Quick Guide for Site Teams

Contents

1. KEY CONTACTS AND LINKS

Trial management group email: TMG@roadmaptrial.com
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Trial co-ordinator/monitor (Outer Sydney/ACT): Marline.Squance@newcastle.edu.au
Trial co-ordinator/monitor (VIC, SA. TAS): divirgilio.m@unimelb.edu.au
Trial co-ordinator/monitor (WA, QLD, Central Sydney): alana.digiacomo@uwa.edu.au

LIVE Spinnaker trial database: https://roadmap.spinnakersoftware.com/Login
(Real data – don't use this one to practice!)
Username and Password are individual, and will be sent to you on site activation

REDCap Database (*for entering patient identifiers for data linkage):*
https://redcap.hmri.org.au/
Username and Password are individual, and will be sent to you on site activation

"Sandpit" Spinnaker trial database: https://roadmap-stage.spinnakersoftware.com/Login
(For mucking around, practicing – no real data should be entered here)

USERNAME: RoadmapAEST/AEDT
USERNAME: RoadmapACST
USERNAME: RoadmapAWST
USERNAME: RoadmapNZST
} PASSWORD: Roadmaptesting

Note: we have generic logins however usernames are time zone dependent

2. TRIAL OVERVIEW

SILOS	DOMAINS		
	Surgical management	*Antibiotic duration*	*Antibiotic type*
Early* PJI	No randomisation options (Clinicians' discretion[1])	For DAIR – No randomisation options (12 weeks recommended) For one stage: Total 6 weeks versus 12 weeks post the one-stage For two-stage – No extended prophylaxis versus extended prophylaxis (12 weeks) after the 2nd stage	Backbone regimen with or without adjunctive rifampicin
Late acute* PJI	DAIR versus revision[1]		
Chronic* PJI	No randomisation options (Clinicians' discretion[2])		

*Early ≤30 days post implant. "Late acute" = >30 days post implant and ≤21 days of symptoms at diagnosis. "Chronic" =>30 days post implant AND a sinus or >21 days of symptoms. **DAIR=Debridement, Antibiotics and Implant Retention.

Table 1. ROADMAP Domains and Silos

3. CORE (PLATFORM) ELIGILITY CRITERIA

INCLUSION CRITERIA

1. "Confirmed" or "Likely" Prosthetic joint infection of a large joint according to EBJIS criteria
2. Physically present at participating hospital at time of eligibility assessment
3. "Current" prosthetic joint infection, meaning symptoms and/or signs of the PJI are present at the time of eligibility assessment.
4. Aged≥18 years

EXCLUSION CRITERIA

1. The index prosthetic joint is a shoulder, elbow, wrist or ankle.
2. Known previous participation in the randomised ROADMAP randomised platform for the index joint.
3. Known previous participation in the randomised ROADMAP platform for a joint other than the index joint within the 12 months prior to eligibility assessment
4. Treating clinician believes that death is imminent and inevitable.
5. Treatment is not with curative intent.
6. Patient is not classifiable into one of the three defined silos.
7. Patient is unlikely to be accessible for follow up over the 12 months following platform entry.
8. Treating team deems enrolment in the study is not in the best interests of the patient.

4. WHAT TO DO IN WHAT ORDER IF YOU HAVE A POTENTIALLY ELIGIBLE PATIENT

1. "Pre-screen" with Platform inclusion criteria – if they are not met, go no further, don't enter anything into the database or site log

2. If platform inclusion criteria are met, contact the treating team (mainly the orthopaedic surgeon) to ascertain three key things (if initial definitive surgery has already occurred, 2.2 and 2.3 are not relevant)

2.1 Is the plan to treat the infection with curative intent?

2.2 Does the surgeon feel that either DAIR or revision would be appropriate for this patient (late acute silo only)?

2.3 If the patient were randomised to revision, would the surgeon do a one or two-stage?

3. Go to the trial database https://roadmap.spinnakersoftware.com/Login check all platform exclusion criteria (even if >=1 of them are met) and enter these for ALL patients who meet the core inclusions at your site.

4. Approach the patient for consent. You may need to leave the PICF with them and allow them to watch the videos on their phone/tablet/laptop if desired (most people choose not to). You will need to consent them for all *potentially* eligible domains (since you may not yet know which ones the patient will be eligible for).

5. If the patient declines platform consent, ask them for registry consent ("can we collect your information, but not change any of your treatment, and contact you for follow up in 1 year").

6. If registry consent is given, fill out registry baseline form, and (if data linkage consent given), the REDCAP identifiers form: https://redcap.hmri.org.au/surveys/?s=78XKD9ALANX9FD4T

7. If platform consent is given, *start* the baseline form, ensuring you complete the "Details of PJI and Index Prosthesis" section at the top of the form first. The rest can be done over the next few days if needed. If data linkage consent is given, please complete the REDCap identifiers form (this applies to both Registry and Platform participants).

If participant has consented to Surgical Domain

8. **Fill in the Surgical Domain eligibility assessment** – if they enter this domain and randomisation allocation is revealed, make sure you talk with the treating surgeon/team to let them know if the participant has been randomised to DAIR or revision.

If participant has consented to the Antibiotic Choice Domain

9. Once the initial definitive surgical management has occurred (i.e. a DAIR, a 1-stage revision or the first stage of a 2-stage revision), then 2-7 days later, **screen for Antibiotic Choice eligibility assessment**. If they enter this domain and randomisation allocation is revealed, make sure you liaise with treating team and either you or they immediately chart the correct antibiotics (see AB choice domain table 2 – also below).

If participant has consented to Antibiotic Duration Domain

10. If the patient has had a one-stage revision, then within 7 days of the operation, **screen for Antibiotic Duration part A eligibility assessment**. Eligibility for all potential domains is now complete for this patient.

11. If the patient has a two-stage revision as their initial definitive management strategy, then wait until the second stage has been completed. Once it has, then 4-10 days later (7+/-3 days), **screen for Antibiotic Duration part B eligibility assessment**. Eligibility for all potential domains is now complete for this patient.

12. If the patient is in the platform but ends up not being eligible for any of the domains, they are considered a Platform Only participant and should have data collected at days 100 and 365 as below.

13. Over the next 100 days, as important events occur (e.g. operations, culture results, death or hospital discharge), cumulatively fill out the Day 100 form on the Spinnaker ROADMAP trial database. Most questions will need to be completed *after* day 100 (as they refer to the first 100 days). Aim to complete this by day 120.

14. Between days 101-365, do as above (e.g. if operations occur enter them into the day 365 form). Most of the day 365 form will need to be filled out after day 365, but it is really important that this be done ASAP after day 365, as the primary endpoint which drives the interim analyses is derived from this form. Aim to do this before day 370. ***Not completing the Day 365 form by day 395 is a protocol deviation***.

5. SURGICAL DOMAIN ELIGIBILITY CRITERIA

INCLUSION CRITERIA

1. Patient is in the Late Acute silo:

a. >30 days between implantation of the index joint and diagnosis of the index infection

b. <=21 days since the onset of symptoms of this episode of infection

c. There is no proven or suspected sinus from the skin to the joint space.

2. Onset of symptoms is >30 days after implantation of the index joint

3. Treating team feel that either DAIR or revision is appropriate for this patient.

4. The infected prosthesis is a primary arthroplasty

EXCLUSION CRITERIA

1. Any previous episode of native joint septic arthritis or PJI in the index joint

2. A definitive DAIR has already occurred for this episode of infection. (A temporising washout /debridement is allowed prior to randomisation reveal.)

3. A revision has already occurred for this episode of infection

4. Loosening or instability of any component of the prosthesis

5. Predicted inadequate soft tissue coverage for wound closure

6. One or more of the causative organisms is a fungus or a "difficult to treat" bacterium*.

7. Treating team deems enrolment in this domain is not in the best interests of the patient.

*Difficult to treat bacterium means any meropenem-R Gram negative, or any XDR (extensively drug resistant) bacterium. XDR means R to at least one drug in all but <=2 drug categories relevant to that organism. (https://www.sciencedirect.com/science/article/pii/S1198743X14616323?via%3Dihub)

6. ANTIBIOTIC CHOICE DOMAIN ELIGIBILITY CRITERIA

INCLUSION CRITERIA

1. The time of eligibility assessment is between 48h and 7 days following initial surgical treatment.
2. One or more of the causative organisms is a Gram-positive of interest* OR the infection is culture negative.

*Gram positive of interest means all G+ve cocci (Staphs, Streps, Enterococci, Peptococci etc.), Cutibacterium spp. and Corynebacterium spp.

EXCLUSION CRITERIA

1. Previous hypersensitivity reaction to rifampicin
2. The patient is receiving a concomitant medication with an expected clinically significant drug interaction with rifampicin, which cannot be ceased, substituted for an alternative agent, or compensated for by dose adjustment (see table 4 below).
3. One or more causative organisms have known *in-vitro* evidence of resistance to rifampicin.
4. Known pregnancy or breastfeeding
5. Treating team deems enrolment in this domain is not in the best interests of the patient.

7. ANTIBIOTIC CHOICE DOMAIN RECOMMENDED ANTIBIOTICS

	Intravenous phase	Oral phase
MSSA	Preferred - Cefazolin Alternate – (Flu)cloxacillin	Preferred - Cefalexin Alternate - Doxycycline
MRSA	Preferred - Vancomycin Alternate – Daptomycin	Preferred - Doxycycline Alternate - Cotrimoxazole
Streptococcus	Preferred - Benzylpenicillin Alternate – Cefazolin	Preferred - Amoxycillin Alternate - Cefalexin
Ampicillin susceptible Enterococci	Preferred – Ampicillin/Amoxicillin Alternate – Vancomycin	Preferred - Amoxycillin Alternate - Linezolid
Ampicillin resistant, Vancomycin susceptible Enterococci	Preferred - Vancomycin Alternate – Daptomycin	Preferred - Linezolid Alternate - Pristinamycin
Vancomycin resistant Enterococci	Preferred – Daptomycin Alternate - Linezolid	Preferred - Linezolid Alternate - Pristinamycin
Cutibacterium	Preferred - Benzylpenicillin Alternate – Cefazolin	Preferred - Amoxycillin Alternate - Cefalexin
Corynebacterium	Preferred – Benzylpenicillin (Pen- S) or Vancomycin (Pen-R) Alternate – Daptomycin	Preferred – Amoxycillin (Pen-S) or Doxycycline (Pen-R) Alternate - Linezolid
Culture Negative	Preferred – Vancomycin plus cefepime Alternate – Vancomycin plus ciprofloxacin	Preferred – Doxycycline Alternative - Cotrimoxazole
Mixed infection (Gram-positive plus Gram-negative)	Chosen by site PI according to susceptibilities	Chosen by site PI according to susceptibilities

Table 2. Recommended antibiotics for Antibiotic choice domain.

Recommended oral agents, their bioavailability and dosing

Agent	Oral Bioavailability	Recommended dosing (80kg adult, normal renal function)
Amoxycillin	80%	1g TDS
Cefalexin	90%	1g QID
Ciprofloxacin	70%	750mg BD
Cotrimoxazole	70-90% (both components)	DS (800/160mg) ii BD
Clindamycin	90%	450mg TDS
Doxycycline	90%	100mg BD
Fusidic acid	90%	500mg TDS
Linezolid	100%	600mg BD
Moxifloxacin	90%	400mg daily
Pristinamycin	Unknown	1g TDS

Table 3. Recommended oral agents, their bioavailability and dosing.

Dosing of rifampicin

If allocated to rifampicin, dose at **300mg BD PO** (for a patient>90kg use **450mg BD PO**) as a default, but any dosing preferred by the site is allowed up to a total of 900mg per day, and up to three times daily dosing. Start rifampicin as soon as randomisation is revealed, and continue it as long as antibiotics are given, as long as this is not more than 12 weeks.

Consideration of interactions

Drug	Likely effect	Monitoring	Recommendations
Amiodarone	Reduced amiodarone	For arrhythmia	Monitor. Effect reduced for days to weeks after rifampicin ceased.
Apixaban/Rivaroxaban/Dabigatran	Moderate reduced apixaban (AUC_{0-24} reduction of 54%)	Therapeutic drug monitoring	The product inserts either recommend avoid (US) or avoid for prior history of PE/DVT (UK). Alternative anticoagulation with LMWH or warfarin can be considered. If indication for DOAC is atrial fibrillation without a history of stroke, an individualised risk/benefit assessment can be made.
Oral hormonal contraceptives	Reduced contraceptive effect		Use an alternative effective contraceptive (e.g. IUDs). For less than 2 months use of enzyme inducing drugs, consider additional, consistent use of condoms, during and for at least 28 days after stopping the enzyme inducing drug. Note, the WHO advise that implants can generally be used.
Digoxin	Reduced digoxin	Digoxin levels	Monitor
Long-acting opioids	Moderate (buprenorphine, codeine, fentanyl morphine, oxycodone, tapentadol) Severe (methadone)	For pain/ withdrawal.	Monitor – increase dose where necessary. Tramadol (mild-moderate reduction in effect). Monitor and adjust dose where necessary.
Ticagrelor	Reduced ticagrelor		Avoid per US/UK PI
Warfarin	Reduced warfarin	INR	May need 2-5 fold dose increase overall. Effect occurs within 1 week. May persist 2-5 weeks post rifampicin cessation.
Levothyroxine	Possible reduced or increased thyroxine	TFTs	Monitor. May persist for several days post rifampicin cessation.
Beta blockers	Reduced beta blocker	HR/BP	Monitor – increase dose where necessary

Atorvastatin/Pravastatin/Simvastatin	Reduced atorvastatin		Give statin at same time as rifampicin.
Selective serotonin reuptake inhibitors (SSRI)	Reduced concentrations		The interaction with SSRIs and rifampicin could theoretically occur with any of the SSRIs, however it's only been reported with citalopram and sertraline in case reports to date. As expected, loss of efficacy of the SSRI and withdrawal/depressive/anxiety symptoms were reported, with the need to increase the SSRI dose. Do not increase the SSRI pre-emptively, but monitor and then increase if necessary.

Table 4. Drug interactions and dose adjustments with Rifampicin

8. ANTIBIOTIC DURATION PART A (SHORT VS LONG DURATION AFTER A 1-STAGE REVISION) ELIGIBILITY CRITERIA

INCLUSION CRITERIA

1. A single stage revision procedure has been performed
2. The single stage revision was the initial definitive procedure for the index PJI

EXCLUSION CRITERIA

1. One or more of the causative organisms is a fungus or a 'difficult-to-treat' bacterium
2. Long-term antibiotic suppressive therapy is planned following the revision operation
3. Treating team deems enrolment in this domain is not in the best interests of the patient
4. The single stage revision was >7 days ago
5. Patient no longer willing to participate in the domain

A one-stage revision means:

- Arthrotomy
- Removal of all prosthetic components
- Comprehensive synovectomy
- Placement of "definitive" new components
  - could be primary or revision components
- ***With no plans for a second stage operation***
  - Hence surgeon intention needs to be ascertained post-operatively
  - Hence a "Kiwi" operation (known variably depending on region as a "kiwi", "CUMARS" or "1.5 stage revision") will be considered a single stage if there are no definitive plans for a second stage operation ("leave it in and see how the patient goes"). Conversely if there is a plan for a second stage, a 'Kiwi' procedure will be considered as an articulating spacer inserted as the first part of a 2-stage.

Additional recommended elements (not part of definition, but considered 'ideal' elements of this procedure):

- Removal of all loose cement; well-fixed cement may be retained.

- Double set up (using a separate set of sterile instruments and drapes for the reimplantation)

9. ANTIBIOTIC DURATION PART B (EXTENDED PROPHYLAXIS AFTER A 2-STAGE REVISION) ELIGIBILITY CRITERIA

INCLUSION CRITERIA

1. A two-stage revision procedure has been performed
2. The infected prosthesis was a primary arthroplasty
3. At least 6 weeks of antibiotics have been received following the first stage revision, intended as treatment of the index infection
4. The reimplantation operation was done 7+/-3 (i.e. 4 to 10) days ago

EXCLUSION CRITERIA

1.>6 months has passed since platform entry
2.One or more of the causative organisms is a fungus or a 'difficult-to-treat' bacterium
3.No perioperative tissue or fluid cultures were collected at the reimplantation operation
4.Perioperative cultures collected at reimplantation grew a significant organism*
5.Long term antibiotic suppressive therapy is planned following the reimplantation operation
6.Treating team deems enrolment in this domain is not in the best interests of the patient
7.Patient no longer willing to participate in the domain

*Significant organism defined as any of i) One or more of the initial causative organisms is isolated in one or more peri-operative tissue or fluid samples; ii)A new 'virulent' causative organism is identified in one or more peri-operative tissue or fluid samples iii)A low virulence causative organism is identified in two or more peri-operative tissue or fluid samples.

"Virulent organism" is defined as *S. aureus*, β-haemolytic streptococci, coliforms, Gram negative anaerobes, fungi or any organism which the lead ID site investigator or local clinical microbiologist considers virulent. A "new" organism means a different species, OR the same species but with a different antibiogram (i.e. different "strains" of the same organism are considered as distinct organisms). "Low virulence organism" means coagulase negative staphylococci, *Corynebacterium spp.*,*Cutibacterium spp.*, *Bacillus spp.*, and any other organism which the lead ID site investigator or local clinical microbiologist considers low virulence or likely skin or environmental contaminants.

A two-stage revision means:

- Removal of all existing prosthetic components (including metal, ceramic, polyethylene) and any loose cement
- Placement of a temporary prosthesis or spacer ***with the intention to replace this at a later time point with a permanent prosthesis***
- The intention to subsequently replace of the temporary spacer with a definitive prosthesis at a reimplantation operation in the future

Additional recommended elements (not part of definition, but encouraged):

- Use of antibiotic-loaded cement as the spacer
- Use of an articulating spacer which is capable of withstanding weight-bearing

A reimplantation procedure as the second stage of a two-stage revision means:

- Removal of the temporary prosthesis and all associated cement
- Implantation of a new prosthesis; considered the 'destination prosthesis'