RATIONAL Platform Trial

Role of Antibiotic Therapy or Immunoglobulin

On iNfections in hAematoLogy

Domain-Specific Appendix:

Starting Immunoglobulin (Start Ig)

PROTOCOL NUMBER:	TRU-RPT-22
CHIEF INVESTIGATORS:	Prof Zoe McQuilten
	Prof Erica Wood
SPONSOR:	Monash University
VERSION NUMBER:	1.0
DATE OF PROTOCOL:	12 NOVEMBER 2023

START Ig Domain-Specific Appendix Development Protocol History

Version Number	Date	Author	Change
1.0	12-Nov-2023	Prof Zoe McQuilten	Original version

Domain Specific Appendix Protocol Development Group:

Name	Affiliation	Authors Contributions
Prof Zoe McQuilten	Monash University, Melbourne, Australia	ZM and EW initiated the trial design and implementation. EW and ZM are the grant holders. JR, ER and TL provided statistical expertise in clinical trial design and are conducting the primary statistical analysis. All authors contributed to refinement of the trial protocol and approved the final version. LF and DP designed the health economics analysis. OM designed the correlative sampling protocol. KLC and CP designed the qualitative substudy protocol.
Dr Khai Li Chai	Monash University, Melbourne, Australia	
A/Prof John Reynolds	Monash University, Melbourne, Australia	
Prof Erica Wood	Monash University, Melbourne, Australia	
Dr Laura Fanning	Monash University, Melbourne, Australia	
Prof Dennis Petrie	Monash University, Melbourne, Australia	
Prof Orla Morrissey	Monash University, Melbourne, Australia	
Dr Catriona Parker	Monash University, Melbourne, Australia	
Dr Elizabeth Ryan	Monash University, Melbourne, Australia	
Dr Thao Le	Monash University, Melbourne, Australia	
Dr Robert Weinkove	Malaghan Institute of Medical Research, Wellington, New Zealand	
Prof Jeannie Callum	Queen's University, Ontario, Canada	

TABLE OF CONTENTS

Acronyms and Abbreviations	
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AR	Adverse reaction
AST	Aspartate transaminase
CI	Chief Investigators
CLL	Chronic lymphocytic leukaemia
CTCAE	Common terminology criteria for adverse events
DSA	Domain-specific Appendix
DSMC	Data safety monitoring committee
DSSAP	Domain-Specific Statistical Analysis Plan (DSSAP)
eCRF	Electronic case report form
EFS	Event-free survival
eGFR	Estimated glomerular filtration rate
FAS	Full analysis set
FBE	Full blood examination
GCP	Good clinical practice
GGT	Gamma-glutamyl transferase
HREC	Human research ethics committee
ICH	International conference on harmonisation
Ig	Immunoglobulin
IgRT	Immunoglobulin replacement therapy
ITSC	International Trial Steering Committee
IV	Intravenous
IVIg	Intravenous immunoglobulin
MM	Multiple myeloma
NHL	Non-Hodgkin Lymphoma
NHMRC	National Health and Medical Research Council (Australia)
OAC	Outcome adjudication committee
PI	Principal Investigator
QoL	Quality of Life
RCT	Randomised Clinical Trial
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SCIg	Subcutaneous immunoglobulin
SUSAR	Suspected unexpected serious adverse reaction
TMC	Trial management committee
UAR	Unexpected adverse reaction

1. DOMAIN SUMMARY

1.1. Domain Summary

Strata	Myeloma, Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukaemia
Domain-specific inclusion criteria	None.
Domain-specific exclusion criteria	**Exclusion Criteria** Patients will not be eligible for this domain if they fulfil any of the following criteria: 1. Prior or planned allogeneic haematopoietic stem cell transplantation. 2. Already receiving systemic antibiotic prophylaxis for the purpose of preventing bacterial infection (NB: patients may receive antiviral, antifungal and PJP prophylaxis). 3. Received immunoglobulin replacement in the preceding three months. 4. Objection to receiving immunoglobulin products. 5. Known history of IgA deficiency with anti-IgA. 6. History of severe allergy to immunoglobulin products. 7. Current active infection requiring systemic antibiotics. 8. Allergy or intolerance of all domain antibiotic options. 9. Pregnant or breastfeeding. 10. Severe renal impairment (estimated or measured creatinine clearance of < 30 mL/min). 11. Previous splenectomy. 12. Previous participation in this domain. 13. Treating team deems enrolment in the domain is not in the best interest of the patient.
Interventions to be compared	**Arm A: Start prophylactic oral antibiotics:** Once daily trimethoprim-sulfamethoxazole (co-trimoxazole) 160mg/800mg. NB: Doxycycline 100mg daily as an alternative for patients with hypersensitivity to co-trimoxazole. **Arm B: Start immunoglobulin replacement** IVIg every 4 weeks ± 1 week at a dose of 0.4g/kg, modified to achieve an IgG trough level of at least lower limit of age-specific serum IgG reference range; or SCIg, weekly, may be used in patients who meet local criteria for home-based self-administration in centres with established SCIg programs. Dosing is usually given at 100mg/kg/week, modified to achieve an IgG steady state level of at least the lower limit of the serum reference range. A loading IVIg dose may be given in the first month if required. Planned treatment duration for all arms (A and B) is 12 months.

Trial hypotheses	1. Prophylactic oral antibiotics are non-inferior to Ig replacement for the prevention of severe, and/or recurrent infection in patients with secondary hypogammaglobulinaemia due to B-cell malignancies.
Primary outcome measure	Primary RATIONAL-PT Endpoint: refer to RATIONAL-PT Core Protocol
Secondary outcome measures	Secondary RATIONAL-PT Endpoints: refer to the RATIONAL-PT Core Protocol.

2. PROTOCOL APPENDIX STRUCTURE

The structure of the RATIONAL Platform Trial protocol is different to that used for conventional trials because this trial is adaptive and the description of these adaptations is better understood and specified using a 'modular' protocol design.

The protocol has multiple modules, in brief, comprising a Core Protocol (overview and design features of the study); a Master Statistical Analysis Appendix (details of the current statistical analysis plan and models); Domain-Specific Appendices (DSA) (detailing all interventions currently being studied in each domain); and Region-Specific Appendices (RSA) (detailing regional management and governance).

The Core Protocol contains all information that is generic to the trial, irrespective of the regional location in which the trial is conducted and the domains or interventions that are being tested.

The DSA contains information about the intervention(s), within each domain, because one of the trial adaptations is that domains and interventions will change over time. These Appendices are anticipated to change over time, and each modification to a DSA will be subject to a separate ethics application for approval.

Information that is specific to a particular region in which the trial is conducted is contained within a RSA. This includes information related to local management, governance, and ethical and regulatory aspects. Within each region, only that region's RSA, and any subsequent modifications, will be submitted for ethical review in that region.

In addition to the Master Statistical Analysis Appendix, a Domain-Specific Statistical Analysis Plan (DSSAP) will be prepared that will outline additional aspects of the statistical analysis for this domain.

3. DOMAIN GOVERNANCE

3.1. Domain members

Chair: Prof Zoe McQuilten

The members of the Start Ig Domain are members of the ITSC.

3.2. Start Ig Domain-Specific Working Group Authorisation

The Start Ig Domain-Specific Working Group have read this appendix and authorise it as the official Start Ig Domain-Specific Appendix for the RATIONAL Platform Trial. Signed on behalf of the committee

Chair Date

4. BACKGROUND AND RATIONALE

4.1. Domain definition

This is a domain within the RATIONAL Platform Trial to test the effectiveness and safety of prophylactic antibiotics as an alternative Ig replacement in patients who have not yet commenced Ig replacement therapy.

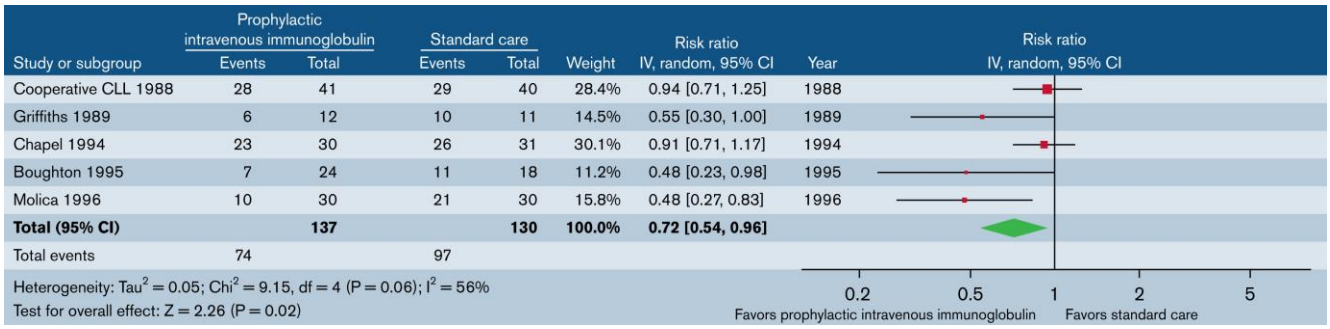
4.2. Domain-specific background

4.2.1. Overview

4.2.2. Immunoglobulin replacement therapy in acquired hypogammaglobulinemia due to haematological malignancies

Evidence supporting the use of Ig replacement therapy (IgRT) in patients with haematological malignancies is limited. IgRT used to prevent recurrent bacterial infections for patients with MM, NHL & CLL is provided under Australian Criteria for government-funded Ig – with the caveat of "*Evidence of probable benefit – more research needed*".[1] This recommendation is based on outdated data. Whilst the most recent Cochrane review which showed IgRT reduced infections in patients with secondary hypogammaglobulinemia due to blood cancers, it only included only 3 trials published between 1988 and 1995 with *a total of only 205 patients*.[2-5] In our recently completed systematic review of interventions to prevent infections in CLL, MM and NHL we ***did not identify any new evidence*** to guide Ig use.[6] We found no difference in risk of all-cause mortality in patients allocated to IgRT compared to standard of care (relative risk 1.35, 95% CI 0.57-3.18), however a reduction in risk of clinically documented infections (RR 0.70, 95% CI 0.54-0.96, see figure 1). However, our certainty in the evidence was low due to small sample size of included trials, classification of infection outcomes, high risk of bias in the included studies and lack of contemporary data applicable to the current standard of care.[6] These trials did not specify if routine prophylactic antibiotics were administered. Since these trials, there have been major changes to cancer therapy and supportive care. Intensive and novel therapies have improved outcomes for patients who respond, with varying degrees of immunological recovery. Therefore, it is very uncertain as to whether results from these early trials of IgRT still apply to our current practice. We have no current data to inform which patients should receive IgRT. This lack of evidence has led to substantial variation to the use of IgRT, both internationally and within Australia.[7]

Figure 1. Immunoglobulin replacement vs standard of care on one or more clinically documented infection



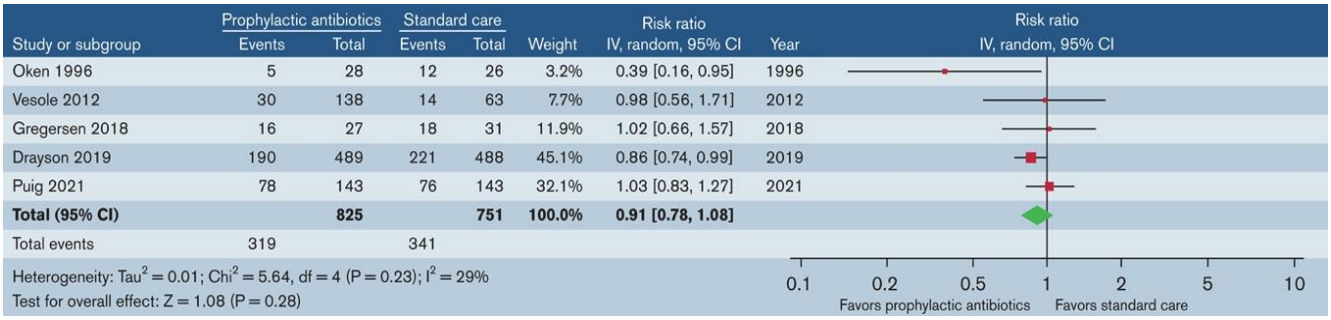
Study or subgroup	Prophylactic intravenous immunoglobulin Events	Total	Standard care Events	Total	Weight	Risk ratio IV, random, 95% CI	Year
Cooperative CLL 1988	28	41	29	40	28.4%	0.94 [0.71, 1.25]	1988
Griffiths 1989	6	12	10	11	14.5%	0.55 [0.30, 1.00]	1989
Chapel 1994	23	30	26	31	30.1%	0.91 [0.71, 1.17]	1994
Boughton 1995	7	24	11	18	11.2%	0.48 [0.23, 0.98]	1995
Molica 1996	10	30	21	30	15.8%	0.48 [0.27, 0.83]	1996
Total (95% CI)		**137**		**130**	**100.0%**	**0.72 [0.54, 0.96]**	
Total events	74		97				

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 9.15$, df = 4 (P = 0.06); $I^2 = 56\%$
Test for overall effect: Z = 2.26 (P = 0.02)

4.2.3. Prophylactic antibiotics as an alternative to immunoglobulin replacement

Short-term prophylactic oral antibiotics have been shown to reduce infections by 30-50% in neutropenic haematology patients following chemotherapy,[8] and in non-haematologic patients with bronchiectasis,[9] supporting the rationale for their use in acquired hypogammaglobulinaemia. A recent systematic review of prophylactic antibiotics in MM showed infection reduction in the first 3 months after diagnosis, but no mortality difference.[10] Our systematic review identified 4 trials of prophylactic antibiotics in patients with MM, and although antibiotics did not reduce all-cause mortality (RR 1.11, 95% CI 0.85-1.45) or infection in our review (RR 0.84, 95% CI 0.34-2.09, Figure 2), the included studies did not specify whether patients had hypogammaglobulinaemia or whether they were also receiving IgRT.

Figure 2. Prophylactic antibiotics vs standard care on one or more clinically documented infections



Study or subgroup	Prophylactic antibiotics Events	Total	Standard care Events	Total	Weight	Risk ratio IV, random, 95% CI	Year
Oken 1996	5	28	12	26	3.2%	0.39 [0.16, 0.95]	1996
Vesole 2012	30	138	14	63	7.7%	0.98 [0.56, 1.71]	2012
Gregersen 2018	16	27	18	31	11.9%	1.02 [0.66, 1.57]	2018
Drayson 2019	190	489	221	488	45.1%	0.86 [0.74, 0.99]	2019
Puig 2021	78	143	76	143	32.1%	1.03 [0.83, 1.27]	2021
Total (95% CI)		**825**		**751**	**100.0%**	**0.91 [0.78, 1.08]**	
Total events	319		341				

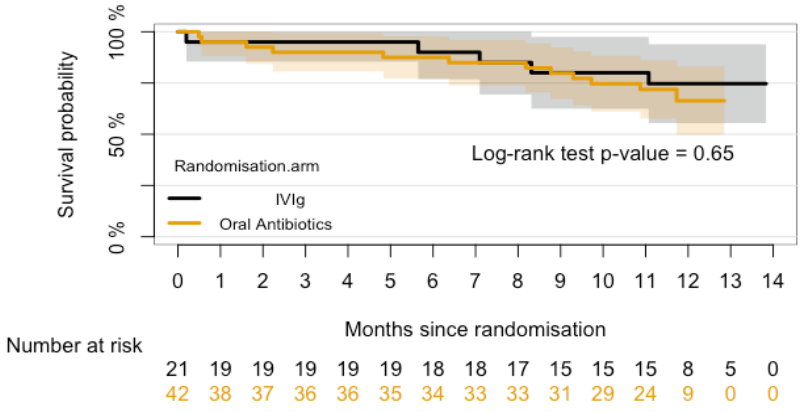
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 5.64$, df = 4 (P = 0.23); $I^2 = 29\%$
Test for overall effect: Z = 1.08 (P = 0.28)

Despite the limited evidence for their use, some international guidelines recommend a trial of prophylactic antibiotics prior to commencing IgRT,[11] but this is not required in Australia or other jurisdictions. Potential advantages of antibiotics include reduced total healthcare costs, possible improvements to QoL with fewer hospital attendances for infusions, and reduction in Ig adverse effects. On the other hand, antibiotic resistance is a concern with wider use of prophylactic antibiotics.[9,12] Antibiotics also have different safety profiles to IgRT. Therefore, the use of prophylactic antibiotics should be properly evaluated with respect to efficacy, safety, QoL, and healthcare costs.

4.2.4. Comparison of IgRT with prophylactic antibiotics

In our systematic review, the only trial that we identified that directly compared starting prophylactic antibiotics with starting IgRT in patients with acquired hypogammaglobulinemia was our recently completed the RATIONAL phase II feasibility trial (ACTRN12616001723471). This trial compared the use of IgRT vs prophylactic oral antibiotics in 63 patients with CLL, MM & NHL.

Figure 3: Time to first major (grade 3+) infection



RATIONAL demonstrated recruitment feasibility and tolerability of oral antibiotics. Although not powered for clinical outcomes, RATIONAL data suggested that infection rates were not increased in the antibiotic arm (the lower quartile for time to first major infection was 11.1 months in the immunoglobulin and 9.7 months in the antibiotic arm Figure 3).[13] Clinically documented infections averaged 1.86 per participant in the immunoglobulin treatment arm and 1.33 per participant in the prophylactic antibiotic treatment arm. As this was a feasibility study, our results need to be confirmed in a larger trial.

4.2.5. Potential risks of Ig therapy

Regular IgRT is associated with hospital day-admissions (for intravenous administration) and known adverse effects associated with Ig use. Common adverse effects include headache, lethargy, nausea/vomiting, allergic reactions, arthralgia, myalgia, hypersensitivity reactions, abdominal pain

and dyspnoea. Aseptic meningitis can also occur, although this is less common. Regular use of Ig has also been associated with risk of thromboembolic events.[14] Renal impairment and renal failure have also been reported in patients receiving IVIg. In patients receiving subcutaneous Ig (SCIg), there may also be injection site irritation and there is a requirement for training and equipment to self-administer the product. Reduction in use of Ig may help reduce healthcare expenditure on Ig product costs and associated healthcare administration costs.

4.2.6. Potential risks of prophylactic antibiotic therapy

Some common adverse events to the prophylactic antibiotics used within this protocol include nausea, vomiting, diarrhoea and rash. Other less common adverse reactions include anaphylaxis and hypersensitivity reactions. Another possible risk of prophylactic antibiotics is development of resistant organisms, but its impact on development of infection is unknown.

4.2.7. Summary

Secondary hypogammaglobulinemia is common in patients with haematological malignancies and associated with infections (approximately 25% of participants in our pilot trial experienced at least one grade 3 or higher infection). Substantial variation exists in the approach to use of IgRT and alternative therapies such as prophylactic antibiotics in patients with acquired hypogammaglobulinaemia secondary to haematological malignancies, both internationally and within Australia.[7,15]

4.3. The need for a trial comparing IgRT with prophylactic antibiotics

Our current treatment decisions on whether to use IgRT or prophylactic antibiotics in patients with acquired hypogammaglobulinaemia secondary to haematological malignancies are not evidence-based because there is limited data on efficacy of IgRT or prophylactic antibiotics, and the available trial evidence is limited by small patient numbers, risk of bias and lack of contemporaneous and comparative data. These have been identified as priority evidence gaps in the recent Australian Medical Services Advisory Committee review of the cost-effectiveness of IgRT, specifically:

-Consideration for eligibility criteria used in Europe (trial of antibiotics before starting Ig therapy)

-Cost effectiveness of Ig in NHL (the largest patient group), as there are no Ig studies in these patients.

Therefore, a clinical trial is required to evaluate the comparative efficacy, safety and cost-effectiveness of prophylactic antibiotics compared with IgRT.

4.3.1. Domain hypothesis

Prophylactic oral antibiotics are non-inferior to IgRT replacement for the prevention of severe, and/or recurrent infection in patients with secondary hypogammaglobulinaemia due to B-cell malignancies.

5. DOMAIN OBJECTIVES

5.1. Aims

The aim of this domain is to determine the effectiveness of prophylactic antibiotics compared to IgRT in patients with haematological malignancies and acquired hypogammaglobulinaemia on event-free survival (as defined in the core protocol).

6. DOMAIN DESIGN

This RATIONAL Platform Trial is an investigator-initiated open-label, randomised controlled adaptive platform trial open in multiple sites. The platform design allows many treatment approaches to be tested simultaneously on different patient subpopulations, within the same framework, and for pre-specified interim analyses that can be used to stop recruitment early to arms showing insufficient evidence of efficacy or overwhelming evidence of efficacy. The platform allows the addition of new domains via protocol amendments and DSAs to answer new questions of interest, including different treatments or patient groups. Details of the overall platform trial design are included in the Core Protocol.

The Start Ig DSA is one of multiple domains in the RATIONAL Platform trial. This domain is testing whether commencing prophylactic antibiotics is non-inferior to the standard dose of IgRT in patients with secondary hypogammaglobulinemia due to haematological malignancies.

7. SELECTION AND WITHDRAWAL OF PARTICIPANTS

7.1. Population

The RATIONAL Platform Trial enrols patients with acquired hypogammaglobulinemia due to haematological malignancies, including multiple myeloma [MM], chronic lymphocytic leukaemia [CLL] and non-Hodgkin lymphoma [NHL]. This domain is available for patients who are not currently receiving IgRT for prevention of bacterial infections due to hypogammaglobulinaemia.

7.2. Eligibility criteria

Patients are eligible for the RATIONAL Platform Trial if they meet all of the platform-level inclusion and none of the platform-level exclusion criteria outlined in the Core Protocol. Patients eligible for the RATIONAL Platform Trial may have conditions that exclude them from this Domain.

7.2.1. Domain inclusion criteria

None.

7.2.2. Domain exclusion criteria

1. Prior or planned allogeneic haematopoietic stem cell transplantation.
2. Already receiving systemic antibiotic prophylaxis for the purpose of preventing bacterial infection (NB: patients may receive antiviral, antifungal and PJP prophylaxis).
3. Received immunoglobulin replacement in the preceding three months.
4. Objection to receiving immunoglobulin products.
5. Known history of IgA deficiency with anti-IgA.
6. History of severe allergy to immunoglobulin products.
7. Current active infection requiring systemic antibiotics.
8. Allergy or intolerance of all domain antibiotic options.
9. Pregnant or breastfeeding.
10. Severe renal impairment (estimated or measured creatinine clearance of < 30 mL/min).
11. Previous splenectomy.
12. Previous participation in this domain.
13. Treating team deems enrolment in the domain is not in the best interest of the patient.

7.2.3. Intervention exclusion criteria

Nil

7.3. Randomisation

Randomisation will occur following confirmation of participant eligibility for the domain, between the baseline and Start Domain Day 1 visit. Randomisation will be conducted through a password-protected secure website using a central randomisation programme. Eligibility for randomisation will be assessed with reference to the Platform-level and Domain-level inclusion and exclusion criteria and there will be no exception to eligibility requirements at the time of randomisation.

8. TREATMENT OF PARTICIPANTS

8.1. Interventions

8.1.1. Interventions

This domain has two interventions:

- Commencement of prophylactic antibiotics (Arm A)
- Commencement of immunoglobulin replacement (Arm B)

8.1.2. Commencement of prophylactic antibiotics (Arm A)

Participants will be treated with once daily trimethoprim-sulfamethoxazole (co-trimoxazole) 160mg/800mg, with dose adjustments as listed below, from study day 1. For patients with hypersensitivity to co-trimoxazole, or who are taking a medication with potential for a significant interaction with co-trimoxazole as outlined below, 100mg doxycycline daily will be permitted as an alternative prophylactic antibiotic. If participants encounter cytopenias which are exacerbated by the study antibiotics, participants can be switched to the other antibiotic. Participants must be able to tolerate at least one of the study antibiotics to be eligible for entry into the study.

Medications which cannot be administered with co-trimoxazole include (but are not limited to): antiarrhythmics (dofetilide, amiodarone), antivirals (amantadine/memantine, lamivudine), antineoplastics (paclitaxel), antibiotics (dapsone). Co-trimoxazole may increase the effect of the following agents, and increased monitoring of their drug levels and/or effect is required if co-administered with co-trimoxazole: digoxin, phenytoin, warfarin, oral hypoglycaemics (repaglinide, rosiglitazone, pioglitazone, glipizide), methotrexate, drugs that cause potassium retention (such as ACE inhibitors) and cyclosporin (increased monitoring of renal function).

Medications which cannot be administered with doxycycline include (but are not limited to): isotretinoin, etretinate and methoxyflurane. Doxycycline may increase the effect of the following agents, and increased monitoring of drug levels and/or effect is required if co-administered with doxycycline: warfarin, cyclosporin, phenytoin.

8.1.2.1. *Co-trimoxazole dose adjustments for cytopenias and renal impairment*

For participants with grade 2 or greater anaemia, neutropenia or thrombocytopenia, whether attributed to concomitant medications, underlying haematologic disorder or co-trimoxazole itself,

the dose of co-trimoxazole may be reduced by 50% (to 80/400mg daily) at the discretion of the investigator.

Co-trimoxazole dose will be adjusted for participants with renal impairment, defined by eGFR (or, if available, measured creatinine clearance)

eGFR or creatinine clearance	Dose
> 50 mL/Min	Full dose (160/800mg)
30 to 50 mL/Min	50% dose reduction (to 80/400mg)
< 30 mL/Min	Consider switching to doxycycline, or discontinue study treatment

8.1.3. Commencement of immunoglobulin replacement (Arm B)

8.1.3.1. *Intravenous immunoglobulin (IVIg)*

Participants will receive monthly (every 4 weeks ± 1 week) intravenous immunoglobulin at a dose of 0.4g/kg, modified to achieve an IgG trough level of at least lower limit of age-specific serum IgG reference range. In the first month of therapy, if IgG <4g/L then an additional (loading) dose of 0.4g/kg may be given at the clinician's discretion.

8.1.3.2. *Subcutaneous immunoglobulin (SCIg)*

Subcutaneous immunoglobulin weekly may be used in patients who meet local criteria for home-based self-administration in centres with established SCIg programs. Dosing is usually given at 100mg/kg/week, modified to achieve an IgG steady state level of at least the lower limit of the serum reference range. A loading IVIg dose may be given in the first month if required.

Study participants may transition from IVIg to SCIg, or vice versa, using a conversion factor of 1:1 for total monthly IV to SC dosing. Where IVIg is used in this protocol, unless explicitly stated, it shall be taken to include SCIg.

8.1.4. Cross-over

If a participant on the prophylactic antibiotic intervention arm (Arm A) experiences a Grade 3 or higher infectious complication, they may commence IgRT, as directed by their treating clinician.

In the absence of a Grade 3 or higher infectious complication, patients will stay on their assigned treatment. However, the treating clinician may start IgRT if this is deemed in the participant's best interest. This will not be regarded as an event for EFS in the primary analysis, however it will be recorded on the relevant eCRF for the purposes of supplementary analyses.

For participants on the immunoglobulin replacement (Arm B) who develop a grade 3 or higher infection, their subsequent treatment will be according to standard care as directed by their treating clinician.

In these situations, trial participation will not end and the participant will continue to follow the schedule of assessments until M12, except in the case of patients who also choose to withdraw from the study.

8.1.5. Duration of therapy

Participants will remain on assigned treatment for 12 months. Participants do not need to stop their trial-assigned treatment at 12 months, but all treatment decisions including for prevention of infection after completion of trial treatment (at 12 months from Day 1 of study) will be managed by the participant's treating clinician.

8.1.6. Discontinuation of study assigned treatment protocol

Site investigators/clinicians may discontinue a patient from their assigned trial treatment if this is no longer in the participant's best interest. Reasons for treatment discontinuation may include:

- Grade 3 or higher adverse event
- Grade 3 or higher infectious complication
- Unrelated medical illness or clinical condition representing potential risk, such as change to therapy for underlying malignancy
- Participant's request
- Poor compliance
- Participant is no longer deemed eligible to participate (e.g. if they develop a contraindication to treatment allocation)

If a participant is discontinued from the assigned treatment protocol for any reason, the end-of-treatment (EOT) visit assessments should be completed 4 weeks (+/- 7 days) after the final administration of the participant's assigned treatment. Trial participation will not end and the participant will continue to follow the schedule of assessments until M12.

8.1.7. Concomitant care

All other aspects of care, including other antimicrobial prophylaxis (including antivirals, antifungals) and vaccinations, will be according to usual care and local practice. For example, patients already taking low-dose (80mg/400mg) daily or intermittent (three times a week) co-trimoxazole for *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis may continue, if necessary with a dose increase if allocated to Arm A. Higher doses of PJP prophylaxis are not permitted in the immunoglobulin treatment arm.

It is recommended that all participants receive routine vaccinations, including pneumococcal, influenza and COVID-19 vaccines, as part of their usual care, and have measurement of pre- and post-vaccination pneumococcal responses, where polysaccharide pneumococcal vaccine is due to be given on study.

Patients who are commenced on therapy to treat underlying malignancy may continue on the study. Patients may receive granulocyte colony stimulating factor (G-CSF) for prophylaxis or treatment of neutropenia according to local guidelines.

9. DOMAIN ENDPOINTS

The Start Ig domain aims to demonstrate the efficacy and safety of prophylactic antibiotics compared to IgRT in adults with a diagnosis of MM, CLL or NHL who are eligible to receive immunoglobulin replacement for recurrent or severe infections or an IgG <4g/L (excluding paraprotein).

9.1. Primary Endpoint

The primary endpoint for this domain is the primary endpoint specified in the Core Protocol.

9.2. Secondary Endpoints

All secondary endpoints specified in the Core Protocol.

10. ASSESSMENTS AND FOLLOW-UP

10.1. Domain Schedule of Assessments

Please see Domain Schedule of Assessments over page. This is in addition to the Schedule of Assessments in the Core Protocol.

All participants enrolled in the platform and any one of the domains are to be followed according to the Schedule of Assessments in the core platform protocol. The following additional assessments are to be completed for all participants enrolled in this domain. All visits for the domain must align with the core protocol visits and visit windows, for example the Month 1 visit on the domain is the Month 1 visit on the platform schedule of assessments.

Period	**Screening**	**Treatment Period**												**Follow-up**
Procedure	**Visit BL**	**Visit D1***	**Visit M1**	**Visit M2**	**Visit M3**	**Visit M4**	**Visit M5**	**Visit M6**	**Visit M7**	**Visit M8**	**Visit M9**	**Visit M10**	**Visit M11**	**Visit M12/EOT**
Domain Informed Consent	X													
Treatment details[#]	X													
Domain eligibility assessment	X													

*D1 is Day 1 of trial treatment. BL and D1 assessment may occur on the same day. D1 must occur no more than 7 days after randomisation.

[#]Updated information on treatment for underlying malignancy if this has changed from platform enrolment

10.2. Domain-specific data collection

In addition to the data collection specified in the core protocol, the following data will be collected for the Start-Ig domain:

BL visit – Updated information on treatment for underlying malignancy if this has changed from platform enrolment

10.3. Blinding

All interventions will be administered on an open-label basis.

11. SAFETY ASSESSMENT

Refer to the Core Protocol.

12. STATISTICAL CONSIDERATIONS

For information regarding the statistical analysis of this domain, refer to the Core protocol Master Statistical Analysis Appendix and the DSSAP.

12.1.1. Domain Sub-groups

Model-based, sub-group analyses, to be detailed in the DSSAP, will include, but are not limited to:

- Patients receiving active therapy for their primary disease at time of randomisation
- Patients with IgM below reference range at randomisation
- Patients in partial or complete remission of their primary disease at time of randomisation
- Country

13. ETHICAL CONSIDERATIONS

13.1. Risks and benefits of participation

There are no specific benefits for patients from participation in this domain. Both of the treatment arms in this domain are within normal standard of care.

14. GOVERNANCE ISSUES

14.1. Funding of the Start Ig Domain

The RATIONAL Platform Trial funding sources are specified in the Core Protocol.

15. REFERENCES

1. NBA. Criteria for Immunoglobulin Use in Australia. 2018.
2. Gale RP, Chapel HM, Bunch C, et al. Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia. A randomized, controlled clinical trial. *N Engl J Med.* 1988;319(14):902-907.
3. Raanani P, Gafter-Gvili A, Paul M, Ben-Bassat I, Leibovici L, Shpilberg O. Immunoglobulin prophylaxis in hematological malignancies and hematopoietic stem cell transplantation. *Cochrane Database of Systematic Reviews.* 2008(4).
4. Chapel HM, Lee M, Hargreaves R, Pamphilon DH, Prentice AG. Randomised trial of intravenous immunoglobulin as prophylaxis against infection in plateau-phase multiple myeloma. The UK Group for Immunoglobulin Replacement Therapy in Multiple Myeloma. *Lancet.* 1994;343(8905):1059-1063.
5. Griffiths H, Brennan V, Lea J, Bunch C, Lee M, Chapel H. Crossover study of immunoglobulin replacement therapy in patients with low-grade B-cell tumors. *Blood.* 1989;73(2):366-368.
6. Chai KL, Wong J, Weinkove R, et al. Interventions to reduce infections in patients with hematological malignancies: a systematic review and meta-analysis. *Blood Adv.* 2023;7(1):20-31.
7. Wong J, Wood EM, Crispin P, et al. Managing hypogammaglobulinaemia secondary to haematological malignancies in Australia and New Zealand: a clinician survey. *Int Med J.* 2019;49(3):358-363.
8. Gafter-Gvili A, Fraser A, Paul M, et al. Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy. *Cochrane Database Syst Rev.* 2012;1:CD004386.
9. Wong C, Jayaram L, Karalus N, et al. Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2012;380(9842):660-667.
10. Mohyuddin GR, Aziz M, McClune B, Abdallah AO, Qazilbash M. Antibiotic prophylaxis for patients with newly diagnosed multiple myeloma: Systematic review and meta-analysis. *Eur J Haematol.* 2020;104(5):420-426.
11. Oscier D, Dearden C, Eren E, et al. Guidelines on the diagnosis, investigation and management of chronic lymphocytic leukaemia. *Br J Haematol.* 2012;159(5):541-564.
12. Fennelly KP, Griffith DE. Azithromycin in non-cystic-fibrosis bronchiectasis. *Lancet.* 2013;381(9860):27.
13. McQuilten Z WR, Crispin P et al. EHA2021 Virtual Congress Abstract Book. *HemaSphere.* 2021;5:e566.
14. Ammann EM, Jones MP, Link BK, et al. Intravenous immune globulin and thromboembolic adverse events in patients with hematologic malignancy. *Blood.* 2016;127(2):200-207.
15. Paxton L, Hawkins C, Crispin P. Selecting haematological malignancy patients for intravenous immunoglobulin. *Intern Med J.* 2016;46(10):1216-1218.