RATIONAL-PT

Role of Antibiotic Therapy or Immunoglobulin On iNfections in hAematoLogy Platform Trial:

Core Protocol

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SPONSOR:	Monash University
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A randomised platform trial evaluating the role of interventions to prevent infection in patients with acquired hypogammaglobulinemia secondary to haematological malignancies.

Development Protocol History

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

Protocol Development Group:

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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
DSSAP	Domain-specific statistical analysis plan
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. GENERAL INFORMATION

1.1. Trial Synopsis

Scientific title of clinical trial	Role of Antibiotic Therapy or Immunoglobulin On iNfections in hAematoLogy Platform Trial
Public title of clinical trial	Role of Antibiotic Therapy or Immunoglobulin On iNfections in hAematoLogy Platform Trial
Protocol short title/Acronym	RATIONAL-PT
Protocol version and date	Version 1.0, dated 21-Aug-2023
Primary sponsor	Monash University
Sponsor contact details	Transfusion Research Unit Department of Epidemiology and Preventive Medicine School of Public Health and Preventive Medicine, Monash University 553 St Kilda Road Melbourne, Victoria, 3004 AUSTRALIA Phone: +61 3 9903 0791 or 1800 811 326
Funders	Australian National Health and Medical Research Council, Medical Research Future Fund
Primary clinical trials registry number	ANZCTR: TBC ClinicalTrials.gov: TBC
Date trial registered	
Trial design	Adaptive platform trial
Health condition(s) or problem(s) studied	Patients with hypogammaglobulinemia secondary to haematological malignancies
Key inclusion and exclusion criteria	**Core Inclusion criteria** 1. Aged ≥ 18 years of age 2. Diagnosis of haematological malignancy, including CLL, MM or NHL 3. Eligible to receive or currently receiving Ig (IV or subcutaneous - SCIg) replacement for history of recurrent or severe infection(s) and IgG less than the lower limit of the reference range (excluding paraprotein) OR IgG<4g/L (excluding paraprotein) 4. Life expectancy > 12 months 5. Able to give informed consent **Core Exclusion criteria** 1. Treating team deems enrolment in the study is not in the best interests of the patient. Additional eligibility criteria will apply for each domain and will be described within the relevant DSA.
Setting	This trial will be conducted by haematology or haematology/oncology units at participating hospitals in participating regions.
Aims	The primary aim of this platform trial is to determine the optimal supportive care interventions for patients with haematological malignancies.

Primary outcome measure	Event-free survival (EFS), defined as time from randomisation (or, in domains with a single treatment arm, time from registration) until occurrence of a Grade 3 or higher infection (as defined by CTCAE Version 5), or death from any cause. This is the primary outcome for trial results for each domain, unless otherwise specified in the Domain Specific Appendix.
Core secondary outcome measures	1. Occurrence of at least 1 Grade 3 or higher infection(s) from randomisation to 12 months. 2. Occurrence of one or more clinically documented infections (symptoms/signs of infection requiring antimicrobial treatment) from randomisation to 12 months. 3. Number of clinically documented infections (symptoms/signs of infection requiring antimicrobial treatment) from randomisation to 12 months. 4. Occurrence of one or more microbiologically documented infections from randomisation to 12 months. 5. Number of microbiologically documented infections from randomisation to 12 months. 6. All-cause mortality at 12 months 7. Infection-related mortality at 12 months 8. Time free from hospitalisation with antimicrobial administration with therapeutic intent from randomisation to 12 months. 9. Occurrence of one or more treatment-related adverse events 10. Number of treatment-related adverse events. 11. Isolation of fluoroquinolone resistant organisms, co-trimoxazole resistant organisms, extended spectrum beta lactamases or multidrug resistant organisms from randomisation to 12 months. 12. Number of infections with fluoroquinolone resistant organisms, co-trimoxazole resistant organisms, extended spectrum beta lactamases or multidrug resistant organisms isolated from randomisation to 12 months 13. QoL measured at randomisation, 3, 6, 9 and 12 months (EQ-5D-5L, EORTC QLQ-30 and FACT-N.). 14. Costs associated with allocated treatment arm and infections during study.
Duration of trial	There is no set duration of the trial as this is an adaptive platform trial. The trial may be extended with addition of new domains and interventions.
Target sample size	There is no set sample size as this is an adaptive platform trial. The sample size may change with addition of new domains and interventions
Contact details for public queries	sphpm.rationalise@monash.edu
Contact details for scientific queries	Prof Zoe McQuilten: zoe.mcquilten@monash.edu
Lay summary of trial	Some blood cancers, or the medications used to treat them, can cause low levels of immunoglobulins (antibodies) in the blood, resulting in increased risks of serious infection. Immunoglobulin (Ig, a blood product

	made from human plasma) is commonly prescribed to reduce the risk of infection in patients with blood cancers but the evidence for Ig replacement therapy is based on historical data and it is uncertain if this is still beneficial as there have been many changes to treatment of cancer and infection. Ig is also very expensive and Australia is one of the highest users of Ig in the world, at a cost of $130 million annually for this indication alone. There is considerable variation in the approach to Ig replacement therapy both internationally and within Australia, including the ideal duration of therapy and requirements for alternative therapies. Some countries require a trial of oral antibiotics prior to commencing Ig therapy. Even though blood products like Ig are very safe, they do still carry some risks and should only be used when needed. Other options (such as long term, low-dose antibiotics) also carry risks (for example, risk of antibiotic resistance). We need more information on how different treatment options compare in terms of benefits, risks and costs. The RATIONAL Platform trial seeks to determine which treatments are most effective in reducing infections and which patients are most likely to benefit from the treatments.

1.2. Schedule of Assessments

The following Schedule of Assessments is to be followed for all participants who are enrolled in the platform and any one of the domains. Refer to the Domain-Specific Appendix for additional domain-specific assessments (if applicable).

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^**
Time	**≤2 weeks prior to D1**	**+/- 3d**	**+/- 7d**	**+/- 7d**	**+/- 7d**	**+/- 7d**	**+/- 7d**	**+/- 7d**	**+/- 7d**	**+/- 7d**	**+/- 7d**	**+/- 7d**	**+/- 7d**	**+/- 7d**
Phone call			X	X		X	X		X	X		X	X	
Clinic visit	X	X			X			X			X			X
Platform informed Consent	X													
Diagnosis details	X													
Platform eligibility assessment	X													
Demographics	X													
Medical history	X													
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event review	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Infections review	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hospitalisations review	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Performance Status (ECOG)	X	X			X			X			X			X
Haematology assessment: FBE (all timepoints), lymphocyte subsets (BL)	X				X			X			X			X
Biochemistry assessment[!] - Renal and liver function	X				X			X			X			X
Ig Levels (trough)[+]		X			X			X			X			X

Biobank substudy, additional blood collection		X[β]			X			X			X			X[-]
For patients on biobank substudy, faecal sample collection[@]		X			X									X
For patients on qualitative substudy, interview to be scheduled between D1 & M12.		X[β]												X
For patients on PK/PD sub-study, additional Ig samples to be scheduled around <u>one</u> Ig dose from D1 to M11.		X[~]												
For patients on Patient Preferences study, online discrete choice experiment survey to be completed prior to D1		X												
Quality of life: EQ-5D-5L, EORTC QLQ-C30[#] and FACT-N	X				X			X			X			X
Treatment compliance			X	X	X	X	X	X	X	X	X	X	X	X

*Refer to relevant DSA for definition of D1

[%]For the purpose of scheduling and follow-up, each trial month is defined as 4 weeks (or 28 days). Please note M1 is to be scheduled 4 weeks (+/-7 days) after D1.

^End of Treatment visit (EOT): These assessments should be performed at a clinic visit, 4 weeks (+/-7 days) after the final administration of the participant's assigned treatment. EOT visits/assessments may line up with a scheduled visit.

[β]Prior to initial treatment dose.

[+]Ig trough levels (steady-state if on SCIg) to be taken prior to the next Ig treatment for participants receiving Ig; Ig levels include IgG, IgA and IgM and IgG subclass if reported

[#]If participant reports having had an infection requiring treatment, an additional EORTC QLQ C-30 is to be completed retrospectively for period of infection, once the infection has resolved.

[!]Liver function tests: Bilirubin, ALT, and ALP. Renal function tests: Electrolytes, creatinine.

[@]If collected at home, participants must return their faecal samples to site within 24 hours of collection.

[-]Correlative blood samples are not required at the EOT visit, unless the visit coincides with the M12 visit.

~PK/PD samples to only be collected for participants who are randomised to receive IgRT and have consented to the PK/PD sub-study. All PK/PD samples must be taken prior to the next administration of IgRT and are to be collected as follows:

<u>SCIg PK/PD samples</u>: pre-infusion (-120 to -1min), 10 ±5 min prior to end of infusion, 2 ±1 h after infusion, and 1, 2, 3, 4 and 7 days after infusion.

<u>IVIg PK/PD samples:</u> pre-infusion (-60 to -1 min), 3 to 20 min post-infusion, 24 ±2 h, 3 ±1 days, 7 ±1 days, 10 ±1 days, 14 ±1 days, 21 ±1 days and 28 ±2 days post-infusion. NB: participants receiving IVIg on a 3-weekly schedule will not require the PK/PD sample 28 days post-infusion.

BL – baseline; ECOG – European Cooperative Oncology Group; FBE – full blood examination; Ig – immunoglobulin; PD – pharmacodynamic; PK – pharmacokinetic;

2. INTRODUCTION

2.1. Background and rationale

2.1.1. Overview

2.1.1.1. *Infections in patients with blood cancers*

Serious or major infection is common in patients with chronic lymphocytic leukaemia (CLL), multiple myeloma (MM) and non-Hodgkin lymphoma (NHL). These blood cancers are associated with major morbidity and mortality, substantial impact on patient quality of life (QoL), and high health resource use and costs. Infections occur secondary to a multifactorial immune deficiency attributable to both the underlying cancer and/or its treatment.[1-4] Hypogammaglobulinaemia occurs in up to 85% of people with CLL, >90% newly diagnosed MM and variably in NHL, and is associated with recurrent and/or severe bacterial, fungal & viral infections.[3,5,6] Infections account for up to 50% of all CLL deaths, and 50% of early MM deaths.[5,7] When serious infections occur, they are complex and costly to manage, and impair cancer treatment delivery by causing dose reductions or treatment delays. Prevalence and severity of immune deficiency generally correlates with disease stage and duration; however infectious risk prediction for individual patients remains difficult. Identifying interventions to prevent infection is therefore a priority to improve infectious outcomes, survival and QoL of patients living with these cancers.

2.1.1.2. *Immunoglobulin replacement and other interventions to prevent infection*

Immunoglobulin (Ig) replacement therapy (IgRT) is commonly used to prevent recurrent bacterial infection, with access provided under Australian Criteria for government-funded Ig – with the caveat of "*Evidence of probable benefit – more research needed*".[8] This recommendation is based on outdated data: the most recent Cochrane review which showed infection reduction with Ig for patients with secondary hypogammaglobulinemia due to blood cancers included only 3 trials (1988-95) with a total of only 205 patients.[6,9-11] There is no evidence that IgRT improves mortality, however prior trials had very small numbers, and since these trials, there have been major changes to cancer therapy and supportive care, and hence many confounding factors potentially explaining the lack of a survival signal. Intensive and novel therapies result in better outcomes for some patients, with varying degrees of immunological recovery. Therefore, it is very uncertain whether results from these early trials of IgRT still apply to our current practice and can be used to inform which patients should receive Ig replacement, when it should be started, and when it is safe to stop treatment. Similar evidence gaps exist for use of prophylactic antibiotics.

Ig therapy also carries risks: while mostly well tolerated, it is not uncommon for patients to stop therapy due to side-effects (see below) which can occasionally be serious.[12]

Australia has one of the highest uses per capita of intravenous Ig (IVIg) in the world, with Canada and the United Kingdom also high users of Ig per capita. Patients with acquired hypogammaglobulinaemia due to haematological malignancies are the largest single group for whom IVIg is issued in Australia, accounting for 23% of all IVIg issued in 2018, with an estimated product costs for these patients in 2019-2020 of approximately $95 million rising to nearly $130 million by 2023-2024.[4,8,13,14]

Substantial variation exists in the approach to IgRT, both internationally and within Australia, in relation to optimal duration of Ig therapy and requirements for alternative therapies.[4,15]

2.1.1.3. *Need for a trial to evaluate interventions to prevent infections in patients with blood cancers*

Infections are common in patients with secondary hypogammaglobulinemia due to haematological malignancies. At present, the most proven intervention to prevent infections is Ig replacement, however significant evidence gaps exist:

- There have been significant changes to patient populations, therapeutic agents and protocols and consequent effects on immune function and supportive care since the largest clinical trials of Ig were performed. Whether results of these trials are still applicable to current practice is unknown.
- Effectiveness of Ig compared with other potential options, such as prophylactic antibiotics or vaccinations, in terms of compliance with therapy, clinical outcomes, adverse effects, QoL, and healthcare costs, is unknown.
- Clinical demand for Ig replacement continues to increase, with haematological malignancies the largest single indication. Identifying which patients are most likely to benefit is therefore a priority for the blood sector in order to meet growing demand.
- No high-quality studies that have compared different methods of administration (intravenous versus subcutaneous), different dosing schedules or when to commence or cease Ig therapy
- Emerging and pandemic infections, shifts in antimicrobial resistance patterns, and changes in vaccines and vaccination strategies are likely to impact the type and burden of infections among people with secondary hypogammaglobulinaemia. There is a need to evaluate immunoglobulin and other existing and new means to prevent infections in this population.

Clinical trials are required to inform clinical policies and healthcare resource allocation, and guide day-to-day patient management and efficient use of Ig.

2.1.2. Bayesian adaptive platform trials

Adaptive platform trials are an innovative trials methodology that is increasingly being used for oncology trials (I-SPY 2[16]) and infectious diseases (SNAP[17], REMAP-CAP[18]).

Conventional randomised controlled trials (RCTs), at the time of design, make assumptions about plausible effect size, incidence of the primary outcome, and sample size, holding these assumptions until trial completion. Adaptive Platform Trials incorporate multiple statistical and design features that are not reliant on these types of pre-trial assumptions. These include the ability to perform analyses on data as they accumulate, with poorly performing interventions being removed, and the potential for new promising interventions to be added. Platform Trials allow multiple questions to be evaluated simultaneously and sequentially within the platform to achieve the goal of determining the optimal interventions as rapidly as possible.

The RATIONAL platform trial will use a number of adaptive platform trial design features to enhance trial efficiency and rapid implementation of trial findings, including:

-Universal core or master protocol with several domains. By addressing multiple questions in parallel the platform will reduce the time required to reach definitive conclusions on optimal therapy.

- Ability for patients to rotate to another domain appropriate to their changed clinical status, rather than randomising to fixed sequence of interventions in advance.

- Frequent interim analyses will be used so that questions can be concluded as soon as there is robust statistical confidence, not when a pre-specified sample size has been recruited. The results of each interim analysis will be reviewed by an independent Data and Safety Monitoring Board (DSMB) responsible for making declarations based on the analysis of accumulating data. Pre-specified stopping rules, informed by pre-trial simulations, will be provided to the DSMB. Details of simulations are provided in the Statistical Appendices for the Core Protocol and Domain Specific Appendices.

2.1.3. Objectives

The overarching objective of the RATIONAL Platform Trial is, for patients with haematological malignancies, to identify the interventional regimen (including, but not limited to: when to start,

when to cease and how to dose IgRT and comparisons with alternative therapies) associated with the highest chance of event-free survival (EFS), defined as time from randomisation until occurrence of a Grade 3 or higher infection (as defined by CTCAE Version 5), or death from any cause.

The trial enrols individuals with haematological malignancies, including but not limited to CLL, MM, and NHL, who have low Ig levels and/or a history of recurrent or severe infection.

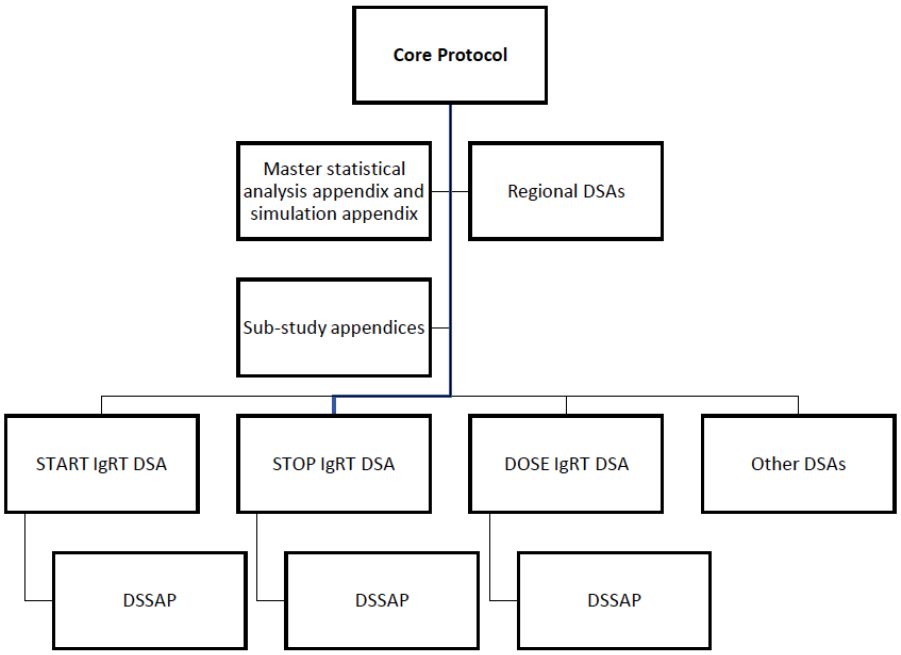
2.2. PROTOCOL STRUCTURE

2.2.1. Core Protocol

The structure of this protocol is different to a conventional trial because this trial is adaptive, designed to allow the trial to evolve over time with the introduction of new domains. The structure of the protocol is outlined in Figure 1. The Core Protocol provides the framework on which different interventions within domains can exist within this trial. The Core Protocol provides the following information:

- Background and rationale for studying Ig replacement and other interventions to prevent infections in individuals with haematological malignancies
- The trial design, including eligibility criteria for entry into the trial platform, randomisation and treatment allocation procedures, trial endpoints, methods to control bias, general principles of the statistical analysis of data, and criteria for termination of the trial
- The trial conduct, including methods of recruitment, data collection and management, and procedures related to participant safety and monitoring
- The trial governance structure (see also Figure 2)

Figure 1: Platform protocol outline



2.2.2. Domain-Specific Appendices

Domain-specific appendices (DSAs) contain more detailed information about specifications of the interventions studied within each domain. Each new DSA will be submitted for ethical approval prior to commencement. Each DSA has the following structure:

- Background and rationale for each of the interventions within that domain
- Domain-specific eligibility criteria
- Domain-specific exclusion criteria
- A description of the interventions and procedures for their delivery
- Domain-specific data collection and outcomes that are additional to those specified in the Core Protocol
- Domain-specific ethical considerations
- Domain-specific organisational considerations

2.2.3. Master Statistical Analysis Appendix

The Master Statistical Analysis Appendix contains a detailed description of generic analyses that are used for assessing the effect of interventions in more than one domain and any platform-wide analyses. This will include the Core definition of the primary endpoint estimand.

2.2.4. Domain-Specific Statistical Analysis Plans (DDSAP)

Domain-Specific Statistical Analysis Plans (DSSAPs) will be developed for each domain. These will include detailed description of the analyses specific to the domain.

2.2.5. Region-Specific Appendices

The RATIONAL-PT will be conducted in multiple countries with varying legislative, ethical and governance requirements. Region-Specific Appendices (RSAs) contain information specific to the conduct of the trial in that region, including:

- Definition of the region
- The governance structure within a region
- Ethical and governance issues relevant to a region not covered in the Core Protocol
- The availability of trial domains and interventions within a region
- Region-specific treatment allocation and data management procedures

2.2.6. Sub-study and Biospecimen Appendices

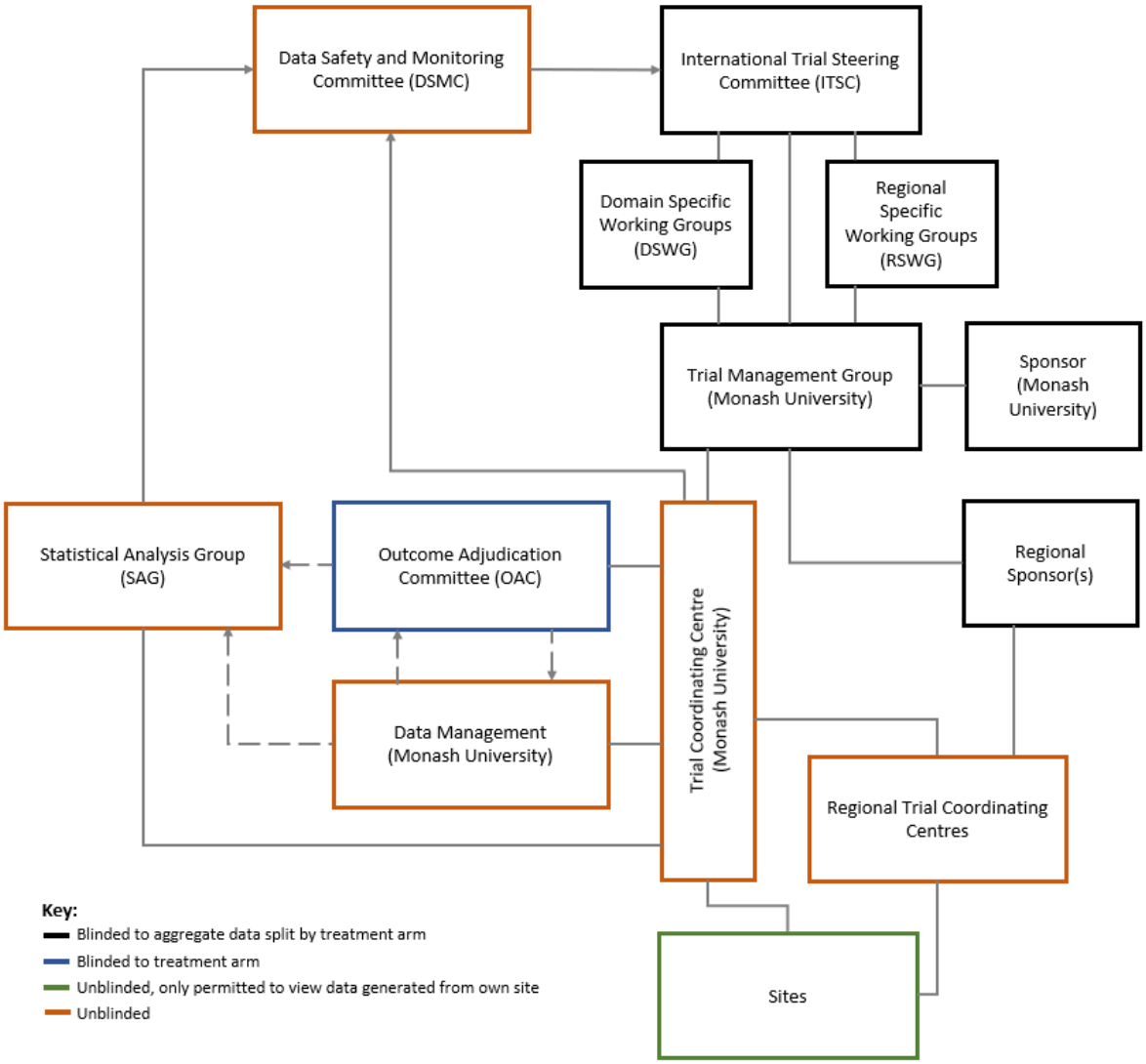
Sub-studies will be fully described within appendices. These will contain the following information relevant to the sub-study:

- Background and rationale for the sub-study
- Sub-study procedures required for the conduct of the sub-study

2.3. STUDY GOVERNANCE

The trial governance structure is shown in Figure 2.

Figure 2: Trial Governance Structure



2.3.1. International Trial Steering Committee

The International Trial Steering Committee (ITSC) will include members with experience and knowledge regarding the overall study design, domain-specific expertise and regional-specific expertise. The responsibilities of the ITSC are:

- Development and amendment of the Core Protocol
- Recruitment and approval of new regions (including Regional Sponsors) to the platform
- Liaison with Sponsors in various countries or regions
- Liaison with the Data Safety and Monitoring Committee (DSMC) (see below) and Outcome Adjudication Committee (OAC, see section 4.6)
- Consideration of requests and approval of the addition of domains and their interventions to the platform, including prioritisation of new domains and new interventions within a domain

- The analysis and reporting of results, in conjunction with the DSWGs
- Approval of manuscripts reporting results
- Obtain ongoing funding for the platform
- Determine the strategic direction of the platform

2.3.2. Trial Management Group (TMG)

The Trial Management Group (TMG) will oversee the day-to-day management and overall conduct of the trial.

2.3.3. Regional Specific Working Groups (RSWG)

The operation of the platform in each region is undertaken by that region's RSWG, the composition of which is to be determined by investigators in each region. The responsibilities of the RSWGs are:

- Development and amendment of the RSA for that region
- Liaison with Regional Sponsor
- Identification and management of sites in that region
- Liaison with regional funding bodies
- Consideration of the feasibility and suitability of interventions (and domains) for that region

2.3.4. Domain-Specific Working Groups (DSWG)

Each active and future domain (or closely related set of domains) will be administered by a DSWG. The responsibility of each DSWG are:

- Development and amendment of the DSA
- Proposal and development of new interventions within a domain
- In conjunction with the ITSC, analysis and reporting results from the domain
- Obtaining funding to support the domain

2.3.5. Data Safety and Monitoring Committee

An independent Data Safety and Monitoring Committee (DSMC), comprising experts in haematology, infectious diseases and statistics will be established before patient enrolment. The DSMC will be responsible for safeguarding the interests of trial participants and assessing the safety and efficacy of the trial. The DSMC will monitor evidence for treatment harm and compliance with the protocol. The DSMC will be advisory to the ITSC. The ITSC will be responsible for promptly reviewing the DSMC recommendations, to decide whether to continue or discontinue treatments within a domain, and to determine whether amendments to the protocol or changes in trial conduct are required.

The DSMC will be guided by a DSMC Charter that delineates the roles and responsibilities of the DSMC, including lines of communication between trial investigators, trial data coordinating centre, and Monash University.

2.3.6. Role of the Sponsor

Monash University plays a lead role in the design and central management of this trial. Monash University will have ultimate authority over the trial design; collection, management, analysis, and interpretation of data; writing of the report; or the decision to submit the report for publication. Monash University is the sponsor of the trial in Australia.

The Platform can have multiple regional Sponsors. Sponsors are organisations that take overall responsibility of the conduct, governance and insurance of the trial in a defined region. The role of the Sponsor in each region is specified in each RSA.

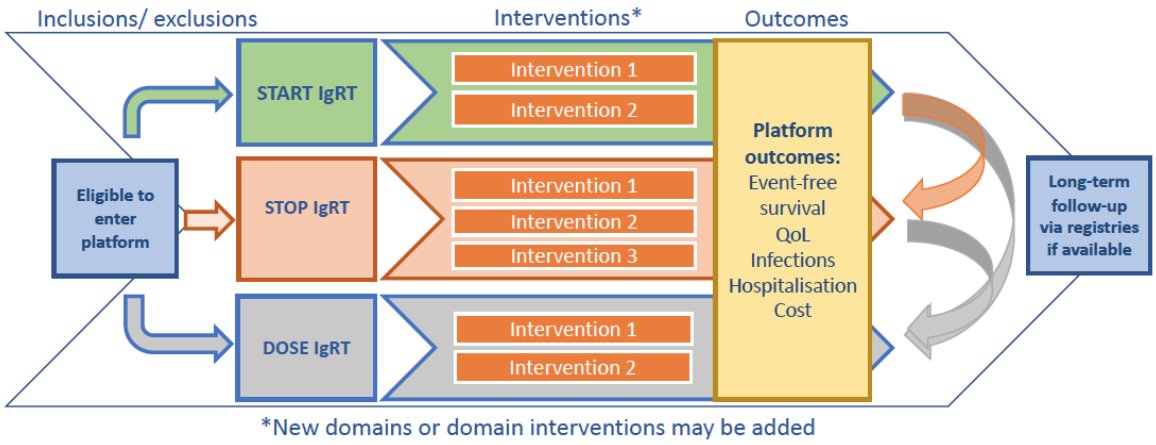
2.3.7. Role of trial funder(s)

The Australian National Health and Medical Research Council (NHMRC) and Medical Research Future Fund (MRFF) are the initial funders of the platform. The funders have no role in the design of the trial and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results for presentation or publication.

2.4. TRIAL DESIGN

This 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, 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 overview of the platform is shown in Figure 3. Participants who have enrolled in and completed one domain may be rotated and invited to participate in another domain appropriate to their changed status and subject to meeting domain-specific eligibility criteria.

Figure 3: Overview of trial platform



3. AIMS AND OUTCOMES

3.1. AIMS

The primary aim of this platform trial is, for patients with haematological malignancies, to determine the optimal supportive care interventions.

3.2. OUTCOMES

3.2.1. Primary outcome

Event-free survival (EFS), defined as time from randomisation (or, in domains with a single treatment arm, time from registration) until occurrence of a Grade 3 or higher infection (as defined by CTCAE Version 5), or death from any cause.

This is the primary outcome for trial results for each domain, unless otherwise specified in the Domain Specific Appendix.

3.2.2. Secondary outcomes

1. Occurrence of at least 1 Grade 3 or higher infection(s) from randomisation to 12 months.
2. Occurrence of one or more clinically documented infections (symptoms/signs of infection requiring antimicrobial treatment) from randomisation to 12 months.
3. Number of clinically documented infections (symptoms/signs of infection requiring antimicrobial treatment) from randomisation to 12 months.
4. Occurrence of one or more microbiologically documented infections from randomisation to 12 months.
5. Number of microbiologically documented infections from randomisation to 12 months.
6. All-cause mortality at 12 months
7. Infection-related mortality at 12 months

8. Time free from hospitalisation with antimicrobial administration with therapeutic intent from randomisation to 12 months.
9. Occurrence of one or more treatment-related adverse events
10. Number of treatment-related adverse events.
11. Isolation of fluoroquinolone resistant organisms, co-trimoxazole resistant organisms, extended spectrum beta lactamases or multidrug resistant organisms from randomisation to 12 months.
12. Number of infections with fluoroquinolone resistant organisms, co-trimoxazole resistant organisms, extended spectrum beta lactamases or multidrug resistant organisms isolated from randomisation to 12 months
13. QoL measured at randomisation, 3, 6, 9 and 12 months (EQ-5D-5L, EORTC QLQ-30 and FACT-N.).
14. Costs associated with allocated treatment arm and infections during study.

4. METHODS

4.1. STUDY SETTING

This trial will be conducted by haematology or haematology/oncology units at participating hospitals in participating regions.

4.2. SELECTION OF SITES/CLINICIANS

The platform will be coordinated by the Monash University Transfusion Research Unit.

Participating sites must complete and sign a clinical trial research agreement (CTRA).

All sites participating in the platform will complete a delegation log and forward this to the Trial Management Group (TMG). Each person working on the trial must sign off a section of this log indicating their responsibilities. The TMG must be notified of any changes to trial personnel and/or their responsibilities and an updated delegation log completed.

Following substantial amendments, sites will be notified of relevant documents and training required and if and when they are able to participate in the trial.

4.3. SELECTION OF PARTICIPANTS

Patients will be considered eligible for enrolment in this platform based on eligibility criteria applied at two levels. The first level is the inclusion and exclusion criteria that determine eligibility for enrolment within the platform. Once eligible for inclusion within the platform trial, additional criteria are applied that are specific to each domain.

Patients are eligible for this trial if they fulfil all the inclusion criteria and none of the exclusion criteria in the core protocol, and the criteria for at least one of the domains.

4.3.1. Core participant Inclusion criteria

1. Aged ≥ 18 years of age
2. Diagnosis of haematological malignancy, including CLL, MM or NHL
3. Eligible to receive or currently receiving Ig (IV or subcutaneous - SCIg) replacement for history of recurrent or severe infection(s) and IgG less than the lower limit of the reference range (excluding paraprotein) OR IgG<4g/L (excluding paraprotein)
4. Life expectancy > 12 months
5. Able to give informed consent

4.3.2. Core participant exclusion criteria

1. Treating team deems enrolment in the study is not in the best interests of the patient.

Additional eligibility criteria will apply for each domain and will be described within the relevant DSA.

4.4. CO-ENROLMENT GUIDELINES

The RATIONAL-PT platform trial seeks to evaluate supportive care interventions to prevent infection, including in therapeutic settings. Co-enrolment to other therapeutic studies is not excluded, except where these studies include interventions which might directly affect the interventions or endpoint assessments within RATIONAL-PT. In case of uncertainty, the ITSC will evaluate suitability for co-enrolment.

4.5. TRIAL PROCEDURES

4.5.1. Participant timeline

A summary of the study and follow up schedule is shown in Figure 3 and Table 1 (Schedule of Assessments).

4.5.2. Screening/recruitment

The local PI or delegate will be responsible for identifying suitable patients by reviewing the eligibility criteria and inviting them to participate in the trial.

A screening log will be completed on all patients considered for the trial including those approached but who decline to participate and ineligible patients. Patients will be screened against the eligibility

criteria outlined in this core protocol as well as those in the domain-specific appendix for which the participant is being considered.

Before commencing screening activities of patients for trial participation, consent from patients will be sought using the participant information and consent form (PICF).

All screening assessments are part of routine clinical care, therefore results from tests that are performed no more than 14 days prior to registration can be used to assess patient eligibility.

Each participant will be assigned a unique trial number when they are enrolled in the platform.

4.5.3. Treatment allocation

Participants will receive a treatment allocation after confirmation of eligibility for the Platform and at least one domain. For domains involving randomisation, 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 inclusion and exclusion criteria and there will be no exception to eligibility requirements at the time of randomisation.

After completion of trial procedures in one domain, participants may then be eligible to rotate to a different domain. In this case, participants will re-enter the screening period at the time of informed consent to the subsequent domain. If the participant is eligible for the subsequent domain, they will be reassessed against platform criteria and then be randomised within that domain and continue to be followed according to the Schedule of Assessments.

4.5.4. Blinding

Acknowledging the difficulty in blinding to regular administration of parenteral immunoglobulin replacement, the current standard of care in many regions, treatments will be provided on an open-label basis, unless otherwise specified in the DSA. Where interventions are conducted on an open-label basis, all members of the ITSC will remain blinded to aggregate reports until a platform conclusion is reported by the DSMC.

4.5.5. Withdrawal of participants

4.5.5.1. *Early withdrawal from trial*

Participants should be encouraged to remain in the trial and complete continue to follow the Schedule of Assessments, including adverse events and infection review, until M12, even if they discontinue their assigned trial treatment. Participants who simply discontinue trial treatment are not considered an early withdrawal. Investigators can withdraw participants at any time if they consider this in the best interests of the participant.

Any participant withdrawn from the trial at any time, for any reason, before the last follow up visit is considered an early withdrawal. An End of Domain eCRF form is to be completed for all participants withdrawing from a domain prior to the last domain scheduled visit. Unless a participant withdraws completely (i.e. does not consent to any follow-up), participants will be followed for all adverse reactions and infectious outcomes up to 30 days after their last on-study treatment dose.

4.5.5.2. *Participants lost to follow-up*

Every effort should be made to obtain information on patients who do not attend a scheduled appointment, to obtain at least minimal efficacy and safety data (including Serious Adverse Events). A patient will be considered lost to follow-up if they miss 3 consecutive visits and cannot be contacted by the site on 3 separate, consecutive attempts (these attempts must be documented on the patient's notes).

4.5.6. Treatment of participants

Treatments are outlined in the relevant Domain Specific Appendices.

4.5.7. Trial assessment schedule

Please see Schedule of Assessments in Section 1.2.

For the purpose of scheduling and follow-up, each trial month is defined as 4 weeks (or 28 days).

4.5.8. Assessments by visit

The following data will be collected:

4.5.8.1. *Screening/baseline*

- Medical history, including
    - Demographics
    - Disease information
    - Disease-specific therapy, including:
        - Prior anticancer therapy for the underlying malignancy
        - Prior additional steroid use for the underlying malignancy in the prior 12 months to screening
    - Concomitant medications (ALL) (including vaccinations, and current, ongoing anticancer therapy)
    - Covid-19 vaccination history
    - Pneumococcal antibody response (if available)
    - Infection history for the 12 months prior to screening

- ECOG Performance Status
- Haematology – FBE, lymphocyte subsets by flow cytometry (if available)
- Biochemistry – Renal function tests (Electrolytes and creatinine) and liver function tests (includes Bilirubin, ALT and ALP), IgG
- Quality of life (EQ-5D-5L, EORTC QLQ-C30 & FACT-N)

4.5.8.2. *Day 1*

- ECOG Performance Status
- Concomitant medications (ALL)
- Ig levels (trough if on 4-weekly IVIg, steady-state if on SCIg)
- Safety monitoring
- Infectious event details
- Biobank sub-study only
    - Peripheral blood (whole blood and serum) for correlative studies, including COVID-19 anti-spike protein levels.
    - Faecal sample

4.5.8.3. *Clinic Visits – M3, M6, M9, M12/EOT*

- ECOG Performance Status
- Haematology - FBE
- Biochemistry – Renal function tests (Electrolytes and creatinine) and liver function tests (includes Bilirubin, ALT and ALP)
- Ig levels (trough if on 4-weekly IVIg, steady-state if on SCIg)
- Concomitant medications: Treatment for underlying haematological malignancy, other immunosuppressive therapies (including steroids) for any indication, and non-trial antibiotic, antifungal and antiviral use and vaccinations. See site manual and eCRF for further details.
- Safety monitoring
- Infectious event details (including review of patient diary entries)
- Compliance with therapy
- Quality of life assessment (EQ-5D-5L, EORTC QLQ-C30 & FACT-N)
- Biobank sub-study only

- Peripheral blood (whole blood and serum) for correlative studies, including COVID-19 anti-spike protein levels (Month 3, Month 6, Month 9 and Month 12 only. Not required at EOT unless the EOT visit coincides with Month 12)
- Faecal sample (Month 3 and Month 12/EOT only)

If for any reason it is not considered in the participant's best interests to attend the trial site for an in-clinic assessment (as per local Investigator discretion), this Protocol allows for tele-health appointments to be conducted instead of on-site visits. Any such decisions are to be documented in the participant's source notes.

4.5.8.4. *Monthly phone calls – M1, M2, M4, M5, M7, M8, M10, M11*

- Concomitant medications: Treatment for underlying haematological malignancy, other immunosuppressive therapies (including steroids) for any indication, vaccines and non-trial antibiotic, antifungal and antiviral use. See site manual and eCRF for further details.
- Safety monitoring
- Infectious event details (including review of patient diary entries)
- Compliance with therapy

4.6. OUTCOME ADJUDICATION COMMITTEE (OAC)

An independent outcome adjudication committee, comprising of infectious disease experts and haematologists, will be established. The OAC will be responsible for reviewing and adjudicating on: grade of all infection outcomes, time of major infections; clinically documented infections; microbiologically documented infection; susceptibility profile of microbiologically documented infections and infection-related mortality.

The OAC will be provided with the details of all infectious events. Details will be provided in a blinded fashion, to ensure that the OAC are not aware of which treatment arm the participant was receiving. Committee members will individually assess the events according to the secondary outcomes as outlined above. All members will subsequently participate in a series of teleconferences for final consensus decision on the primary and secondary end-points for each trial patient.

5. Statistical Methods

Summary statistics, analyses and data visualisations will be generated using R version 4.0.0 or later or documented procedures in SAS (9.4 or later) or Stata (V. 17 or later) as appropriate. A detailed

description of the trial estimands, approaches to reporting, statistical models, adaptations and decision criteria, and justification of the trial design by simulation are presented in the Master Statistical Analysis Appendix to the Core Protocol and the Domain-specific Statistical Analysis Plans (SAPs). A Simulations Appendix will be updated periodically as an operational document which will contain the results of Monte Carlo simulations that are conducted to demonstrate and understand the operating characteristics of a domain or comparison of interest, across a range of plausible assumptions regarding the outcome rates, treatment effects, and recruitment rates.

The RATIONAL-PT has an adaptive platform design which means that it does not have a fixed sample size that determines when the study will end. Individual domains may have fixed caps on sample size as described within their DSAs.

The primary analysis will be a standalone analysis of each comparison within each domain of the RATIONAL-PT.

Interim analyses will be conducted according to the schedules specified in the relevant domain-specific appendices/SAPs and DSMC Charter, which will be reviewed and approved by the DSMC. The adaptations that can be made may be domain-specific and will be conducted according to pre-specified rules that will be used to reach conclusions regarding the effectiveness of the interventions that are under investigation. These may include: declaration of proof-of-concept, early stopping of arms for futility, early stopping of arms for efficacy and response adaptive randomisation (RAR). The values for the thresholds for the adaptations will be domain-specific and will take into account the design and monitoring plan for the domain. These will be appraised and ratified by the ITSC prior to the first interim analysis being conducted. The results of the interim analyses will remain confidential unless a trigger has been met and a recommendation is made by the DSMC to the ITSC that a conclusion has been reached and that they should be unblinded.

Blinding and randomisation: If domain-specific RAR is not invoked, computer-generated, randomised, allocation sequences will be based on permuted blocks of variable size; fixed allocation proportions will be adopted in the randomization of patients to the treatment arms in the domain and randomisation will be stratified by haematological malignancy.

6. SAFETY ASSESSMENT

6.1. Definitions of adverse events

6.1.1. Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and that does not necessarily have a causal relationship with this treatment.

6.1.2. Adverse Reaction (AR)

Any untoward and unintended response to an investigational medicinal product related to any dose administered. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable possibility of a causal relationship to an investigational medicinal product would qualify as adverse reactions. A causal relationship between the trial treatment (or medication error, misuse/abuse of medicinal product) and an adverse event occurs where there is at least a reasonable possibility that the trial treatment caused the event, i.e. the relationship cannot be ruled out.

6.1.3. Serious Adverse Event (SAE) / Serious Adverse Reaction (SAR)

Any adverse event/adverse reaction, at any dose, that

- Results in death
    - Is life-threatening (NB: 'life-threatening' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Results in persistent or significant disability/incapacity
- Requires in-patient hospitalisation or prolongs existing hospitalisation
- Results in congenital anomaly or birth defect
- Is otherwise medically significant (i.e. all accidental or intentional overdoses whether they result in an adverse event or not, or any event which the investigator considers significant but which is not covered by the above)

Planned hospitalisations for a pre-existing condition, without serious deterioration in health, is not considered a serious adverse event.

6.1.4. Unexpected Adverse Reaction (UAR)

This is defined as an adverse reaction, the nature or severity of which is not consistent with the trial's reference safety information (i.e. current Investigator's Brochure or Product Information).

6.1.5. Suspected Unexpected Serious Adverse Reaction (SUSAR)

An adverse reaction to one or more of the interventions administered in this study, that is both serious and unexpected.

A serious event or reaction is not defined as a SUSAR when:

- it is serious but expected
- it does not fit the definition of an SAE, whether expected or not

6.1.6. Significant Safety Issues (SSIs) and Urgent Safety Measures (USMs)

An SSI is defined as a safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial. An example of an SSI is an SAE associated with trial procedures that requires modification to trial conduct.

An USM is a measure required to be taken in order to eliminate an immediate hazard to a participant's health and safety. An USM is a type of SSI that requires the Investigator or Sponsor to act immediately to protect the participant. For this reason, USMs can be instigated by an Investigator or Sponsor before seeking approval from HRECs or Institutions.

All Urgent Safety Measures instigated at the site must be reported to Monash University as soon as possible and within 24 hours of the measure being taken.

6.2. Adverse event reporting

6.2.1. All Adverse Events (AEs)

All AEs that occur between the first trial-related procedure (i.e. screening) and 30 days following end of domain intervention must be recorded on the AE log.

Investigators must record their opinion concerning details of the nature, onset, duration and severity of the AE, and assess any relationship to the trial intervention. Assessment criteria are defined below.**Severity**

Severity for each adverse event, including any lab abnormality, will be determined by the Investigator using the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) as a guideline, wherever possible. In those cases where the CTCAE criteria do not apply and where there is no accepted alternative grading system, severity should be defined according to the following criteria:

Mild	Awareness of sign or symptom, but easily tolerated
Moderate	Discomfort enough to cause interference with normal daily activities
Severe	Inability to perform normal daily activities

Life-threatening	Immediate risk of death from the reaction as it occurred.

Causality

Relationship to trial treatment will be determined by the Investigator as follows:

Unrelated	No relationship between the experience and the administration of the trial treatment; related to other aetiologies such as concomitant medications or participant's clinical state
Unlikely	The current state of knowledge indicates that the relationship is unlikely
Possibly related	Temporal association, but other aetiologies are likely to be the cause
Probably related	Temporal association, other aetiologies are possible but unlikely
Related	Established temporal or other association and event not reasonably explained by the participant's known clinical state or other modes of therapy administered

Expectedness

An expectedness assessment needs to be conducted for all SAEs by the Sponsor with regard to the trial intervention, using the appropriate investigator brochure or treatment information.

Expected	The event is listed in the investigator brochure or the trial protocol as expected with the trial treatment or is commonly seen in clinical experience (patient population, dosage).
Unexpected	The event is not listed in the investigator brochure or in the trial protocol, or the severity of the event is greater than that listed in the investigator brochure or the trial protocol.

6.3. Reporting of Serious Adverse Events (SAE)

An adverse event that meets one of the seriousness criteria (6.1.3) is classified as a SAE. SAEs are reported on the SAE eCRF which is emailed to the Transfusion Research Unit at Monash University (sphpm.rationalise@monash.edu). A copy of the report will be forwarded to the site Pharmacy.

At a minimum, the following attributes must be assigned at the initial report:

- Adverse event term
- Seriousness criterion
- Date of onset and outcome

- Severity of the event (CTCAE Grade)
- Assessment of relatedness to the assigned intervention (Section 6.2 Causality)
- Assessment of expectedness for the assigned trial intervention

Subsequent reports must contain:

- A detailed description of the event
- Relevant laboratory findings and hospital reports
- Other concomitant drugs or devices

All SAEs will be followed until resolution. The investigator will be asked to provide interim and follow-up reports, as necessary, if the SAE has not resolved at the time of initial report.

6.3.1. Adverse Events that require expedited reporting (within 24 hours)

Any SAEs or SARs or unexpected (but not serious) adverse reactions (UARs) must be reported to Monash University within 24 hours of the investigator becoming aware of the event, unless these have been specifically excluded from expedited reporting. These are SAEs that are associated with the participant's underlying disease, and will not impact on the scientific interpretation of the results of the trial.

Due to the seriousness of the underlying diseases from which the participants in this trial are suffering, the following situations that fulfil the definition of an SAE are excluded from expedited notification, but should be recorded on the SAE form and reported within 5 working days:

- Hospitalisation for pre-existing conditions that, in the investigator's opinion, have not been exacerbated by trial intervention
- Any other serious event related to the underlying disease or other medications used to treat the disease. Serious infections are not excluded from expedited notification.

6.3.2. Death

All deaths occurring on trial must be reported as an outcome on the SAE form and on the eCRFs. For all deaths, available autopsy reports (or death certificate if available) should be sent with the notification.

NB: Death is the outcome of a SAE; it cannot be the AE term unless no other information is available.

6.3.3. Investigator responsibilities

All SAEs must be assessed by, and reports signed, by an Investigator.

It will be left to the investigator's clinical judgment whether or not an adverse reaction is of sufficient severity to require that the participants should be discontinued from the treatment. A participant may also voluntarily withdraw from treatment due to what they perceive as an intolerable adverse event. If either of these occurs, it must be made clear if the participant is being withdrawn from the trial or just the trial intervention.

The Investigator is responsible for reporting SUSARs arising at their site, Significant Safety Issues (SSIs) and Urgent Safety Measures (USMs) to their Institution.

6.3.4. Sponsor responsibilities

Monash University is the trial sponsor and has ultimate responsibility for the ongoing safety evaluation of the trial. Where required, Monash University is responsible for the reporting of Australian SUSARs to the Therapeutic Goods Administration (TGA), annual safety reports to the HREC, and Significant Safety Issues (SSIs) and Urgent Safety Measures (USMs) to the TGA, HREC and Investigators. Reporting requirements in other regions is outlined in the relevant RSA.

All adverse events will be reviewed by the Chief Investigator (or a medically qualified delegate). The Chief Investigator will provide listings of all events for review by the DSMC and reports of AEs will be forwarded to the DSMC for review as often as required by the DSMC.

6.3.5. Statutory reporting

6.3.5.1. *Reporting to the Therapeutic Goods Administration*

For trials conducted under the Clinical Trials Notification (CTN) scheme Sponsors must report AEs that meet TGA criteria.

6.3.5.2. *Reporting of suspected reactions to trial treatments*

Adverse events or suspected transfusion reactions to Ig should be reported to the site's transfusion service in accordance with hospital requirements, and to the product sponsor, national blood service and/or haemovigilance programs in line with national guidelines and reporting criteria. UARs to trial antibiotics should also be reported in accordance with site and national pharmacovigilance program requirements.

6.3.6. Out of hours emergency contact information

Phone: +61 3 9903 8291

7. ETHICAL CONSIDERATIONS

7.1. Compliance

This trial is to be performed in accordance with the ethical principles of the Declaration of Helsinki (October 2013), the Integrated Addendum to ICH E6 (R1): guideline for Good Clinical Practice ICH E6 (R2) (November 2016) annotated with Therapeutic Goods Administration comments, and the NHMRC National Statement on Ethical Conduct in Human Research 2007 (Updated 2018). Sites in jurisdictions other than Australia are responsible for ensuring that their safety and ethical reports also comply with their region, as documented in the RSA.

7.2. Ethical conduct of the trial

In order to safeguard the rights, safety and well-being of participants, this protocol will be submitted to a Human Research and Ethics Committee (HREC) constituted according to the local requirements. Approval of the protocol, template Patient Information and Consent Form (PICF), participant education and recruitment materials, and other relevant trial documents will be obtained prior to the start of the trial.

The Sponsor will ensure that all conditions for approval of the trial are met and that subsequent amendments are notified to, and approved by the HREC prior to implementation.

The Sponsor will produce progress and safety reports for the HREC in accordance with their requirements. The Sponsor will keep an up to date record of all applicable documentation and correspondence with the HREC.

It is the responsibility of the Principal Investigator at each participating site to ensure that the protocol, site-specific PICF, participant education and recruitment materials, and other requested documents, as well as all subsequent amendments, are notified to the applicable local governance office. Approval must be obtained from the Sponsor, ethics committee and local governance office for the platform, and any domains in which the site plan to participate, prior to participation in those domains.

7.3. Protocol amendments

Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be agreed upon by the ITSC, and approved by the HREC prior to implementation and notified to the health authorities in accordance with local regulations.

Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be agreed upon by the TMG, and will be documented in a memorandum. The HREC may be notified of administrative changes at the discretion of the TMG.

7.4. Consent

Informed consent will be sought by the Principal Investigator or appropriately trained delegates. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH GCP and all applicable regulatory requirements. Additionally, where required per national or local guidelines, local consent for a specific study intervention (e.g. immunoglobulin replacement) will be taken by the investigator or a delegate, and stored in institutional records - this is the responsibility of the Principal Investigator.

The participant will be provided with a Patient Information and Consent Form (PICF) about the trial and written consent sought once the participant has been given the opportunity to discuss the trial with the PI or delegate.

Participants will not take part in the trial unless fully-informed consent has been obtained. No trial-specific procedures may be conducted prior to informed consent. However, any tests or procedures conducted as part of participants' routine clinical care (e.g., non-trial-specific blood tests etc.), may be utilised for baseline purposes, provided those procedures were conducted within the designated baseline period, and according to protocol requirements.

Participants who are already enrolled in the platform and are rotating from one domain to the next will not need to be re-consented to the platform at the time of rotation, but they will need to be consented to the subsequent domain. Per local Investigator discretion and local site procedures, the participant may be reconsented to the platform if a considerable amount of time has lapsed since the original platform consent was obtained.

7.5. Patient confidentiality and access to data

CRFs, clinical notes and administrative documentation should be kept in a secure location (for example, locked filing cabinets in a room with restricted access) and held for a minimum of 15 years after the end of the trial, depending on regional requirements. During this period, all data should be accessible to the competent authorities and the Sponsor with suitable notice.

All laboratory specimens, reports, data collection, process, and administrative forms will be identified by a coded ID [*identification*] number only to maintain participant confidentiality.

Following completion of analysis, the trial database will be archived for at least 15 years in accordance with Monash University policy.

8. INDEMNITY AND FINANCE

Indemnity arrangements will be described in the clinical trial research agreement (CTRA) which will be in place with each participating site.

Initial funding for this trial has been provided by the National Health and Medical Research Council (NHMRC) and Medical Research Future Fund with clinical trial management support from the TRU, Monash University, Australia. Details of payments to sites to cover the research costs will be provided in the CTRA.

Declaration of interests

None of the individuals named in this protocol have any competing interests to declare.

9. PUBLICATION

9.1. Dissemination

The results from different centres will be analysed together and published as soon as possible. Individual clinicians must not publish data concerning their patients that are directly relevant to questions posed by the trial until the ITSC has published its report. The ITSC will form the basis of the Writing Committee and will advise on the nature of publications.

9.2. Authorship

Authorship of final papers will consist of persons who have made a significant contribution to design, management and/or recruitment of the clinical trial and in accordance with the trial authorship policy. Authorship of the publication and significant contribution shall be considered by the Trial Writing Committee.

9.3. Timing

No data may be made public before publication and never without agreement from the CIs.

9.4. Acknowledgements

The Study Funder, Sponsor and the relevant Trial Committees must be acknowledged on all publications as well as the role of the Clinical Trials Unit in providing support for and running this study. All contributing PIs must be listed.

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