NZ SPECIFIC ROADMAP TRIAL SITE HANDBOOK

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2 CONTACT DETAILS FOR TRIAL MANAGEMENT GROUP

NZ Lead Investigator
• Dr Tom Hills THills@adhb.govt.nz
Regional Trial Management
• Alex Mowday – NZ Trial Manager (alexandra.mowday@aotearoatrials.nz) • Georgia Fowler – NZ Trial Coordinator (georgia.fowler@aotearoatrials.nz) • Aotearoa Clinical Trials email: grants@aotearoatrials.nz
Trial Website
• **https://www.roadmaptrial.com/**

3 INTRODUCTION

The purpose of this handbook is to provide sites with general guidance regarding trial procedures. This document is intended as a guide only. Please contact the regional management team, using the contact details provided above if further information or guidance is required. See also the site "Quickguide" for a shorter summary of key steps when screening and recruiting participants.

Further reading and additional guidance documents are referenced throughout this manual within the **purple-coloured boxes.**

3.1 TRIAL OVERVIEW AND PROTOCOL STRUCTURE

The ROADMAP trial is a multicentre, pragmatic, multi-arm, open label adaptive platform trial addressing multiple therapeutic questions in patients with prosthetic joint infections.

The ROADMAP trial will include sites across Australia, New Zealand, Canada, Europe and the United Kingdom, with the potential to recruit in other regions.

The ROADMAP trial includes a Registry; in New Zealand we have a waiver of consent meaning we do not need to obtain consent to enter patients into the registry.

- If a patient is eligible for the trial, they will be asked to consent to the platform. They will automatically be enrolled into the registry.
- Patients not eligible for, or not consenting to, enrolment into the ROADMAP platform will be entered into ROADMAP Registry only.

3.1.1 THE PRAGMATIC TRIAL APPROACH

The ROADMAP Trial incorporates design features to enhance the trial efficiency, whilst also ensuring the trial is highly pragmatic and embedded within routine care:

- The inclusion criteria are easily identified
- The exclusion criteria are minimal
- Recruitment uses a simplified consent process
- All interventions are within the spectrum of current standard care
- All interventions will be delivered by routine clinical staff
- All interventions will be delivered in the same way that superior interventions would be implemented in clinical practice
- Wherever possible, routine clinical and administrative data will be used for data collection

3.1.2 THE PROTOCOL STRUCTURE

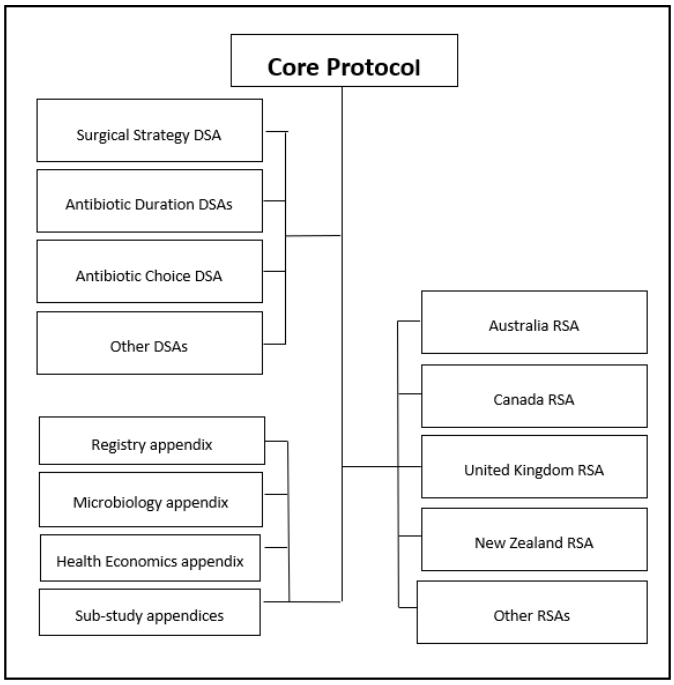


Figure 1: The Protocol Structure

The ROADMAP Trial protocol is presented in a modular format. This format includes:

- **Core Protocol**
  The Core Protocol contains all information relevant to international trial processes and applies to all regions and to all domains for the duration of the trial. The Core Protocol is anticipated to require only rare modification.

- **Domain-Specific Appendices (DSAs)**
  Each intervention examined within the ROADMAP trial will be fully described within a DSA. As domains are added, removed, or changed, the DSAs will be updated accordingly.

- **Registry Appendix**
  This appendix describes the design, operation and analysis of the clinical quality registry that sits adjacent to the ROADMAP trial domains and includes both randomised and non-randomised eligible patients with prosthetic joint infections.

Health Economics Appendix

- This appendix outlines the protocol for the economic evaluation to be conducted alongside the ROADMAP trial, to identify the treatment regimens that represent the most cost-effective use of healthcare resources.

Microbiology Appendix

- This appendix outlines the required laboratory procedures and details the ROADMAP isolate repository.

3.2 DEFINITIONS

Please see the table below for ROADMAP Trial-specific definitions and for further clarifications as to what the use of certain terms means within the trial.

Term	Description
DAIR	Debridement, Antibiotics and Implant Retention.
Domain	Groups of alternative interventions to which participants can be randomized
Response Adaptive Randomisation (RAR)	Allows for randomisation ratios adapt over time, based on the accumulated platform data, allowing for more patients to be randomised to the treatments that appear to be performing better, and

	randomise fewer patients to the treatments that appear to be performing poorly. These adaptations are performed by the algorithm and are blinded to the investigators.
ROADMAP Platform	The randomised portion of the trial, where a participant will be allocated to receive different treatment regimes
ROADMAP Registry	The data collection portion of the trial for patients with a PJI whether or not they are enrolled in the in the ROADMAP platform.
ROADMAP Trial	The project as a whole – this ROADMAP Trial consists of both the ROADMAP Platform and the ROADMAP Registry
Silo	Subgroup of patients categorised by the timing of symptoms after a joint replacement

3.3 SILOS, DOMAINS, CELLS AND REGIMENS

The ROADMAP Platform is organised into different groupings, which are detailed in the figure below.

<table>
<tr><th rowspan="2">SILOS</th><th colspan="3">DOMAINS</th></tr>
<tr><th>Surgical management</th><th>Antibiotic duration</th><th>Antibiotic choice</th></tr>
<tr><td>Early PJI</td><td>Clinicians' choice
(DAIR recommended)</td><td rowspan="3"><u>For DAIR:</u>
Clinicians' choice
(12 weeks recommended)
<u>For one stage</u>:
Total 6 weeks
versus 12 weeks
<u>For two-stage:</u>
No extended prophylaxis versus Extended prophylaxis (12 weeks post 2nd stage)</td><td rowspan="3">Backbone antibiotics
+
adjunctive rifampicin
versus
Backbone antibiotics alone</td></tr>
<tr><td>Late acute PJI</td><td>DAIR
versus
revision</td></tr>
<tr><td>Chronic PJI</td><td>Clinicians' choice
(Revision recommended)</td></tr>
</table>

4 DATABASES

There are 2 databases used for the ROADMAP Trial.

1. **Spinnaker:** This is the main trial database/eCRF and will be used to collect all data for both the platform and the registry
2. **REDCap:** A regional REDCap database will be used to collect patient identifiers.

To use the databases in the ROADMAP Trial, each investigator will need to be granted individual access. Not all investigators will require access to one or both databases; the site team will decide who will require access for study data or patient identifier data entry.

To be granted access, the investigator will need to complete a Database User Activation Form, and ensure their access is recorded on the training and delegation logs as appropriate.

4.1 SPINNAKER DATABASE – RECORDING CLINICAL DATA

The ROADMAP Trial uses the Spinnaker electronic database provided by Spiral Software as the primary platform for clinical data collection. All data should be entered into the Spinnaker database as soon as possible on the specified study days.

THE SPINNAKER DATABASE CAN BE ACCESSED HERE:

https://roadmap.spinnakersoftware.com/Login

Please contact the ROADMAP management team with any issues you may have regarding Spinnaker access.

For more information regarding database entry procedures, please view the ROADMAP Spinnaker Video Guide.

If you would like access to the Spinnaker staging (test) site, to trial recruitment of participants or to test the database, please contact the ROADMAP management team.

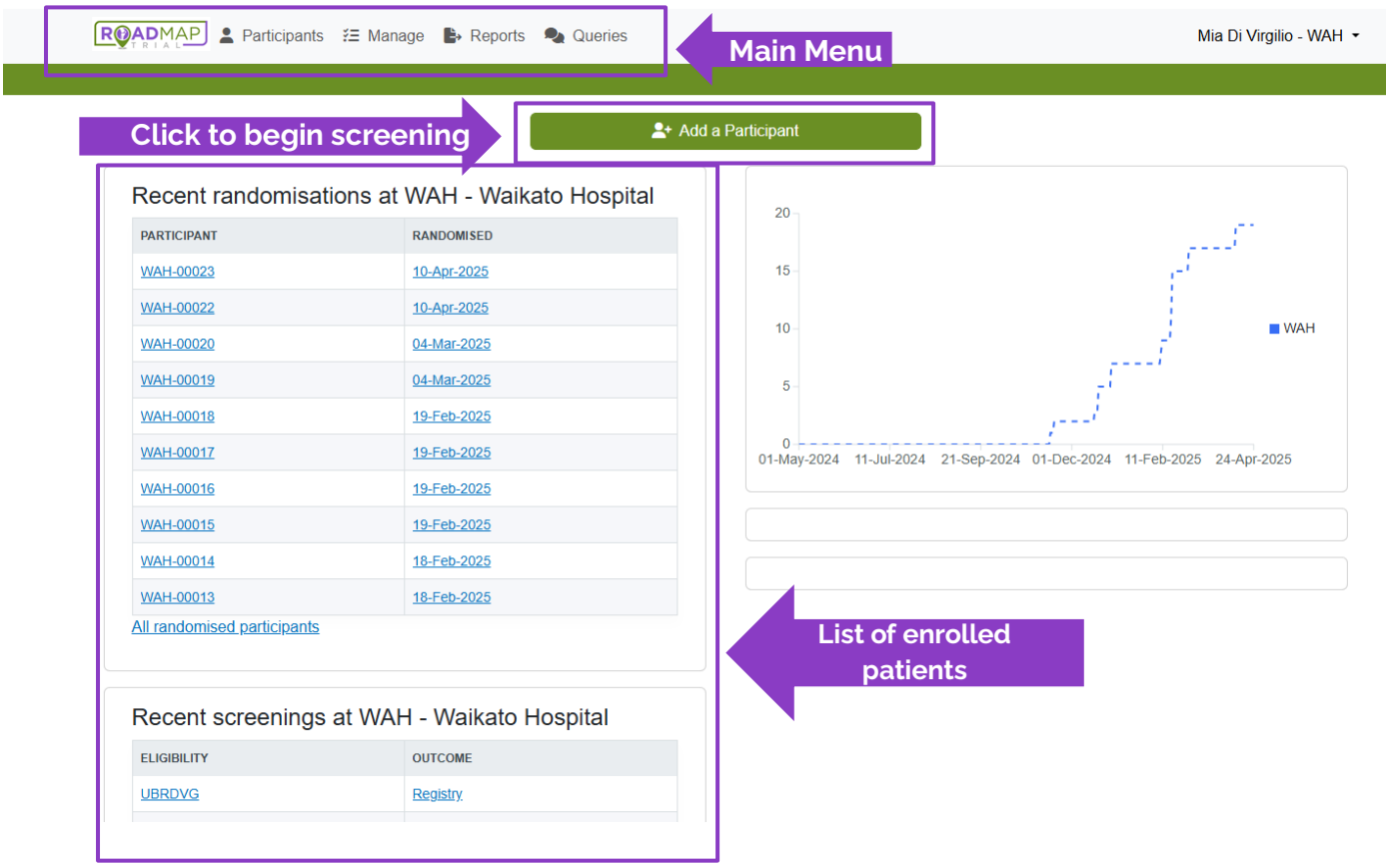
Generic user accounts on the staging site are **time zone** specific

- **Username**: RoadmapNZST **Password:** Roadmaptesting

4.1.1 DATABASE LAYOUT

The ROADMAP Database has four main tabs: home, participants, reports and queries. Each tab has a list of actions beneath that will help you enter, maintain and review patient data. Please see the video guide for a more detailed userguide to the ROADMAP database.

- **Landing Page (Home)**
  The home page can be accessed when you first log in, or by clicking the ROADMAP logo (top left corner). The landing page contains several informative panels to help you manage enrolments and track the progress of the trial. Each record in a patient list is hyperlinked – you can click on a single row to jump to the summary for that patient and start entering data.
- **Participants**
  The Participant tab takes you to a list of all patients enrolled at your site. From here, you can search for a patient, start eligibility screening, or view the screening list using the links in the purple sub-menu.
- **Reports**
  Reports are available to users who have been granted permission to query the database and/or generate data exports. An email is sent to the account registered in your user profile, to notify you when the report has been generated.
- **Queries**
  The queries tab takes you to a list of any queries that are pending at your site. These may arise from routine monitoring visits, central management review of data, etc. You can filter the queries to show only 'open', 'resolved' queries or both. This section acts like a message board and allows you to respond directly to queries using the database itself.
- **User Profile**
  Go to My Profile to edit your user information, email address, profile photo or password. You can also amend your email/notification settings in your profile. Some users may work across multiple trial locations; to change the location, click Change Location by clicking on the dropdown in the top righthand corner.



REDCAP DATABASE – RECORDING PARTICIPANT IDENTIFIERS

Identifiable data from ROADMAP Trial and Registry participants will be collected so that their data can be linked to external data registries (e.g., National PJI registry) after the trial has been completed. While the patient identifiers should be entered into the REDCap database as soon as practicable and every effort should be made to keep the records up to date, **please prioritise data entry into Spinnaker** as there are no time constraints on recording participant identifiers into REDCap.

Management of participant identifiers will vary from region to region and the Regional Manager can provide further guidance if needed.

THE REDCAP DATABASE CAN BE ACCESSED HERE:

https://redcap-cmh.hanz.health.nz/

Please contact the ROADMAP Regional management team with any questions or issues relating to collecting participant identifiers in ROADMAP.

5 PATIENT SCREENING, CONSENT AND RANDOMISATION

5.1 PATIENT SCREENING

Sites can choose to participate in one, two, or all three domains, however, it is highly recommended that each site participate in all treatment domains available.

If the site is not participating in all domains, the Participant Information and Consent Forms (PISCFs) should be amended to reflect the domain(s) the site is participating in. The master PISCF includes help text to indicate where to delete sections that are not relevant.

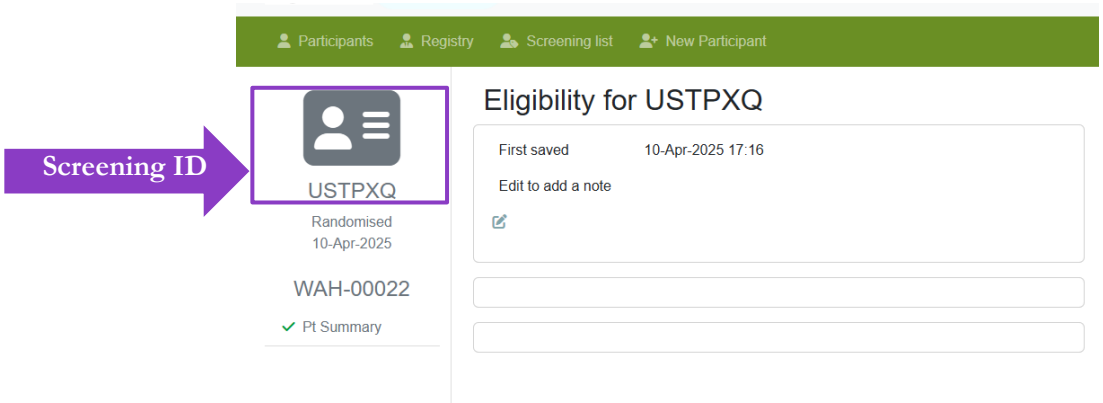
A reminder that:

- **100% of PJIs that meet the core inclusion criteria should be screened in the database**, even if the site know they meet one or more exclusions.
- For representativeness and validity of data against all patients hospitalised with PJIs, **every single patient who meets core inclusion criteria should be entered into the registry**

Screening ID

Upon screening in the database, participants will be allocated a unique 6-letter screening ID generated by the database.

The screening ID can be found on the Screening List page for patients pending or excluded, or in the Eligibility CRF section for patients enrolled in the trial platform or registry only.



Once the patient has been randomised, they will be allocated a study ID number _ _ _ _ _ - XXXXX where the 5 letters at the beginning are the site code, and a 5-digit participant number at the end.

Enrolment of the participant must be documented in the patient's medical record and the site screening and enrolment log, for the ROADMAP platform.

5.2 INFORMED CONSENT

ROADMAP is using a simplified consent model called integrated or 'layered' consent.

Integrated consent differs from regular approaches to consent in that it allows the participant to receive the information in a method of their choice, and to choose how much information they read/watch before making a decision.

Integrated consent includes tiered information that is available to the participant in a variety of different platforms to allow the participant to gather as much information about the trial as they would like to make an informed decision.

1. **Layer 1 – Written Simplified PISCF**
   This form covers the typical consent sections; however, it has been shortened to make the information more digestible for the reader. It contains essential information, provided in paper or electronic format, with links to the explanatory videos and further information on the ROADMAP website, if the patient wants to further understand aspects of the trial prior to consenting.

2. **Layer 2 – Explanatory Videos & Patient Information on the ROADMAP Website**
   The explanatory videos, found in the Patient section of the website, contain more detailed information for the participants to view, if they are interested along with other patient information.

3. **Layer 3 – Detailed Documents and other resources (such as data collection, and risks of surgery and antibiotics etc.)**
   Finally, there are links on the ROADMAP website for more detailed patient information for those who would like to see a more scientific or comprehensive explanation about the study.

Written informed consent will be obtained from all participants prior to entry into the randomised platform. Consent is not required for the ROADMAP registry. An interpreter should be used where required, and this needs to be documented on the consent form.

Important things to check when completing consent paperwork:

- The person taking consent should be appropriately trained and delegated this responsibility by the Principal Investigator and have this documented on the delegation log.
- The date of consent should be on or prior to the date of randomisation. If it is the same day as randomisation, it is good practice to record the time (in 24-hour clock) of consent to show that the participant consented prior to randomisation.

Consent must be fully documented in:

- The spinnaker database
- The participant's medical record
- The PISCF
- The ROADMAP Screening and Enrolment Log

More information regarding the consent process can be found in ***Guide: Informed Consent***.

5.3 RANDOMISATION

Once a new patient has been entered into the database, and is eligible for the platform, click on 'Confirm' to initiate randomization (platform entry). The database will automatically randomise the patient to all domains and interventions that they have consented to (and are available at the site).

However, each randomization will not be 'revealed' until the domain-specific eligibility (inclusion/exclusion criteria) have been completed (***see Section 5.5.1***).

A randomisation result page will be visible in the participant's summary page on the database and will contain details of any intervention(s) the participant has been randomised to.

RANDOMISATION FOR ALL DOMAINS OCCURS IN THE DATABASE ON CONFIRMATION OF CONSENT, BUT WILL ONLY BE REVEALED WHEN THE PARTICIPANT'S ELIGIBILITY IS CONFIRMED FOR EACH DOMAIN

5.4 PARTICIPANT WITHDRAWAL

If a participant withdraws or is withdrawn, please complete the following steps:

1. Complete a withdrawal form (Not essential, verbal withdrawal is acceptable)
2. Complete the withdrawal CRF in the database.
3. Record the withdrawal on the screening and enrolment log.

If possible, please ascertain a reason why the participant/treating clinician are withdrawing consent.

5.4.1 ROADMAP PLATFORM

Trial participants may discontinue their participation from the entire trial, or from individual aspects as detailed below.

- **Allocated treatments**
  The participant/treating clinician may wish to withdraw the participant from one or more treatments allocated within the platform. The participant will continue standard treatment, and all data points will continue to be collected up to day 365.

- **Ongoing contact and/or the use of their health data**

The participant may also wish to withdraw from ongoing contact and/or ongoing collection of the participant's health data, including use in data linkage. However, the data collected up until the time of withdrawal will continue to be used in the data analysis.

5.5 INTERVENTION ALLOCATION REVEAL

As mentioned above, participants are randomised to all available domains and interventions at the time of platform entry; however, their allocations are only revealed based on a timeline and domain-specific eligibility criteria. Please refer to the Patient Pathway detailed in **Appendix 1**.

Platform entry is defined as the timepoint when the patient has met core eligibility criteria, given informed consent for the platform, and has been randomised = Platform Day 1.

5.5.1 Domain Eligibility Timelines

- **Surgical Domain:** Eligibility assessment must be completed on **Platform Day 1 (+/- 1 day).** The randomised surgical strategy should take place ideally within 24hrs but within 7 days at the latest.
- **Antibiotic Choice Domain:** Eligibility assessment must be completed **with 48hrs and 7 days** following the initial surgical treatment (*if patient is having a 2-stage revision, screening for this domain should take place after the first stage of the revision*).
- **Antibiotic Duration Domain (Part A):** Eligibility assessment must be completed **within 7 days of the single stage revision.**
- **Antibiotic Duration Domain (Part B):** Eligibility assessment must be completed within **7 days (+/- 3 days of the second stage of the two-stage revision.**

6 SCHEDULE OF DATA COLLECTION

The summary provided in this handbook is for quick reference only. For more detailed information regarding the required data and sample collection for each region, domain and special population, please refer to the corresponding appendices

Data Entry Reminders:

- Each treatment domain has data collection additional to the core protocol
- Data should be entered directly into the Spinnaker database
- As an adaptive study with frequent analysis, it is important that your site keep up to date with data entry; reminder emails will be sent out when deadlines for data completeness are near

Visit Day	Day 1			Day 100*	Day 365**
Platform Eligibility screening	X				
Informed consent		X			
Randomisation			X		
Collect PROMS			X		X
Collect data as per CRFs			X	X	X

*These data can be collected cumulatively from the time the baseline form is completed until after day 100. Some elements cannot be completed until after day 100. Site teams should aim to have this form completed before platform day 120.

***These data can be collected cumulatively from days 101 until after day 365. Some elements cannot be completed until after day 365. Site teams should aim to have this form completed before platform day 395 otherwise it will be considered a protocol deviation.

7 LABORATORY AND MICROBIOLOGY

All sites globally will be asked to collect and store the index bacterial isolate(s) for all confirmed culture positive PJI cases. Two duplicates of the representative index isolate should be stored.

Once a participant is enrolled into the ROADMAP platform, and their causative organism(s) is/are identified, please liaise with your microbiology laboratory and ask them to store down (in a -80 freezer) the most important isolate in duplicate.

These will then be batch transferred to a central laboratory (Middlemore Hospital) every 6-12 months.

For polymicrobial infections the isolate stored should be selected according to the below recommended hierarchy:

1. ***Staphylococcus aureus***
2. ***Streptococcus* spp.**
3. **Coagulase negative staphylococci**
4. **Other gram-positive pathogens**
5. **Gram-negative pathogens**
6. **Other**

For further guidance please refer to the ***Microbiology Appendix.***

8 PROTOCOL DEVIATION AND BREACH REPORTING

The ROADMAP Trial protocols **allow for clinical decisions to be respected** regarding patient management. In general, if the change in patient management is *due to a clinical decision*, this does not need to be reported as a protocol deviation, and the change in management will be captured in the CRFs.

For this trial, a protocol deviation **HAS** occurred when an event deviates from the study protocol **AND one or more of the following three conditions are met:**

- This deviation is due to an **error or mistake OR**
- This deviation is due to **clinician override OR**
- This deviation is a **specified protocol deviation**
    - Randomisation, or performance of any study-specific procedure (apart from screening), that occurred prior to obtaining informed consent.
    - Randomisation (into the core platform or a domain) of an ineligible participant
    - Primary endpoint data not entered into the database by Day 395 (from platform entry)

Please consider whether a protocol deviation should be assessed as a serious breach.

As a pragmatic study, it is unlikely that any serious breaches will occur. However, if a suspected serious breach is identified at the site, the **PI** or their delegate should email details to the regional management team **within 72 hours of becoming aware of the suspected breach.**

Management will then assess the report. The **PI** or their delegate should report any confirmed serious breach to their Llocality office within 72 hours.

For more information for further details and examples of protocol deviations and serious breaches, please refer to **Guide: Protocol Deviations and Serious Breaches or NZ Protocol Deviation Summary**.

9 ESSENTIAL DOCUMENTS AND INVESTIGATOR SITE FILES

Site-specific essential documents are to be maintained in an Investigator Site File (ISF) in electronic (eISF)or paper format. Sites are expected to maintain the (e)ISF in a timely manner and make them available for review by the monitor and sponsor/trial management team as required.

Please view ***Guide: Site File or Table of Contents – NZ Site Files Template*** *for more detailed information about the setting up and managing the ISF how to set it up, and how it is structured for ongoing document management for the ROADMAP Trial.*

10 INVESTIGATOR TRAINING AND RECORDING

Most training will be conducted online through a combination of videos and documents, that can be reviewed on the site teams' own time. The ROADMAP Trial uses a combination of Dropbox and the ROADMAP website to provide access for all site staff to undertake their required training.

If you need any assistance locating documents on the ROADMAP website, please contact the ROADMAP Management Team.

Key Reminders:

- All training should be recorded appropriately on the assigned logs and signature pages, and any changes to the site personnel should be reported to the sponsor, HDEC and the Locality Office, as per institutional, sponsor or local requirements.
- All new investigators/site staff should undergo the required training, delegation, and be formally added to the study prior to beginning any work on the study.
- All site staff must ensure they have a current GCP certification filed in the site eISF. This will be checked through routine monitoring and site audits.

*Please view **Guide: Training and Delegation** for more detailed information about how to appropriately train investigators, and documenting training for trial monitoring purposes.*

11 MONITORING AND TRIAL OVERSIGHT

Routine Monitoring Visits (RMVs) will be conducted either on-site or remotely by a monitor from MRINZ.

The study will use a risk-based approach to monitoring, whereby only a minimal set of datapoints will be monitored.

The following will be monitored at each visit:

- 100% of Platform PISCFs
- Source data verification of select data points for a randomly selected 10% of participants
- Review of the ISF including locality submissions/approvals, site personnel documentation and delegation and training logs.

11.1.1 MONITORING VISIT SCHEDULE

The first visit will be conducted 6-8 weeks following enrolment of the first platform participant. Subsequent visits will be conducted every 24 months **OR** when 50 participants have been recruited (whichever occurs first) to verify patient enrolment and that consent processes are being followed.

A monitoring report will be sent to PIs and site coordinators and should be retained in the investigator site file.

Triggered monitoring visits will also be conducted if any issues (recurrent serious breaches, ongoing consent issues etc.) arise at site that need to be addressed.

*Please refer to the **Monitoring Plan** for more detailed information about the monitoring process.*