RATIONAL Platform Trial

Role of Antibiotic Therapy or Immunoglobulin

On iNfections in hAematoLogy

Domain-Specific Appendix:

Dosing Immunoglobulin (Dose Ig)

PROTOCOL NUMBER:	TRU-RPT-22
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SPONSOR:	Monash University
VERSION NUMBER:	1.0
DATE OF PROTOCOL:	12 NOVEMBER 2023

Dose 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.
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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
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
PID	Primary immunodeficiency
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 IVIg replacement at standard dose for prevention of bacterial infections due to hypogammaglobulinaemia for at least 6 consecutive months. 2. Patient is not eligible for trial of Ig cessation in the opinion of the treating clinician and local investigator.
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. Major infection (Grade 3 or higher) in preceding 3 months, and or current active infection requiring systemic antimicrobial treatment. 3. Previous splenectomy. 4. Known history of bronchiectasis. 5. Previous participation in this domain. 6. Treating team deems enrolment in the domain is not in the best interest of the patient.
Interventions to be compared	**Arm A: Low dose IgRT:** Participants will be treated with intravenous immunoglobulin monthly (every 4 weeks ± 1 week) at a dose of 0.25g/kg. No dose adjustment for trough serum IgG levels is required. **Arm B: Usual dose:** Participants will be treated with intravenous immunoglobulin monthly (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.
Trial hypotheses	1. That a lower dose of IgRT is non-inferior to the standard IgRT replacement dose 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 Dose Ig Domain are members of the ITSC.

3.2. Dose Ig Domain-Specific Working Group Authorisation

The Dose Ig Domain-Specific Working Group have read this appendix and authorise it as the official Dose 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 lower dose Ig replacement compared to standard dose Ig replacement.

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. Whilst the most recent Cochrane review which showed IgRT reduced infections in patients with secondary hypogammaglobulinemia due to haematological malignancies, it included only 3 trials published between 1988 and 1995 with *a total of only 205 patients*.[1-4] In our recently completed systematic review of interventions to prevent infections in chronic lymphocytic leukaemia (CLL), multiple myeloma (MM) and non-Hodgkin lymphoma (NHL) we did not identify any new evidence to guide Ig use.[5] We found no difference in risk of all-cause mortality in patients allocated to IgRT compared to standard of care (relative risk [RR] 1.35, 95% CI 0.57-3.18), and a reduction in risk of clinically documented infections (RR 0.70, 95% CI 0.54-0.96). However, our certainty in the evidence was low due to small sample size of included trials, high risk of bias in the included studies and lack of contemporary data applicable to the current standard of care.[5] 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.

4.2.3. Dose of IgRT used in clinical trials in secondary hypogammaglobulinemia due to haematological malignancies

The current standard of care for IgRT in patients with acquired hypogammaglobulinaemia secondary to haematological malignancies is intravenous immunoglobulin (IVIg) 0.4g/kg every 4 weeks, adjusted to maintain IgG trough levels within normal reference range. However, the evidence to support this dosing is weak, derived from a few small studies from the 1990s which evaluated doses ranging from 0.2g/kg to 0.5g/kg every three to four weeks.[5]

In our meta-analysis which showed that IgRT reduced clinically documented infections, the doses used in the included studies were 18g IVIg every 3 weeks,[6], 0.3g/kg IVIg every 4 weeks,[7,8] and 0.4g/kg IVIg every 4 weeks.[3,4,9]. Our systematic review[5] only identified one study that compared two doses of IVIg, 0.25g/kg compared to 0.5g/kg every 4 weeks.[10].

These studies suggest that the evidence to support current practice is weak, and that doses lower than the current standard dose may be effective at preventing infections. It is known from pharmacokinetic studies in primary immunodeficiency that half-life of IgG varies in and between patients and that disease-related factors may play a role in determining the IgG dose to prevent infections. However, no such dosing studies have been performed in patients with haematological malignancies.

4.2.4. Pharmacokinetics of immunoglobulin replacement in other patient populations

The pharmacokinetics of therapeutic polyclonal IgG is highly variable with the terminal half-life of intravenous IgG ranging from 20 to 30 days in healthy adults and neonates, 12-56 days in patients with primary immunodeficiency (PID), 6 days in bone marrow transplant patients and 3-7 days in patients suffering from burns.[11] The differences in half-life observed in the various diseases may be due to the pathophysiological elements of the underlying disease.

Following intravenous administration, the serum concentration of IgG declines rapidly in the first seven days (α phase), followed by a more gradual decline (β phase). The rapid decline during the α phase is caused by the redistribution of IgG into extravascular spaces and IgG elimination, while the β phase only represents IgG elimination.[11]

There are key pharmacokinetic differences between subcutaneous Ig (SCIg) and IVIg administration**.** IVIg is infused directly into the intravascular space, resulting in an early, high peak of Ig concentration followed by a redistribution phase (first-order kinetics, concentration-dependent elimination),[11] whereas SCIg must first diffuse through the lymphatic system into the bloodstream (retained as a depot in the SC tissue and slowly redistributed into the intravascular space, first-order absorption),[11] resulting in a more gradual and stable increase in Ig concentration over 2 to 3 days without a high IgG serum peak. Because bioavailability is lower with SCIg versus IVIg, the dose of SCIg must be increased to achieve equivalent immunoglobulin G exposure. Current recommendations indicate that patients receiving SCIG should use a monthly dose that is 130% or 137% of their previous IVIg monthly dose, depending on the concentration of the SCIg product.[12]

The majority of research has mainly focused on the minimum trough levels required to achieve adequate protection against infections, while the upper limit of IgG levels has received much less attention. Instead, adequate dose requirement is mainly driven by clinical responses and cost considerations.[11]

The first evidence that serum IgG levels of ≥5 g/L lead to substantial reduction of acute infections in primary immunodeficiency (PID) patients was published over 30 years ago. Since then, studies have shown that higher serum IgG concentrations may be associated with better protection against infections and decrease in incidence or progression of bronchiectasis in patients with PID.

However, a number of publications have confirmed that there is no absolute protective level for everybody and IgG replacement therapy should be individualised to target the unique "biological" IgG level of every single PID patient.[13] This is based on observations from PID cohorts that there is a wide range in serum IgG levels required to keep patients infection free, with only some patients needing the largest doses.[14]

The evidence for the association between serum IgG levels, "biological" IgG levels and infection risk are all derived from studies in patients with PID. No similar data are available for patients with secondary hypogammaglobulinemia. Given the known variability in the pharmacokinetics of IgG according to underlying disease, studies specific to patients with haematological malignancies are required to inform dosing in this patient populations.

4.2.5. Serum IgG levels in RATIONAL pilot randomised controlled trial

Our recently completed RATIONAL phase II feasibility trial (ACTRN12616001723471) compared the use of IgRT vs prophylactic oral antibiotics in 63 patients with CLL, MM & NHL. The dose of IgRT was according to current standard of care in Australia (0.4g/kg every 4 weeks). We measured trough IgG levels in both treatment groups (Figure 1), which demonstrate that with current dosing the trough level is maintained much higher than 5g/L. The median (interquartile range) trough IgG level in participants allocated to IgRT was 8.9 (1.5) at 3 months following randomisation, 9.2 (2.9) at 6 months, 9.9 (4.8) at 9 months and 8.4 (3.5) at 12 months. RATIONAL infection rates are shown in Figure 2.[15]

Figure 1: Median trough serum IgG levels in RATIONAL pilot by treatment arm

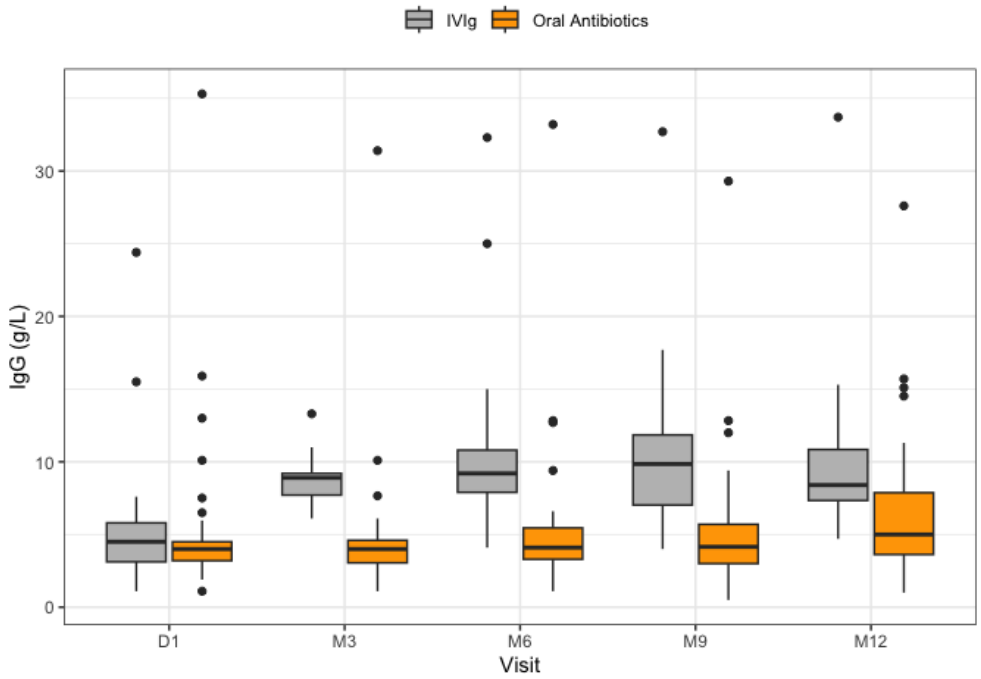
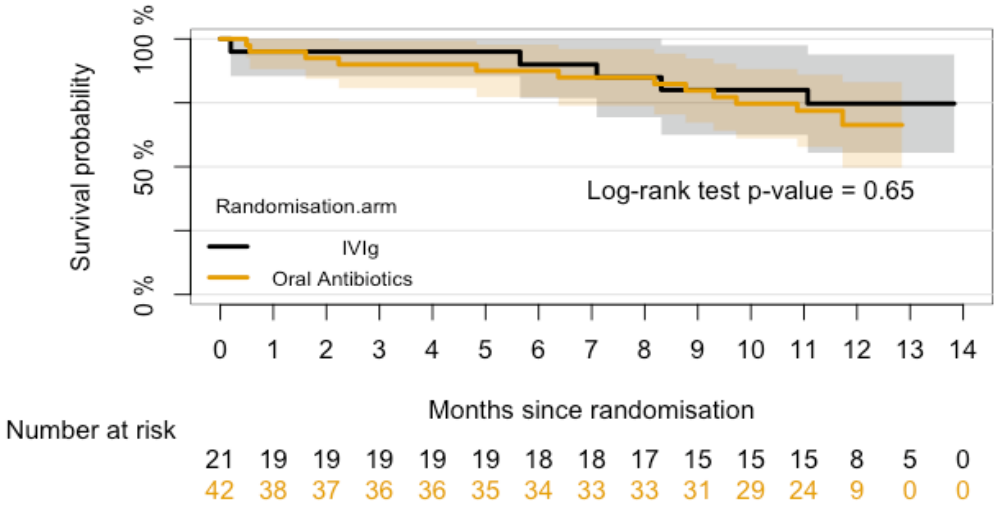


Figure 2: Time to first major infection



4.2.6. Risks of different dosing strategies of IgRT

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.[16] Renal impairment and renal failure have also been reported in patients receiving IVIg.

There is a risk that a lower dose of IgRT may increase infection risk if there is an association with higher serum trough IgG levels and infection risk in this patient population. However, higher doses of IgRT may also be associated with greater risk of adverse events.

4.2.7. Improving cost effectiveness of immunoglobulin replacement

A recent review of the cost effectiveness by the Australian Government Medical Services Advisory Committee found that Ig replacement was not a cost-effective therapy to manage infections in patients with secondary hypogammaglobulinemia secondary to hematological malignancies, noting the small and incomplete evidence base and high and uncertain incremental cost effectiveness ratio. One area highlighted for further research was generating evidence on dosing strategies to improve cost-effectiveness. If lower doses of IgRT were protective for infection risk, then this may improve the cost-effectiveness of immunoglobulin replacement.

4.2.8. The need for a trial comparing low dose IgRT with standard dose IgRT

It is essential to establish the optimal dosing of IgRT. The current standard of care for IgRT in patients with acquired hypogammaglobulinaemia secondary to haematological malignancies is IVIg 0.4g/kg every 4 weeks, adjusted to maintain IgG trough levels within normal reference range. However, the evidence to support this dosing is weak, derived from a few small studies from the 1990s which evaluated doses ranging from 0.2g/kg to 0.5g/kg every three to four weeks. These studies, and our pilot data, suggest that doses lower than the current standard dose may be effective at preventing infections. It is known from pharmacokinetic studies in PID that half-life of IgG varies in and between patients, that disease-related factors may play a role in determining the IgG dose to prevent infections, and that an individualised “biological IgG” level may be more important than serum trough IgG levels. However, no such dosing studies have been performed in patients with haematological malignancies.

4.2.9. Domain hypothesis

- That a lower dose of IgRT is non-inferior to the standard IgRT replacement dose 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 a lower dose of IgRT in patients with haematological malignancies and secondary 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 Dose Ig DSA is one of multiple domains in the RATIONAL platform. This domain is testing whether a lower dose of IgRT 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 MM, CLL and NHL. This domain is available for patients who are currently receiving standard dose IgRT for prevention of bacterial infections due to

hypogammaglobulinaemia and are not suitable for a trial of IgRT cessation (as per the Stop Ig domain).

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 IVIg replacement at standard dose for prevention of bacterial infections due to hypogammaglobulinaemia for at least 6 consecutive months.
2. Patient is not eligible for trial of Ig cessation in the opinion of the treating clinician and local investigator.

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. Previous splenectomy.
4. Known history of bronchiectasis.
5. Previous participation in this domain.
6. 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 Dose 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:

- Low dose intravenous immunoglobulin replacement (Arm A)
- Standard dose intravenous immunoglobulin replacement (Arm B)

8.1.2. Low dose immunoglobulin replacement (Arm A)

Participants will be treated with intravenous immunoglobulin monthly (every 4 weeks ± 1 week) at a dose of 0.25g/kg. No dose adjustment for trough serum IgG levels is required.

8.1.3. Commencement of immunoglobulin replacement (Arm B)

8.1.3.1. *Intravenous immunoglobulin (IVIg)*

Participants will be treated with intravenous immunoglobulin monthly (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.

8.1.4. Cross-over to standard dose IgRT

If a participant on the low dose IgRT intervention arm (Arm A) experiences a Grade 3 or higher infectious complication, they may recommence standard dose 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 increase the dose of 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 continueto 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

If a participant is discontinued from the assigned treatment protocol for any reason, the domain end-of-treatment (EOT) visit assessments should be completed 4 weeks (+/- 7 days) after the final administration of the participant's assigned treatment. Domain 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.

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 Dose Ig domain aims to demonstrate the efficacy and safety of low dose IgRT compared to

standard dose IgRT in adults with a diagnosis of MM, CLL or NHL who are currently receiving immunoglobulin replacement.

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 Dose-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 Dose Ig Domain

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

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