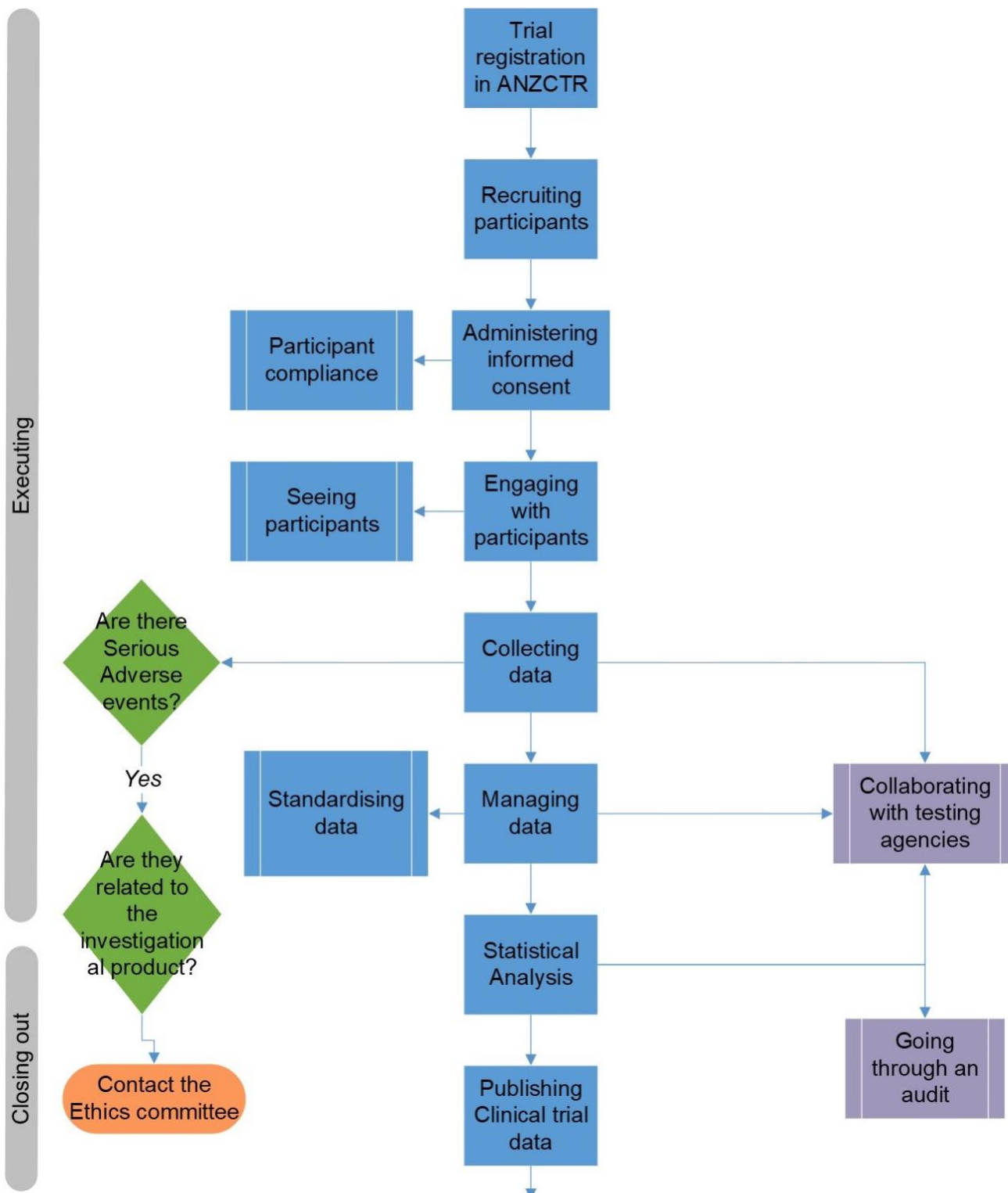


Figure 4- Process Flowchart Executing and Closing Out

4.3.3 Accessing the Market

At the final stage, Accessing the Market (**Figure 5**), the trial is completed, published and the sponsor begins the health claim registration. It is estimated that successful evidence dossiers contain 3-5 preclinical and clinical studies. However, the evidence threshold may vary depending on the target market, with EFSA generally being stricter than FSANZ, for example. So, the target market should be considered at the beginning during the Accessing the Market phase. While putting together the health claim application, a specialist regulatory agent or consultant, familiar with the target market, should be approached for more in-depth advice to ensure the product meets the regulatory criteria and the evidence gathered is sufficient. Depending on the outcome, the process ends at incorporating data into the brand strategy or registering health claims with a regulatory body. Looking further past the end of the processes described here, the organisation can then repeat these regulatory processes by incorporating previous evidence dossiers into new applications or going back to the beginning of the clinical trial process to add new studies to the dossier. There are also considerations for how the claim is used after being acquired (i.e., in-market implementation) but that is beyond the scope of this thesis.

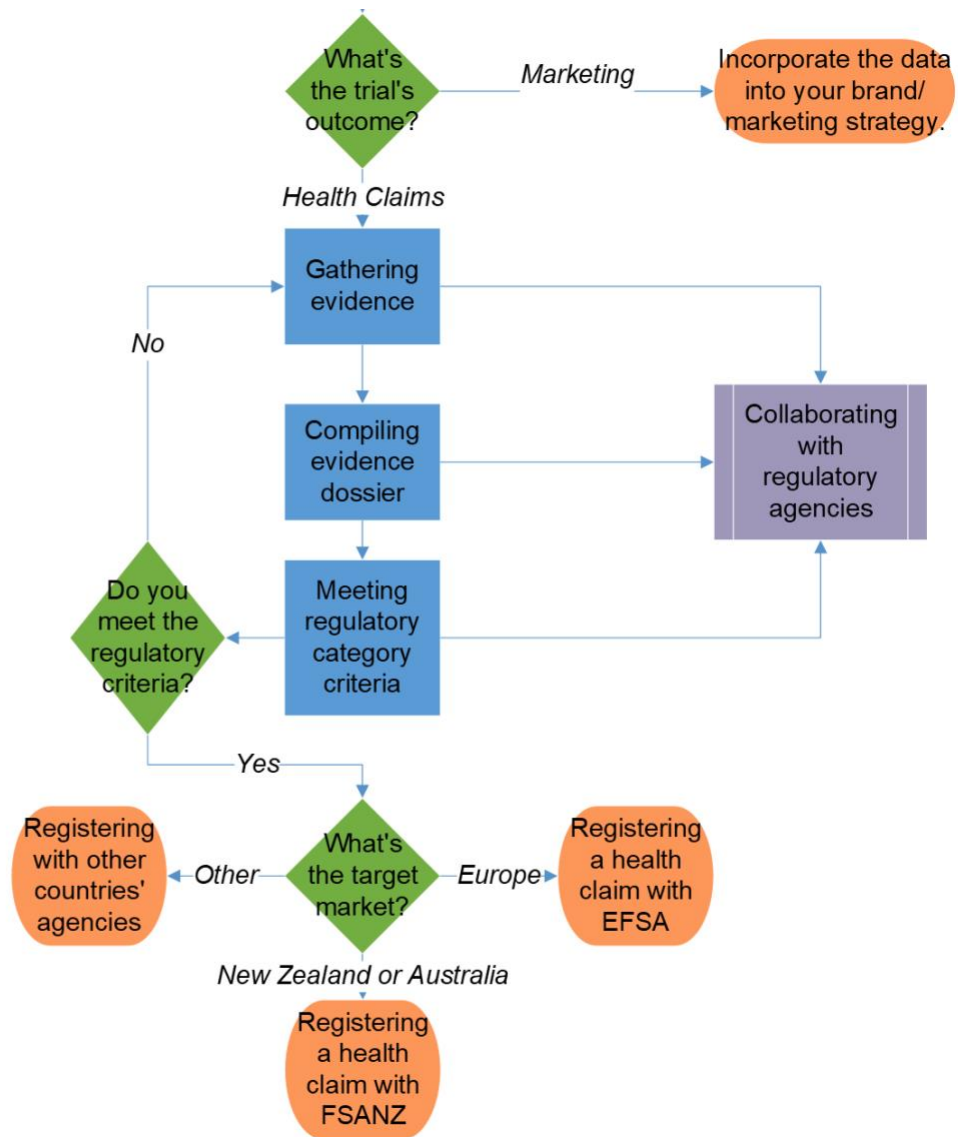


Figure 5- Process Flowchart Accessing the Market

5 Summary & Conclusions

The aim of this qualitative study was to assess how a New Zealand functional food ingredients company can establish a clinical trials programme for functional food products. Outcomes were process maps showing all of the steps required to conduct a clinical trial. This was achieved by interviewing industry professionals to understand the internal processes of organisations already conducting clinical trials. This analysis revealed a series of categories and specific items that contribute to the planning and strategy behind conducting functional food trials in New Zealand. It is evident a company needs expertise, collaboration networks, access to international markets and to follow the relevant regulations in order to embark on such trials. Whilst, in retrospect, the research question posed may have been too broad to answer definitively, three main themes became evident during the interviews: Expertise, orientation towards international markets and technical requirements.

5.1 The Clinical Operations Expertise Pipeline

The findings emphasised the importance of hands-on experience during professional development. Researchers and Technicians differ in responsibilities and outputs, but both share higher degrees in the life sciences. New Zealand's clinical operations expertise is more often generated by chance because there is no clear, direct career pathway. This finding is in line with expectations from the literature¹¹ and expanded upon in my research. Out of all the participants interviewed, none expressed a desire early in their careers to enter clinical operations. For most, clinical research was the logical next step in an academic research career. Others were recruited by industry late after their academic research career or participated in ad hoc projects on behalf of a research institute. However, the most common pathway into a clinical research career featured an integrated pipeline of research thesis students. The students perform the technician role for their own work and are supervised by academic researchers, who then go on to lead academic research themselves. The current pathway yields academic researchers, but not necessarily clinical operations professionals. Clinical operations require industry, academic and governmental collaborations, and a strong understanding of GCP/GMP. Professionals may gain these skills through academic research, but it was shown to be the onus of industry or the CRO to fill training gaps.

This research supported the understanding that someone who makes a good candidate in clinical functional food research, also has a higher degree in the life sciences with research experience. Typically, they highly value safety and reputation. While not directly captured in the data, most have a multicultural background reflected in where they were educated, worked, or personal

background. These values seem to be gained through their careers, with organisations selecting for people with these attributes. Reputation emerged as a value affecting both the organisation and individual, with individuals also possessing a strong sense of equity and benefit to the wider community that can sometimes be at odds with industry's affiliation with financial motivation. For organisations planning to bring on new staff to conduct clinical trials, it's recommended the organisations know what specific scientific expertise is needed and the pathway to integrate quality research staff.

An unexpected finding of this research was how deeply entrenched senior researchers still are in their academic networks. Participants 1, 2, and 5 expressed routinely reaching out to peers in academia for feedback on study protocols, operational feasibility, and product design despite their peers not being involved with the same organisation or project. These three participants' industry involvement occurred later in their careers, so the academic links were still strong. Biases became evident when Participant 5 referred to AgResearch and the Malaghan Institute (which are both CRIs) for her project's sample analysis, rather than accredited commercial testing agencies such as AsureQuality. The motives behind choosing a CRI over a commercial testing company cannot be elucidated from the current data but based on information from the value codes, I suspect it reflects "Ivory Tower" attitudes where researchers position themselves and their networks more favourably than industry. Whether or not their preference for academia persists after moving to industry is uncertain but it's clear "Good Science" is a deeply rooted value in researchers, such that if they associate good science only with academic networks it may come into conflict with the organisation's clinical trial goals. "Financial Motivation" may also influence this choice if it is cheaper to have another academic partner who uses a not-for-profit model compared to a commercial lab that incorporates profit margins into its pricing. Students perform analyses for their thesis projects in lieu of a salaried employee, which further reduces costs.

5.2 The Reliance on International Markets

The results presented in this thesis strongly indicate that the majority of New Zealand functional food clinical trials are targeted to an international market. The factors contributing towards this were not explored in this thesis but may be attributed to New Zealand having a smaller population and demand than the likes of China, Europe, and the United States. Among the positive values identified, multiculturalism is seen as favourable due to the ability for organisations to commercialise overseas through collaborations. The negative values Outdated, and Low Risk Appetite exist in juxtaposition to New Zealand's regulatory and commercial landscape. The fact the interviewees labelled it negative suggests a positive association with international markets.

Combined, Low Risk Appetite and an outdated regulatory system make New Zealand a riskier market to enter compared to Europe, Asia, or the United States.

Operating in an international market isn't only related to exporting and product sales. Various clinical trial processes can run outside of New Zealand depending on the type of trial. Recruitment, data collection, ethical approvals or sponsor collaboration can occur with an international partner such as a CRO, University or a distributor co-sponsor. This opens the opportunities for further funding and expertise. The first processes of the planning stage, identifying emerging research gaps, understanding the market and regulations will need to include international target markets and regulations. The relevant research may reside with an international lab thus requiring partnership. Participant 2 gained his clinical trial experience by working with a British university that was greatly more experienced than anyone he had previously worked within New Zealand.

A global outlook does however raise additional risk. One major risk associated with overseas data processing relates to data sovereignty under recently enacted HDEC and privacy guidelines. The Privacy Principles 11 and 12 set out notification requirements to participants about their data being sent overseas and HDEC now mandates data management plans as a part of the submission process. While these didn't come up as issues during the interviews (possibly due to how recent is the new Privacy Act and HDEC changes are), the changes are anticipated to result in potential conflict with a company's current processes and timelines.

5.3 Relevant Regulations, Guidelines and Accompanying Processes

As outlined in the literature review (**Chapter 2**) and results sections (**Chapter 3**), FSANZ, EFSA, ICH-GCP, and HDEC standards as the most relevant regulatory frameworks to the clinical trial processes because they direct the types of scientific evidence gained for health claims and impact the commercial viability of outcomes. GCP ensures trials are run consistently to a high international standard. It is therefore the basis for how researchers conduct trials and maintain reliable results. So, while the process map described in **Chapter 4** is original work derived from data gathered during the interviews, it confirms already established practices discussed in the literature review. Common themes from the interviews regarding technical requirements were study design, regulatory compliance and confidentiality and privacy. The values corresponding to technical requirements were experience, reputation, and good science.

Study design was emphasised during the interviews, particularly those of Participants 1 and 3. Based on interviews from these two interviewees, EFSA is the benchmark for clinical study design because it outlines the evidence required to achieve health claims at a detailed level not seen

within the FSANZ regulations. Study design is also commercially driven from the start of the planning stage, influences the trial's feasibility and impacts the product design.

Confidentiality and privacy were best represented in the transcript from Participant 4, the data management expert. The process maps broadly describe collecting data, managing data and statistical analysis as key parts of the execution phase. Within this phase, standardising data was mentioned as a key process that impacts how easily organisations can communicate with each other. For example, if a testing agency employs a different labelling scheme than the research group, there could be issues with storing uploading or analysing data resulting in its loss.

5.4 Implications of This Research

This research lays an important foundation for the creation of a general industry roadmap for how to begin functional food clinical trials in New Zealand. While what emerged from the research findings was often in line with the literature and an individual's experience, this research contributes to being the first guide that draws from both literature and experience from academic and commercial sources. While this information is understood by New Zealand academic researchers, it has not been collated in a written form, this is also the first time it's been collated from an industry perspective.

This research was not without difficulty and limitation though. In particular, it was difficult trying to recruit participants for the study because the functional food industry and clinical research field is so small in New Zealand, and information is tightly controlled by the organisations the potential study participants represent. The small sample size also poses issues regarding generalisability of the results and findings to all functional food trials. Hence, there is not intent to suggest that this research is applicable for all functional food products. For example, process maps focussing solely on taonga species may differ from what was presented here due to specific regulations or technical requirements. Unfortunately, this research also occurred during Auckland's COVID-19 lockdown, and as such personal interaction was heavily restricted for most of the interviewing window, and resultant time constraints played a role in scope the thesis; Specifically, rather than conducting a full evaluation up to implementation of the process map, the thesis addresses only the planning stages and factors involved with a research program setup. Similarly, while the findings support technical and managerial aspects of program management, there was a serious lack of funding or budgeting data. There was a bit of insight from participant 6 when he discussed the board and investors, but costs (and who managed them) were rarely mentioned in the transcripts – perhaps due to the relatively narrow demographics of the interviewees.

Rather than a limitation of the thesis research itself, the research findings highlighted a lack of a consistent framework for clinical trial evaluations. Due to the field being so interdisciplinary, evaluations follow convention from medical, education, economic or other domains, within which a variety of methodologies exist. The CIPP framework is grounded in the social sciences so it may have trouble capturing quantitative data, such as Likert scales, that would be found in other types of evaluations. Additionally, the CIPP framework that was used fails to account for wider organisational or industrial implications. However, qualitative research within clinical research provides unique perspectives to the field; specifically, this research investigated individual values. If this process were to be repeated for a full-scale evaluation, I would include organisational policies and recommendations for government and industry to better foster functional food trials and products.

5.5 Future Perspectives

This thesis has opened the door for future evaluation research for clinical trial programmes in New Zealand. The process map generated provides the first industry-specific roadmap for functional food companies looking to establish a clinical trial programme and highlights key points for any organisation looking to establish or build capacity in this area to consider. Again, this research thesis is the first to formalise knowledge that previously was held within specialised silos of expertise. So, this thesis lays groundwork for future research while providing tangible preliminary guidance in the interim. I think there is strong merit in extending this research from a Change Management or Product Innovation perspective. Innovation arose as a minor theme when speaking to Participant 8, which may suggest scope for further evaluation exploring how a clinical trial program can innovate using remote monitoring technology, virtual clinical sites, or hybrid sites (i.e., decentralisation of trials) – of particular relevance and importance in a post-COVID era.

Appendix A- Codebook

Name	Description
Clinical Trial Management	A top-level code containing aspects of managing a clinical trial.
Clinical Study Design	How the study will be conducted, which variables will be used and the end points. The most common type in this context is double-blind randomised controlled trial.
Clinical Trial Strategy	The code was used to mark thought processes and rationale behind planning a clinical trial.
Data Management	The act of collecting, storing, maintaining, and processing data. This code was used to mark Data Management as a topic for later review.
Data Management Plans	A document outlining how a study will collect, manage, and store its participants' data. Now a key requirement of the HDEC application process
Data validity	A code referring to instances when the importance of maintaining valid data was mentioned.
Decentralised Trials	Clinical trials that occur outside a central clinical site. These types of trials use remote monitoring techniques.
Good Clinical Practice	A set of standards on how to conduct clinical trials.
Māori Consultation	A key aspect of the ethics approval process that gains Māori input and perspectives and ensure cultural safety and emphasise the Treaty of Waitangi principles in research.
Participant Compliance	Ensuring participant compliance to the protocol either through phone calls, notifications, or reminders.
Recruitment	The stage of contacting and gaining participants for a clinical trial.
Risk Management	A code used to note when risk or risk mitigation techniques were discussed.
Statistical Analysis	A code used to reference when statistical analysis or data analysis was referenced. There are many types of data analysis, so this code remains broad by not distinguishing the types.
Trial Feasibility	A planning stage evaluation that determines if a trial is operationally and financially feasible.
Evaluation Criteria	Top level code containing the criteria for evaluation as discussed by Stufflebeam.
Capabilities and Capacities	Equipment, expertise, and operational capabilities for establishing a clinical trial program.
Outcomes	Reflect service to beneficiaries, significance and safety, cost effectiveness.
Professional Competence	An individual's obligations associated with membership in a profession. In other words, the skills and proficiencies required to be successful in the role.
Student Training	A general code that refers to a student's involvement for the sake of their own learning. Typically, this meant completion of a master's or PhD degree program.

Name	Description
Program Needs	Conditions or things that are necessary to the conduct or management of a clinical trial program.
Standards and Legislation	An evaluation criterion, this refers to the technical requirements for a program and within this context, technical requirements mean laws, regulations, and guidance for conducting a clinical trial.
Health Claims	A relationship between a nutrient or substance and its physiological benefit.
NZ Reg environment	The regulatory environment in NZ functional food products and supplements.
Regulation Harmonization	Bringing together different regulatory frameworks that many countries abide by.
Regulatory compliance	The state of following local regulatory rules and guidelines.
Negative Value	Code used to mark when data is undesirable, unnecessary, bad, or a barrier to program progress.
Positive Value	Code used to mark when data is desirable, important, necessary, good, or a driver to program progress.
Processes	A top-level organization code used to house process codes (actions ending in -ing)
Administering informed consent	A step in the recruitment process that educates participants on their rights and ensures their compliance and safety.
Applying for ethical approval	A key step where an investigator, sponsor or CRO submits study documents for a review.
Collaborating with academia	The act of a sponsor sharing or gaining knowledge/resources from an academic institution.
Collaborating with other institutions	A broad code to describe instances when an industry agent shares or gains knowledge/resources with another entity.
Collaborating with CRIs	Industry agent shares or gains knowledge/resources with a governmental Crown Research Institute.
Collaborating with regulatory agencies	Industry agent shares or gains knowledge/resources with one or more regulatory agencies.
Collecting data	A step for measuring and recording quantitative and qualitative data.
Compiling evidence dossier	A key stage before registering FSANZ/EFSA claims. The dossier contains all relevant scientific evidence.
Creating SOPs	Standard Operating Procedures are documents that outline the tasks and processes of completing a study.
Designing the product	Refers to steps involved with product design. In this context, the product could mean any functional food ingredient (or supplement) meant for sale.

Name	Description
Designing the study	Choosing the study type, collection methods and protocols. Usually based on the overall trial strategy.
Doing operational feasibility	A broad step that determines if a study is worth pursuing. A feasibility study accounts for cost, time, resources and staffing among other things.
Engaging with participants	Touching base with participants over the phone or email to ensure compliance, gain informed consent, or collect data.
Gathering evidence	The first step of applying for health claims. This could include a systemic review of existing literature or conducting in vivo/in vitro studies.
Going through an audit	Being audited by a third party for proper clinical and manufacturing practices.
Identifying emerging research gaps	Reviewing the literature and understanding which research topics could be further explored in a clinical trial.
Managing data	Adhering to data management practices as set out in GCP guidelines, Health Information Act, and the 2020 Privacy Act.
Meeting regulatory category criteria	An accessing the market stage process where the clinical trial team confirms the product meets the correct criteria according to the studies they've completed.
Preparing the budget	A planning stage process where the clinical trial team compiles the monetary requirements for a study.
Publishing clinical trial data	A process in the closing out stage that includes the dissemination of trial results. Study details may be written as manuscript and sent to a peer-reviewed international scientific journal for publication dependent on how commercially sensitive the data is.
Recruiting participants	Recruitment is a vital process for finding and bringing in participants for a clinical trial.
Registering with EFSA	The administrative process of gaining approval for an EFSA health claim.
Registering with FSANZ	The administrative process of gaining a FSANZ Health claim.
Seeing participants	A process involving physically visiting participants. This code is distinguished by physical presence from "engaging with participants".
Seeking approval from Sponsor	According to HDEC standard operating procedures, a sponsor is "the person or organisation with responsibility for the initiation, management and financing arrangements of the study."
Seeking peer feedback	A formal step of the ethical approval process that consists of academics reaching out to other academics for feedback on study documents and protocols.
Standardising data	This process is a subprocess to managing data and usually considered during creation of the data management plan.
Supervising students and staff	Because academia plays a major part in functional food clinical trials, students and research staff are supervised by more experienced staff.

Name	Description
Understanding regulations	A planning stage process where the clinical trial team determines the regulatory outcomes and key agencies to engage.
Understanding the market	Before a clinical trial can be planned, the commercial goal must be clear based on market values and information.
Science Commercialisation	An organizational code for loosely related concepts concerning the relationships and start-up of products.
Academic	A code to denote a relationship with academia.
Commercial Strategy	A code to mark transcript data that mentions business project planning.
Contract Research Organisation Role	Instances where the human nutrition unit acted like a contract research organization. A contract research organization is a third-party entity that assists sponsors in the pharmaceutical industry with their clinical trials.
Drug Registration	The process of pharmaceutical goes through to register with a regulatory agency. Examples include the FDA, Medsafe, or the TGA.
Industry	A general code used to denote an association or relationship with a functional food business.
Intellectual property	Includes patents trademarks, copyright, and other examples of proprietary intangible assets.
International	A general code is to denote and association or relationship with a four in partner. This could include regulatory agencies industry partners or academic partners.
Pharmaceutical industry	A specific term separating the drug development industry from the nutraceutical industry.
Values	A category for beliefs or views found in the transcripts.
'Good Science'	A positive value held by researchers to perform to a high scientific standard.
Benefit the wider community	A value that motivates researchers to act in the best interest of the community or participant groups being investigated.
Desire to be regulated	A value held by functional food industry professionals for clear, concise, and high-calibre regulations.
Effective communication	A value showing a need for cross departmental communication. E.g., between scientists and regulators.
Equity	A value held by scientists and regulators for proper treatment for study participants. This value is based in the three foundational clinical trial documents.
Expediency (while working)	A value held by industry to complete a task or program quickly and efficiently. E.g., Product validation
Experience	A value or attribute to describe a professional who has a well-developed career in their field. Experience also infers knowledge was gained through career pathway in addition (or instead of) academic research.

Name	Description
Financial Motivation	A value held in opposition by scientists and industry over the role of money in clinical research.
Honesty	A value held by researchers to fully divulge data and intent to effectively collaborate on a project.
Independence	A value held by researchers to be “independent” from industry influence. This could also be linked to Ivory Tower.
Innovation-minded	A value held by industry to push boundaries and break out of conservative business practices (see Low Risk Appetite)
Ivory tower	Preference for academia to help itself. The university system collaborates with government through funding agencies and CRIs, but it doesn't seem that industry has much access to it.
Low risk appetite	A value held by industry directors to continue standard business practices, and product that are guaranteed to make set investment returns.
Multiculturalism	A value or attribute (think multicultural) for industry's interactions with international entities and the positive association of being able to communicate effectively with those entities.
Nutraceutical Skepticism	A value held by the pharmaceutical industry regarding the long-term stability and profitability of functional food products.
Openness to Industry	A value held by some researchers about the importance of being open to industry collaboration.
Outdated	A value held by regulatory professionals that the New Zealand functional food and supplement regulations are outdated compared to international regulations.
Participant-centred	A value held by some researchers and industry to design clinical trials with participant outcomes in mind rather than strictly commercial or scientific outcomes.
Perseverance	A value held by industry to stay the course during periods of uncertainty. Clinical trials entail large amounts of resources and time, so being able to stay in for long-term gains is encouraged.
Reliability	A value for good data and measurement methods.
Reputation	A value for individuals and companies. For scientists, reputation comes from the quality of their research outputs whereas companies' reputation comes from the quality of their branding/products.
Safety	A value held by industry, researchers, and regulators to ensure trials and investigational products are safe for participants.
Scientific Rigour	A value held by the pharmaceutical industry referring to the higher standard of scientific evidence for running a drug trial compared to functional food trial.

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