RATIONAL Platform Trial

Role of Antibiotic Therapy or Immunoglobulin

On iNfections in hAematoLogy

Domain-Specific Appendix:

Immunoglobulin Stopping or Extension (Stop Ig)

PROTOCOL NUMBER:	TRU-RPT-22
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SPONSOR:	Monash University
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STOP 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

A/Prof Zoe McQuilten	Monash University, Melbourne, Australia	ZM and EW initiated the trial design and implementation. EW and ZM are the grant holders.
Dr Khai Li Chai	Monash University, Melbourne, Australia	JR, ER and TL provided statistical expertise in clinical trial design and are conducting the primary statistical analysis.
A/Prof John Reynolds	Monash University, Melbourne, Australia	All authors contributed to refinement of the trial protocol and approved the final version.
Prof Erica Wood	Monash University, Melbourne, Australia	LF and DP designed the health economics analysis.
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Prof Dennis Petrie	Monash University, Melbourne, Australia	KLC and CP designed the qualitative substudy protocol.
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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
DSMC	Data safety monitoring committee
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	1. Patients must be receiving Ig (IV or subcutaneous - SCIg) replacement for prevention of bacterial infections due to hypogammaglobulinaemia for at least 6 consecutive months. 2. Patient is eligible for trial of Ig cessation in the opinion of the treating clinician and local investigator. 3. Patient is willing and able to comply with each of the treatment arms.
Domain-specific 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. Major infection (Grade 3 or higher) in preceding 3 months, and/or current active infection requiring systemic antimicrobial treatment. 3. Already receiving systemic antibiotic prophylaxis for the purpose of preventing bacterial infection (NB: patients may receive antiviral, antifungal and PJP prophylaxis). 4. Intolerance of all trial antibiotic options in either arm A or arm B. 5. Communication, compliance or logistical issues that are likely to limit patient's ability to take prophylactic or emergency antibiotics, or to obtain urgent medical attention for symptoms of infection. 6. Pregnant or breastfeeding. 7. Severe renal impairment (estimated or measured creatinine clearance of < 30 mL/min). 8. Previous splenectomy. 9. Previous participation in this domain. 10. Treating team deems enrolment in the domain is not in the best interests of the patient.
Interventions to be compared	**Arm A: Stop Ig and commence 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: Stop Ig.** Patients will be provided with amoxycillin/clavulanic acid 1750-2000mg/250mg and ciprofloxacin 750 mg *to keep at home for initial use if symptoms of infection develop*, with immediate review by their treating clinical team, or nearest emergency department or medical practitioner with phone contact to treating team if most practical.

	NB: Clindamycin 600 mg is permitted as an alternative to amoxycillin/clavulanic acid for patients with hypersensitivity to penicillin. Ciprofloxacin is omitted for participants with hypersensitivity. **Arm C: Continue Ig.** Participants will continue treatment with their current Ig replacement schedule. 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. For patients who have already had their Ig dose titrated to IgG trough level, they may continue on their current monthly dose of Ig replacement. 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. Planned treatment duration for all arms (A, B and C) is 12 months.
Trial hypotheses	1. Prophylactic oral antibiotics are non-inferior to continuation of Ig replacement for the prevention of severe, and/or recurrent infection in patients with secondary hypogammaglobulinaemia due to B-cell malignancies. 2. A strategy of no antibiotic therapy (with a patient-held emergency antibiotic supply) is non-inferior to the continuation of 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. Secondary Domain-Specific Endpoints: 1. Resumption of Ig treatment over 12 months for patients in Ig cessation treatment arms.

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 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 Erica Wood

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

3.2. Stop Ig Domain-Specific Working Group Authorisation

The Stop Ig Domain-Specific Working Group have read this appendix and authorise it as the official Stop 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 stopping Ig replacement with or without prophylactic antibiotics compare to continuing Ig replacement.

4.2. Domain-specific background

4.2.1. Overview

4.2.1.1. *Duration of Ig replacement – when to cease therapy?*

Evidence to guide duration of IgRT and when to cease it is limited. From the most recent Cochrane review,[1] in clinical trials of Ig replacement, the duration of therapy was for a period of between 6 and 12 months, with follow-up not extending beyond 12 months. A recent single-centre, non-randomised study showed that regular Ig replacement was able to be safety stopped in a small cohort of patients with haematological malignancies who received prophylactic antibiotics and an additional emergency-held antibiotic supply to keep at home.[2] To date, there have been no randomised controlled trials to guide if and when to trial cessation of Ig.

Substantial variation exists in the approach to duration of IgRT and use of alternative therapies, both internationally and within Australia.[3,4] For patients receiving Ig for this indication, Australian government Criteria state: "*Cessation of Ig therapy should be considered at least after each 12 months" of its use*.[5] This statement is not evidence-based, and in this group of immunocompromised patients who are highly infection prone and vulnerable, and for whom infection is their highest risk of mortality, such evidence is essential in order to recommend or mandate such a clinical management directive. UK guidelines (2019) advise that it may be appropriate to consider temporary cessation of Ig in the summer,[6] although at least in Australia from 2009 to 2013, there was no significant seasonal change in IgRT utilisation.[7] In New Zealand (NZ), Ig approvals are reviewed every 12 months.

There is significant variation in clinical practice with regard to duration of IgRT. In a recent survey of Australian and New Zealand haematologists, 21% reported continuing Ig unless an adverse event occurred, 24% routinely stop after a fixed duration, 15% stop if the patient is in clinical remission with recovery from hypogammaglobulinaemia, 6% stop during summer, and 34% decide on a case-by-case basis.[4]

Our current treatment decisions are not evidence-based because no data exist on optimal duration of IgRT or outcomes after stopping: cessation is recommended, but standard of care regarding the

timing of cessation is not defined. We do not know when or how to predict when it is safe to stop, or what to monitor prior to and after stopping. Therefore, a clinical trial is required to evaluate optimal duration of Ig use and/or outcomes after stopping.

4.2.1.2. *Predictors of which patients are at higher risk of infection to guide Ig cessation*

The effects of changes in immune function over time and its association with disease status, treatment with chemotherapy, immunotherapy and other targeted agents, IgRT, as well as infection outcomes is not well understood. Monitoring the immune status in patients with haematological malignancies over time receiving various immunomodulatory treatments may provide useful insights into the risks of development of infection. Analysis of potential changes in the immune profiles in these patients and their association with infection outcomes may provide guidance as to which patients may benefit most from Ig or other anti-infective measures such as prophylactic antibiotics, and which patients may safely cease these therapies.

4.2.2. Potential benefits of ceasing 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.[8] Renal impairment and renal failure have also been reported in patients receiving IVIg. For 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.

4.2.3. Potential risks of ceasing Ig therapy

The risks of ceasing Ig therapy are unknown, but the main possible risk of ceasing Ig therapy is the risk of major or recurrent infections. Major or recurrent infections may lead to increased unplanned visits to hospital, admission to hospital and/or intensive care, and treatment with antimicrobial agents and other therapies. Within this protocol, patients who are allocated to cease Ig therapy and who experience a major infection (see below) will be allowed to recommence Ig replacement therapy.

4.2.4. Prophylactic antibiotics as an alternative to continuing Ig therapy

Short-term prophylactic oral antibiotics have been shown to reduce infections by 30-50% in neutropenic haematology patients following chemotherapy,[9] and in non-haematologic malignancy patients with bronchiectasis,[10] 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.[11]

Some international guidelines recommend a trial of prophylactic antibiotics prior to commencing IgRT.[12] Potential advantages 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.[10,13] In addition, for patients not receiving IgRT the less frequent clinical interactions due to less frequent attendance at day treatment centres have the potential to result in later diagnosis of any infection, which in turn could lead to poorer outcomes. Therefore, the use of prophylactic antibiotics should be properly evaluated with respect to efficacy, safety, QoL, and healthcare costs.

In addition, our recently completed phase II feasibility trial – the RATIONAL (Role of antibiotic therapy or immunoglobulin on infections in haematology) trial – the first to compare starting Ig vs prophylactic oral antibiotics in 63 patients with newly diagnosed CLL, MM and NHL who, as a result were newly eligible to commence IgRT– demonstrated recruitment feasibility and tolerability of oral antibiotics. Although not powered for clinical outcomes, RATIONAL data suggest no increase in infection outcomes in the antibiotic arm (ACTRN12616001723471).[14]

4.2.5. 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.

4.3. The need for a trial assessing immunoglobulin cessation

IgRT is effective at reducing infection in this setting; however:

- There have been significant changes to patient populations, therapeutic agents and protocols and consequent effects on immune function and supportive care since clinical trials of IVIg were performed.

- IVIg, SCIg and oral antibiotics all carry risks.
- Effectiveness of Ig compared with other potential options, such as prophylactic antibiotics, in terms of compliance with therapy, clinical outcomes, adverse effects, QoL, and healthcare costs, is unknown.
- Australian national criteria and New Zealand guidelines recommend that a trial of cessation of Ig therapy should be considered at least after each 12 months of treatment, but there are few prospective studies indicating how this could be achieved.
- IVIg and SCIg costs continue to increase, and haematological malignancies are a growing indication for their use.

No trials powered for clinical outcomes have compared continuing IgRT with Ig cessation with or without prophylactic antibiotics in terms of safety, efficacy and cost-effectiveness. Therefore, a clinical trial is required.

This Domain is designed to assess if Ig therapy for adults with haematological malignancies can be stopped if patients are free of major infection after six months of therapy, and after stopping, whether oral antibiotics should be used to prevent future infection.

4.3.1. Domain hypotheses

- Prophylactic oral antibiotics are non-inferior to continuation of Ig replacement for the prevention of severe, and/or recurrent infection in patients with secondary hypogammaglobulinaemia due to B-cell malignancies.
- A strategy of no antibiotic therapy (with a patient-held emergency antibiotic supply) is non-inferior to the continuation of Ig 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 whether stopping Ig with prophylactic or antibiotics or antibiotics on demand, is as effective as continuing Ig (IVIg or SCIg) 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 Stop-Ig domain is randomising participants receiving IgRT to one of 3 study interventions: IgRT cessation with prophylactic antibiotics, IgRT cessation with antibiotics for emergency use and continuation of IgRT.

The Stop-Ig domain was initially opened as a standalone trial, RATIONALISE. The RATIONALISE trial was amended to a platform trial design during the course of the trial, as described in the Protocol History Table. As part of the amendment, the RATIONALISE interventions became the 'STOP-Ig' domain interventions within the larger platform.

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 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

1. Patients must be receiving Ig (IV or subcutaneous - SCIg) replacement for prevention of bacterial infections due to hypogammaglobulinaemia for at least 6 consecutive months.
2. Patient is eligible for trial of Ig cessation in the opinion of the treating clinician and local investigator.

3. Willing and able to comply with each of the treatment arms.

7.2.2. Domain exclusion criteria

1. Prior or planned allogeneic haematopoietic stem cell transplantation.
2. Major infection (Grade 3 or higher) in preceding 3 months, and/or current active infection requiring systemic antimicrobial treatment.
3. Already receiving systemic antibiotic prophylaxis for the purpose of preventing bacterial infection (NB: patients may receive antiviral, antifungal and PJP prophylaxis).
4. Intolerance of all trial antibiotic options in either arm A or arm B.
5. Communication, compliance or logistical issues (e.g. living long distance from medical facility) that are likely to limit a patient's ability to take prophylactic or emergency antibiotics, or to obtain urgent medical attention for symptoms of infection.
6. Pregnant or breastfeeding.
7. Severe renal impairment (estimated or measured creatinine clearance of <30mL/min).
8. Previous splenectomy.
9. Previous participation in this domain
10. Treating team deems enrolment in the domain is not in the best interests 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 Stop-Ig 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 three interventions:

- Immunoglobulin cessation and commencement of prophylactic antibiotics (Arm A)
- Immunoglobulin cessation without prophylactic antibiotics, with a supply of oral antibiotics immediately available (at home) for emergency use (Arm B)
- Continuation of immunoglobulin replacement at current dose and schedule (Arm C)

8.1.2. Immunoglobulin cessation and 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. Immunoglobulin cessation without commencement of prophylactic antibiotics (Arm B)

Patients will be provided with amoxycillin/clavulanic acid 1750-2000mg/250mg and ciprofloxacin 750mg to keep at home for initial use if symptoms of infection develop, with immediate review by their treating clinical team, or nearest emergency department or medical practitioner with phone contact to treating team if most practical and as clinically required. Diagnosis and management of the infection will be determined by the severity of the suspected infection and coordinated by the patient's treating team.

For patients with hypersensitivity to penicillin, or taking a medication with a significant interaction with amoxycillin/clavulanic acid, clindamycin 600mg is permitted as an alternative to amoxycillin/clavulanic acid. If the patient has a contraindication to ciprofloxacin, this antibiotic will be omitted from the emergency antibiotics. Contraindications to ciprofloxacin include quinolone hypersensitivity (including nalidixic acid) and concurrent tizanidine.

For participants assigned to Arm B, Day 1 of treatment is considered the date of randomisation.

8.1.4. Continuation of immunoglobulin replacement at current dose and schedule (Arm C)

Participants will continue treatment with their current Ig replacement schedule. The recommended dose of Ig replacement is outline below. For participants assigned to Arm C, Day 1 of treatment is considered the first dose of Ig following randomisation.

8.1.4.1. *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. For patients who have already had their Ig dose titrated to IgG trough level, they may continue on their current monthly dose of Ig replacement.

8.1.4.2. *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.

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.

8.1.5. Restarting Ig

If a participant on either of the immunoglobulin cessation intervention arms (Arm A or Arm B) experiences a Grade 3 or higher infectious complication, they may recommence 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 reinstate 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.

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.

8.1.6. 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.

8.1.7. 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

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 follow the schedule of assessments until M12.

8.1.8. 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 Stop Ig domain aims to demonstrate the non-inferiority of immunoglobulin cessation in adults with a diagnosis of MM, CLL or NHL who are currently receiving 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.

Domain-specific secondary endpoints are:

1. Resumption of Ig treatment over 12 months for patients in Ig cessation treatment arms.

10. ASSESSMENTS AND FOLLOW-UP

10.1. Domain Schedule of Assessments

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 for participants on Arm A and Arm C. D1 is day of randomisation for participants on Arm B. 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 Stop-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
- Patients on IgRT for less than 12 months prior to randomization
- Country

13. ETHICAL CONSIDERATIONS

13.1. Risks and benefits of participation

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

14.GOVERNANCE ISSUES

14.1. Funding of the Stop Ig Domain

The RATIONAL Platform Trial funding sources are specified in the Core Protocol. This domain is also supported by a grant from the National Health and Medical Research Council (NHMRC).

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