Patient-focused prognostic tools used to predict outcomes in Total Knee Arthroplasty: A New Zealand external validation study

PROTO-KNEE External Validation Study: New Zealand

Study Protocol
V1.0
25 November 2021

Regulatory

Statement of Compliance

This document is a protocol for a clinical research study. The study will be conducted in compliance with all stipulations of this protocol, the conditions of ethics committee approval, the HRC Research Ethics Guidelines (March 2021) and the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95).

ABBREVIATIONS

Abbreviation	Definition
ANZCTR	Australian New Zealand Clinical Trials Registry
BOPDHB	Bay of Plenty District Health Board
CF	Consent Form
CI	Co-Investigator
CONSORT	Consolidation Standards of Reporting Trials
DHB	District Health Board
EQ-5D-3L	EuroQol health questionnaire
GP	General Practitioner
HDEC	Health and Disability Ethics Committee
NDHB	Northland District Health Board
OA	Osteoarthritis
PI	Principal Investigator
PROM	Patient Reported Outcome Measure
Proto-Knee	Prognostic Tool for Total Knee Arthroplasty by the University of Melbourne
SAGER	Sex and Gender Equity in Research
SMART	St. Vincents Melbourne Arthroplasty Outcomes (Registry)
SoA	Schedule of Assessments
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
TKA	Total Knee Arthroplasty
UKA	Unicondylar Knee Arthroplasty
VR-12	Veterans RAND 12 Item Health Survey

CONTENTS

1. Investigators and facilities

1.1. Study Location(s)

This study will be conducted primarily online with participants recruited from two cohorts

- Northland DHB
- Bay of Plenty DHB

The research team will be based at:

- Orthopaedics Department,
  Whangarei Hospital, New Zealand
- Orthopaedics Department,
  Tauranga and Grace Hospitals, New Zealand
- The University of Melbourne,
  Melbourne, Australia

1.2. Study Management

1.2.1. Principle Investigator

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1.2.2. Co-Investigators:

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1.3. Sponsor / Funding

This study is funded through a research grant by the Wishbone Foundation, New Zealand (Grant Number (2021/2)

2. Protocol Synopsis

2.1. Intervention

The 'PROTO-KNEE' is a prognostic tool that use machine learning algorithms to predict patient satisfaction after Total Knee Arthroplasty (TKA). The tool predicts outcomes in the form of a likelihood score for satisfaction after TKA. The tool is patient focused, meaning it can be used without the input of clinicians.

2.2. Objectives

To evaluate the external validity of the tool in a New Zealand population.

2.3. Design

Prospective multi-centre cohort study

2.4. Population

Patients who are suffering from knee OA and are booked for TKA are eligible for the study. Participants will be recruited from NDHB, BOPDHB and their respective private care providers (Northland Orthopaedic Centre and Grace Hospital).

2.5. Number of Subjects

Based upon our sample size calculations, approximately 200 participants will be required for our study.

2.6. Outcomes

The primary outcome of this study is to validate the tool's predictive performance for the New Zealand population.

2.7. Follow-up

Participants will complete VR-12 and EQ-5D-3L questionnaires preoperatively, and at 6months and 12months post operatively.

2.8. Study Duration

The study duration is expected to take 22 months from first patient enrolment to completion.

3. Introduction and Background

3.1. Terminology

In this study protocol, the term “prognostic tool” refers to the interface (e.g. website or mobile app) that patients interact with to predict outcomes. In contrast, the term “predictive model” refers to the statistical model(s) and/or machine learning algorithm(s) that the prognostic tool uses to calculate predictive outcomes.

3.2. Background

Knee osteoarthritis (OA) is a progressive and debilitating condition for patients. Pain and stiffness are common presenting complaints. Without adequate intervention, functional decline and loss of independence can occur (1). Lifestyle modification, analgesia and physiotherapy comprise the core of non-operative management (2). In certain situations, intra-articular injections may delay the need for surgery (3,4). Failing non-operative management, the definitive treatment option for knee OA is TKA (5).

Based on registry studies, TKA is generally regarded as a successful procedure (6,7). The risk of adverse event associated with the surgery is relatively low and the probability of improving symptoms is relatively high (8,9). However, recent studies have reported that up to 20 percent of patients remain unsatisfied after TKA (10). For these patients, ongoing symptoms from their TKA severely impacts their quality of life (2,11). With a current trend towards more arthroplasty surgery globally, the social and economic impact of TKA dissatisfaction is a fast growing problem (12).

To address this issue, solutions need to arise from multiple fronts. Improvement in surgical technique and implant design seem to be the most obvious path forward. However, substantial progress has already been made from pioneers of the past. The trajectory of progress from technique and implant design alone is reaching a plateau (13,14). An alternative solution would be a completely new treatment for knee OA; a solution that addresses both the symptoms and natural history of the disease. Work is underway to experiment with biologic agents aimed at regenerating cartilage and bone (15–18). However, this process is expensive and time consuming without any guarantee of success. Research must therefore explore complementary pathways to find solutions for TKA dissatisfaction.

One of these pathways is through improvement of patient specific factors. The goal here is to optimise patients to become excellent surgical candidates. Prognostic tools fit into this area of research. These are tools developed to predict surgical outcomes. This is clinically useful in two ways. First, if poor outcomes can be predicted before surgery, then patients can be stratified into groups based on risk. For high risk patients, resources can be set aside to improve modifiable risk factors. This will optimise the patients for surgery. Secondly, prognostic tools can manage patient expectations through informed decision making. A patient who understands their potential outcomes may regress their expectations towards what is realistic for their circumstances. This is based on the understanding that a major driver of dissatisfaction is the imbalance between expected and actual outcomes (19). The

hope is that prognostic tools can better align these two perceptions to improve patient satisfaction and influence patient decision making about surgery for the better.

PROTO-KNEE is a patient focused prognostic tool that predicts outcomes after TKA that is being developed in Australia. The term "patient focused" means that a patient can use the tool by themselves before seeing a clinician. The tool was developed using data from the SMART Registry– an extensive arthroplasty registry with over 10,000 patients and more than 20 years follow up time (20).

This tool is similar in its function to the 'After my surgery' prognostic tool utilized in the NHS and created by York University. It uses data collected as part of the NHS Patient Reported Outcome Measures (PROMs) programme (via the EQ-5D-3L) before surgery and several months after. Similar to PROTO-KNEE, this tool provide users with a likelihood score of satisfaction after surgery.

3.3. Rationale and Hypotheses

Prognostic tools can benefit patient care through two pathways; 1) improves informed decision making for the patient, and 2) manages patient expectations in preparation for TKA. With more information, patients can be empowered to make a decision that is right for their specific circumstances. Furthermore, patient expectations after surgery can be tuned to what is realistic – an important aid to provide patients a sense of satisfaction with their outcomes.

To date, there have not been any prognostic tools for TKA developed with a New Zealand cohort. With the emergence of machine learning in prognostic tools, overfitting of predictions to a specific population is a problem that must be addressed with external validation studies. Therefore, our study aims to use the PROTO-KNEE tool on a representative sample of New Zealand patients to validate predictive outcomes.

There are many similarities between the population in New Zealand and Australia. As a result, we hypothesise that the PROTO-KNEE tool (developed in Australia) will be accurate and applicable in a New Zealand population. As contingency, we will also collect data that will validate the "After my surgery" tool (developed in the UK) in a New Zealand population.

3.4. Research Questions

The overarching research question is "how can we improve patient selection for TKA?" With respect to this cohort, the primary question is "Is the PROTO-KNEE tool applicable to the New Zealand population in terms of predictive performance?"

4. Study Objectives

4.1. Primary Objective

The primary objective of this study is to evaluate the predictive performance of the PROTO-KNEE tool in a New Zealand population.

4.2. Secondary Objectives

To evaluate the predictive performance of the “After my surgery” tool in a New Zealand population. This tool is similar to PROTO-KNEE, using machine learning algorithms to predict TKA outcomes. The “After my surgery” tool was developed using a NHS cohort in the United Kingdom. This is contingency to the scenario that the PROTO-KNEE tool may not be valid for use in a New Zealand population.

5. Study Design

5.1. Study Methodology Overview

This is a multi-centre cohort study. The trial will be registered in the Australian New Zealand Clinical Trials Registry (ANZCTR). Reporting will be in accordance with the CONSORT Statement (21). The trial protocol will be published in line with SPIRIT (22) and SAGER (23) (sex and gender equity) guidelines

Participants with knee OA who are imminently about to have TKA will be selected for the study. Screening for potential participants will occur by review of upcoming operative lists in the individual centres. Participants must be imminently about to have TKA and provide informed consent to participate in the trial.

At the time of surgery, or in the weeks leading up to, participants will have their necessary data captured. (ie, age, gender, BMI, duration of symptoms, VR-12, and EQ-5D-3L).

At 6months and at 12months, the VR-12 and EQ-5D-3L will be sent by email to the participant for completion and return to research team. This will managed through SOCRATES, with the server housed securely at Northland DHB on a password access computer.

The respective prognostic tool predictions can then be applied retrospectively and see if their predictions are accurate to our cohort.

The participant will not be notified of their prediction before or after their surgery as the tool has not been validated in our healthcare system.

5.2. Number of Subjects

As this is an exploratory study, a power analysis calculation was performed to estimate the sample size for this study. Predictive performance of the PROTO-KNEE tool in a New Zealand population is unknown. The approximate c-statistic for the PROTO-KNEE on internal validation was 0.80. Using standard values for alpha at 0.05 and beta at 0.8, we estimate a sample of size of 140-160 participants will be needed to generate statistically significant results. Inflation of the sample size by 20% was deemed reasonable to account for lost to follow up patients. We predict that approximately 200 participants will be required to provide a meaningful outcome to this study.

This number is feasible to recruit across the two DHBs and their respective private facilities. On average, 5 TKAs are performed in Whangarei Hospital per week, and a further 10 by the Northland Orthopaedic Group. A similar number are performed in the Bay of Plenty per week. Accounting for this, the 200 participants could be reached in approximately 8 weeks.

5.3. Expected Duration of Study

This study is expected to be completed in 22 months (see Figure 1).

- Phase 1 – Study planning, logistics, setting up the appropriate infrastructure to ensure all relevant data can be captured.
- Phase 2 – recruitment of patients will occur alongside follow up of patients who have been recruited earlier in the study
- Phase 3- final follow up of the patients recruited later in the study, data analysis, preparing the findings for dissemination in journal publications and conferences.

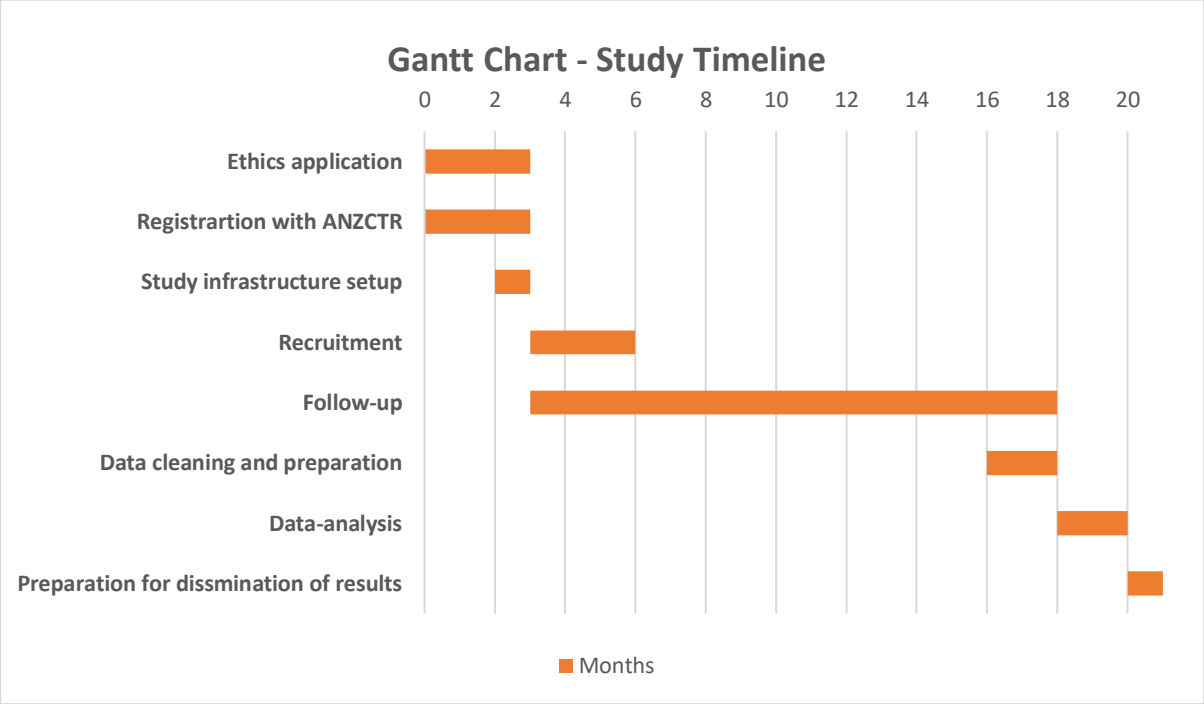

Figure 1. Gantt Chart detailing the timeline of the study

6. Subject Enrolment

6.1. Recruitment

Participants will be recruited from two regions:

- Northland; Northland DHB and the Northland Orthopaedic Centre
- Bay of Plenty; Bay of Plenty DHB and Grace Hospital

Based on our sample size calculations, we will need approximately 200 patients in total for our study to achieve its primary objective. We will approach all consecutive patients that meet the eligibility criteria in these regions.

6.2. Eligibility Criteria

6.2.1. Inclusion Criteria

Inclusion criteria will select for the following participants

- Diagnosed with knee OA
- Imminently about to undergo primary unilateral TKA
    - By imminently, we mean is within 2 to 3 weeks of surgery including up to and on the day of surgery.
- Are willing and able to complete online PROMs tools
- Able to provide informed consent to participate
- Are available to be followed up for the duration of the study

6.2.2. Exclusion Criteria

Exclusion criteria will select out the following participants

- Source of knee symptoms is considered to be from any cause other than knee OA eg, rheumatoid arthritis, hip osteoarthritis, referred lower back pain, post traumatic arthritis, previous septic arthritis of the knee etc.
- Are undergoing bilateral TKA, revision TKA, unicondylar knee arthroplasty (UKA), or patellofemoral arthroplasty
- Significant bilateral knee symptoms
- Intra-articular injection in the affected knee within the last 3 months
- Patients younger than 45years

6.2.3. Eligibility Screening

Participants will be screened for eligibility based on the above criteria. The screening questionnaire will contain the following questions

- Have you been diagnosed with knee OA?
    - If no, patient will be excluded.
- Are you about to undergo joint replacement for your affected knee?
    - If no, patient will be excluded.
- Do you have osteoarthritis symptoms in both knees that significantly affect your life?

    - If yes, patient will be excluded.
- Do you have hip or back symptoms that significantly affect your life?
    - If yes, patient will be excluded.
- Have you had a steroid injection in your affected knee within the last 3 months?
    - If yes, patient will be excluded.

6.3. Subject Withdrawal

6.3.1. Reasons for Withdrawal

The investigator may withdraw a patient from the study and follow-up procedures if the participant:

- Experiences a serious or intolerable adverse event that may impact their ability to participate in the study

The investigators will also withdraw all participants from the study if the study is terminated. Participants are free to withdraw from the study at any time upon their request or the request of their legally acceptable representative.

6.3.2. Handling of Withdrawals and Losses to Follow-up

If a participant withdraws from the study, the reasons for withdrawal shall be recorded on a recruitment spreadsheet. Whenever possible, data already captured about the participant will be retained for analysis. Participants who do not formally withdraw from the study but fail to respond to study assessments will be contacted by the research team to redirect compliance with the protocol. This will consist of two documented phone calls and a letter/email follow up. If these contacts are unsuccessful, the participant will be deemed lost to follow up.

6.3.3. Replacements

Participants who have been lost to follow-up or discontinued from the study may be replaced up until the agreed end date for recruitment. This date will be set at least 1 month prior to the end date as agreed by the research team. Lost to follow up cases that occur after the recruitment phase cannot be replaced and will be noted in the final analysis of data.

6.3.4. Trial Closures

A participant is considered to have completed the trial if they have completed all phases of the trial including the last assessment as shown in the Schedule of Assessments (see section 7).

7. Study Visits, Procedures and Assessments Schedule

7.1. Schedule of Assessments (SoA)

SCHEDULE OF ASSESSMENTS			
	Enrolment	Follow up	
TIME POINT*	t_x	t_1	t_2
Enrolment			
Eligibility Screen	X		
Informed Consent	X		
Assessments			
Baseline questionnaire**	X		
VR-12^	X	X	X
EQ-5D-3L^^	X	X	X

7.2. Definitions for SoA

Definitions of SoA		
Terms	Definitions	
*Time Point	t_x	Time at initial contact
	t_1	6 months post TKA
	t_2	12 months post TKA
**Baseline questionnaire	Questionnaire for all patients who have been recruited into this study. Captures basic demographic data.	
^VR-12	The patient reported outcome measure for use with the 'PROTO-KNEE' tool	
^^EQ-5D-3L	The patient reported outcome measure for use with the 'After my surgery' tool	

8. Clinical Assessments

8.1. Eligibility Screening

Eligibility screening will be performed prior to allocation using the eligibility criteria described in Section 6.2.3. The screening questionnaire will be available in hard copy for the clinician. Further eligibility information will be ascertained during discussion prior to informed consent

8.2. Patient Information Sheet and Consent Form

If a potential participant meets the eligibility screening criteria, they will be provided a PIS which they must read and a CF which they must sign. Following this, the participant will be formally recruited into the study. Please see the attached documentation (Appendix 1).

8.2.1. Baseline Questionnaire and Pre-operative Assessment

The baseline questionnaire will only be used at the first assessment. It is designed to obtain the necessary details that the tools would require if used such as age, gender, height, weight, duration of symptoms. It will also include the obtaining of up to date contact details and the first VR-12 and EQ-5D-3L PROM. Please see the attached documentation (Appendix 2).

8.2.2. Regular Assessments

Regular assessments will be conducted in accordance with the SoA. They will consist of the two PROM assessments. Patients will be followed up through the automated software tool SOCRATES.

8.2.3. PROMs

For this study, we will use the VR-12 and the EQ-5D-3L as the PROMs, as these are the PROMs utilized by the 'PROTO-KNEE' and 'After my surgery' prognostic tools.

8.2.4. Wellbeing Check

All participants will be offered the opportunity to provide feedback or raise concerns about their wellbeing at any point during the study.

9. Study Workflow

This workflow describes the stepwise process for how the study will be conducted

9.1. Initial Screening

9.1.1. Northland Source

Patients booked for TKA at Whangarei Public Hospital, Kensington Hospital or Kaitaia Hospital will be flagged for recruitment in this study by the review of upcoming operative lists

From this pool of flagged patients, exclusion criteria will be applied using information available on the NDHB Concerto and/or the Northland Orthopaedic Centres Records. Potential participants will be excluded if they have:

- Booked for bilateral TKA, UKA, revision TKA
- Diagnosis of rheumatoid arthritis
- Diagnosis of previous septic arthritis to the affected knee
- Under 45 years old

Following initial screening, patients will be contacted for eligibility screening and formal recruitment by research team member.

9.1.2. Bay of Plenty Source

Patients booked for TKA at Tauranga Public Hospital, Grace Hospital or Whakatane Hospital will be flagged for recruitment in this study by the review of upcoming operative lists

From this pool of flagged patients, exclusion criteria will be applied using information available on the BOPDHB Concerto and/or the Grace Orthopaedic Centres Records. Potential participants will be excluded if they have:

- Been booked for bilateral TKA, UKA, revision TKA
- Diagnosis of rheumatoid arthritis
- Diagnosis of previous septic arthritis to the affected knee
- Under 45 years old

Following initial screening, patients will be contacted for eligibility screening and formal recruitment by research team member.

9.2. Eligibility Screening and Formal Recruitment

For participants in the Northland region who pass initial screening, they will be contacted prior to their TKA either by phone call, at ‘Joint Camp’ or in the perioperative bay. For participants in the Bay of Plenty region who pass initial screening, they will be contacted prior to their TKA either by phone call or in the perioperative bay.

All participants will receive the same information, including a short introduction to the study, the PIS and Informed Consent Form.

Eligibility screening can then occur, where the inclusion and exclusion criteria are reviewed with the patient. If at this time, patient does fit these criteria, they will be excluded from the study and thanked for their time.

If they pass the eligibility screening, they will be provided an opportunity to review the patient information sheet, and then complete the informed consent process with the clinician.

9.3. Initial Assessment

All participants who have been formally recruited to the study will now complete the following:

- Baseline Questionnaire
- VR-12
- EQ-5D-3L

9.4. Regular Assessments

Participants will be contacted at the times indicated by the SoA to complete the required VR-12 and EQ-5D-3L. This will be an automated process guided by SOCRATES. A research assistant will be employed to chase up via phone call participants who fail to respond to the SOCRATES follow up questionnaires.

9.5. Data Collection

All data will be sent to the research assistant who enters their information into the SOCRATES database. Data will be stored on secure severs at the Northland DHB and Northland Orthopaedic Centre. See detail data management plan in section 12.

9.6. Trial Closure

After the 12month assessment, the participant will be notified that the study has concluded for them. Contact details will once again be provided to participants should they have queries or concerns after the conclusion of the study.

10. Data Management Plan

10.1. Data Collection

All data collection will follow guidelines as mandated by New Zealand Privacy laws. The consent form will be signed in person on paper. Data will be collected via paper for the initial assessment and online forms used for regular follow up assessments via SOCRATES.

10.2. Data Storage

NDHB, BOPDHB, Northland Orthopaedic Centre and Grace Orthopaedic Centre have their own data and record storage policies that must be adhered to for ethics requirements.

The main study centre will be Whangarei Hospital.

For Northland based patients, their hard copy forms will be handed in to the principal investigator and stored securely in a restricted access office. Data will then be entered online to SOCRATES and stored securely on a NDHB sever.

For Bay of Plenty patients, when hard copy forms are completed, they will be scanned in the hospital and sent electronically via secure internal email (DHB email addresses only) to the principal investigator in Whangarei. The original hard copy forms will be kept in Tauranga Hospital. The data will then be entered into SOCRATES and stored securely on a NDHB sever.

At the end of recruitment, all hard copy documents will be couriered to NDHB via a secure hospital-to-hospital courier company in a sealed and tracked bag.

Access to the study data on the servers will be limited to research members who are directly involved in the study. Access will only be available to research members who are on site (NDHB) or via virtual machine to access NDHB servers. Access will be password protected and auditable.

Data will be deidentified for the data analysis phase of the study.

No data will be sent overseas, including to the University of Melbourne. The University of Melbourne in this study will serve in an advisory capacity. No access to data will be provided.

10.3. General Principles

Participants will only be able to submit their completed forms. They will not have access to any other participants information or completed forms. None of this information will be searchable by a public search engine.

10.4. Study Record Retention

All data collected will be stored for a minimum of 7 years after the conclusion of the study.

11. Administrative Aspects

11.1. Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators, research staff, and the study institution(s). The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval of the sponsoring institutions. Authorized representatives of the sponsoring institution may inspect all documents and records required to be maintained by the PI, limited to their recruited participants, including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by Ethics Committee or regulatory agencies.

11.2. Independent Ethics Committee and Locality Approval

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the Health and Disability Ethics Committee (HDEC) of New Zealand. Locality approval will also be sought in the two regions. A letter of ethics approval by HDEC, letters of locality approval will be obtained prior to the commencement of the study, as well as approval for other study documents subject to the Committees reviews.

11.3. Modifications of the Protocol

This study will be conducted in compliance with the current version of the protocol. Any change to the protocol document, PIS, or consent form that affects the scientific intent, study design, patient safety, or may affect participants willingness to continue participation in the study is considered an amendment, and therefore will be written and filed as an amendment to this protocol and/or consent form. All such amendments will be submitted to the ethics committees for approval prior to becoming effective.

11.4. Protocol Deviations

All protocol deviations must be recorded in the patient record (source document) and reported to the primary investigator. Those deviations deemed to have a significant impact on the integrity of the study results, patient safety, or the ethical acceptability of the trial will be reported to the local ethics committee.

11.5. Participant Reimbursement

Participants are not reimbursed for taking part in the trial

11.6. Financial Disclosure and Conflicts of Interest

All investigators and research staff must declare any conflicts of interest or financial interest relating to the study prior to involvement. This will be disclosed upon publication.

12. References

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