SUPPLEMENTARY APPENDIX

Participating sites and site investigators

Concord Repatriation General Hospital, Sydney, Australia - Prof Judith Trotman

Canberra Hospital, Canberra, Australia - Dr Philip Crispin

Monash Health, Melbourne, Australia - A/Prof Zoe McQuilten

Waikato Hospital, Waikato, New Zealand - Dr Humphrey Pullon

CCDHB, Wellington Regional Hospital, Wellington, New Zealand - Dr Robert Weinkove

Fiona Stanley Hospital, Perth, Australia - Dr Dominic Pepperell

Royal Hobart Hospital, Hobart, Australia - Dr Anna Johnston

Supplementary Methods

Participant inclusion and exclusion criteria:

Patient inclusion criteria

Patients are eligible for this trial if:

- Aged ≥ 18 years of age.
- Acquired hypogammaglobulinemia secondary to a hematological malignancy.
- Meet the Australian National Blood Authority Criteria for the Clinical Use of IVIg for secondary hypogammaglobulinemia (i.e. total IgG below local lower limit of reference range [excluding paraprotein] and history of recurrent or severe bacterial infection(s) OR IgG < 4 g/L [excluding paraprotein]).
- Life expectancy > 12 months.
- Willing and able to attend for monthly IVIg infusion or to self-administer subcutaneous immunoglobulin.
- Able to give informed consent to participate.

Patient exclusion criteria

Patients will not be eligible for this study if they fulfil any of the following criteria:

- Patient unwilling or unable to give informed consent.
- Allogeneic hematopoietic stem cell transplantation recipient.

- Patient has an objection to receiving immunoglobulin.
- Known severe IgA deficiency.
- Patients with an allergy to antibiotics
- History of anaphylactic reaction to human immunoglobulin preparation.
- Patient already receiving daily antibiotic prophylaxis for the purpose of preventing bacterial infection. Patients receiving dapsone or intermittently-dosed cotrimoxazole for PJP prophylaxis are not excluded from the study.
- Patient has received immunoglobulin replacement in the preceding 3 months.
- Current active infection requiring systemic antimicrobial agents.
- Anticipated prolonged (4 weeks or more) significant cytopenias, defined by neutrophils < 0.5 x10^9/L or platelets < 50 x10^9/L, precluding regular cotrimoxazole. Temporary cytopenia/s due to therapy are not an exclusion.
- History of epilepsy.
- Pregnant or breastfeeding.
- Severe renal impairment (creatinine clearance of <30ml/min).
- Previous splenectomy.

Supplementary Results

Supplementary Table 1: All infections by treatment arm

Infection	Overall, **N = 141**[1]	IVIg, **N = 57**	Oral Antibiotics, **N = 84**
Sinus infection	11	6	5
Upper respiratory tract infection	43	18	25
Lower respiratory tract infection	27	7	20
Influenza	1	0	1
Cellulitis	14	11	3
Conjunctivitis	2	2	0
Gastroenteritis	5	2	3
Urinary tract infection	13	6	7
Fever unknown source	9	2	7
Sepsis	1	1	0
Fungal skin infection	1	0	1
Oral infection (not candida)	6	1	5
Oral candida	5	1	4
Central venous access device infection	1	0	1
Herpes zoster virus	2	0	2

Supplementary Table 2: All Grade 3 or higher infections by treatment arm

Infection	Overall, **N = 26**[1]	IVIg, **N = 5**	Oral Antibiotics, **N = 21**
Lower respiratory tract infection	12	3	9
Influenza	1	0	1
Cellulitis	1	0	1
Gastroenteritis	1	0	1
Urinary tract infection	2	0	2
Fever unknown source	6	1	5
Sepsis	1	1	0
Oral infection (not candida)	1	0	1
Central venous access device infection	1	0	1

Supplementary Table 3: All adverse events (Safety set)

Characteristic	**IVIg**, N = 20	**Oral Antibiotics**, N = 40
Patients with any AE, n (%)	19 (95)	37 (92)
Patients with Max Grade = 3, n (%)	8 (40)	15 (38)
Patients with Max Grade = 4, n (%)	1 (5.0)	0 (0)
Patients with Max Grade = 5, n (%)	1 (5.0)	1 (2.5)^

^One death occurred in the antibiotic arm after completion of the 12-month trial period, however the onset date for the infection adverse event was before 12 months.

Supplementary Table 4: Treatment-related* adverse events (Safety set)

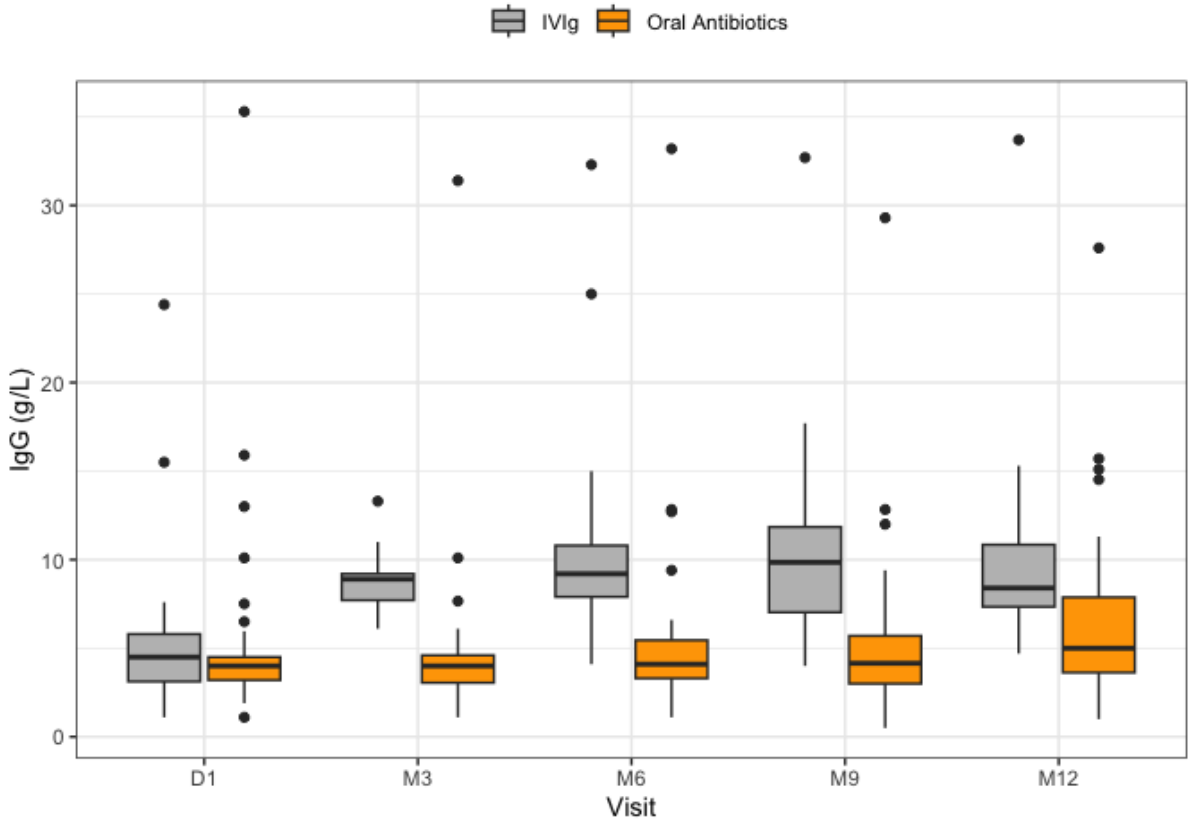
Characteristic	**IVIg**, N = 20	**Oral Antibiotics**, N = 40
Patients with any AE, n (%)	5 (25)	11 (28)
Patients with Max Grade = 3, n (%)	3 (15)	2 (5.0)
Patients with Max Grade = 4, n (%)	0 (0)	0 (0)
Patients with Max Grade = 5, n (%)	0 (0)	0 (0)

*Defined as possibly, probably or definitely related to the allocated treatment intervention

Supplementary Table 5: P-value for the interaction between intervention arm and time for QLQ-C30 measures

QLQ-C30 measure (scale)	p-value
Global health status (QL2)	0.515
Physical functioning (PF2)	0.582
Role functioning (RF2)	0.269
Emotional functioning (EF)	0.679
Cognitive functioning (CF)	0.534
Social functioning (SF)	0.291
Fatigue (FA)	0.59
Nausea and vomiting (NV)	0.083
Pain (PA)	0.287
Dyspnoea (DY)	0.987
Insomnia (SL)	0.076
Constipation (CO)	0.25
Diarrhoea (DI)	0.082
Financial difficulties (FI)	0.649
Appetite loss (AL)	0.587

Supplementary Figure 1: IgG levels by treatment arm at baseline and at 3, 6, 9 and 12 months following randomization



RATIONAL

Role of Antibiotic Therapy or Immunoglobulin On iNfections in hAematoLogy

A randomised controlled feasibility trial comparing the efficacy of prophylactic immunoglobulin with prophylactic antibiotics in patients with acquired hypogammaglobulinemia secondary to haematological malignancies.

Protocol

Version 2.1

06 July 2020

TABLE OF CONTENTS

STUDY ADMINSTRATION AND STRUCTURE

Coordinating Centre & Data Management Centre

Responsibilities

- Overall management of the study including assistance with HREC applications
- Management of study budget and liaison with funding bodies
- Protocol and case report form (CRF) design and production
- Database design and management
- Protocol training of research coordinators and study team
- Preparation and arrangement of investigator payments
- Study set-up
- Coordination of data entry and feedback of data enquiries
- Organisation of investigator meetings
- Serious adverse event notification
- Data analysis and collaboration on publications

Trial Management Committee

Members

Name		Affiliation
Dr Philip Crispin	Consultant Haematologist	Canberra Hospital, Canberra, ACT
Dr Michael Gilbertson	Consultant Haematologist	Monash Medical Centre, Melbourne, VIC
Dr Anastazia Keegan	Consultant Haematologist	Fiona Stanley Hospital, Perth, WA
Dr Zoe McQuilten	Senior Research Fellow Consultant Haematologist	Monash University, Melbourne, VIC Monash Medical Centre, Melbourne, VIC
Dr Orla Morrissey	Consultant Infectious Diseases Physician	Alfred Health, Melbourne, VIC
A/Prof John Reynolds	Scientific Director, Biostatistics Consulting Platform	Monash University, Melbourne, VIC
A/Prof Judith Trotman	Director, Clinical Research Unit & Consultant Haematologist	Concord Hospital, Sydney, NSW
A/Prof Constantine (Con) Tam	Director of Haematology	St Vincent's Hospital, Melbourne, Vic
Dr Robert Weinkove	Consultant Haematologist & Clinical Research Fellow	Capital and Coast District Health Board & Malaghan Institute of Medical Research, Wellington, NZ
A/Prof Erica Wood	Head, Transfusion Research Unit, Monash University	Monash University, Melbourne, VIC Monash Medical Centre, Melbourne, VIC
Ms Amber Degelia Tina van Tonder	Project Co-ordinator	Monash University, Melbourne, VIC
Mr Neil Waters	Project Manager	Monash University, Melbourne, VIC

Responsibilities

Overseeing all aspects of the study management including

- Liaison with coordinating centre staff
- Overseeing funding applications
- Overseeing disbursement & administration of funds
- Ensuring fiscal responsibilities are maintained
- Development and approval of final protocol & study materials
- Development and approval of data collection tools and methods
- General study management issues

Contact Details

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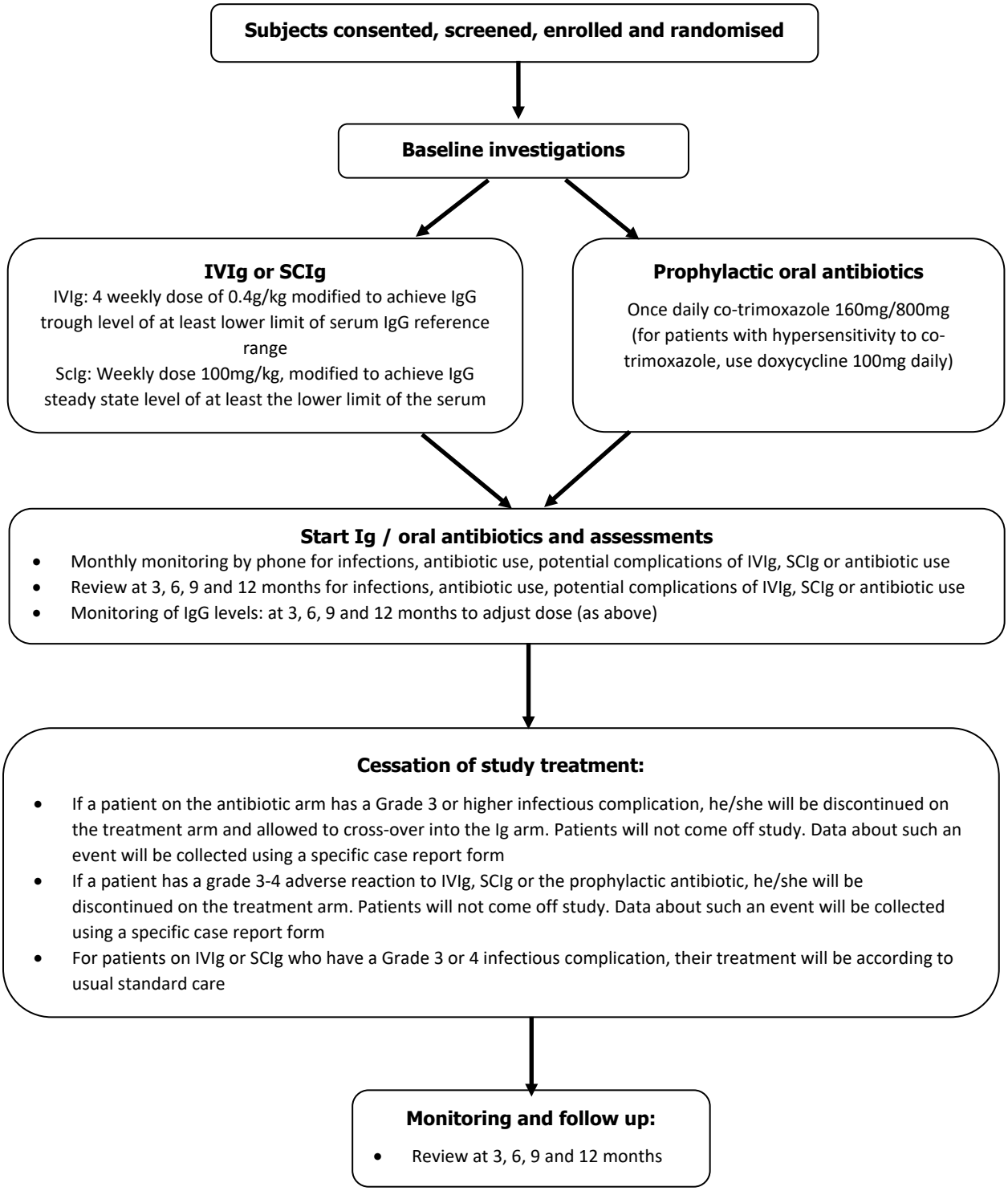
SYNOPSIS

Scientific title of clinical trial	A randomised controlled feasibility trial comparing the efficacy of prophylactic immunoglobulin with prophylactic antibiotics in patients with acquired hypogammaglobulinemia secondary to haematological malignancies.
Public title of clinical trial	Role of Antibiotic Therapy or Ig On iNfections in hAematoLogy
Protocol Short Title/Acronym	RATIONAL
Protocol Version and Date	V2.1 06 July 2020
Primary Sponsor	Monash University
Funders	National Blood Authority (Australia)
Primary Clinical Trials Registry number	ACTRN12616001723471p
Date Trial Registered	16/12/2016
Secondary Identifying Numbers	None
Trial design	• Phase II • Randomised, controlled, parallel, feasibility trial • Patients will be randomised to receive Ig (IV or SC) or prophylactic antibiotics in a 1:2 ratio. Randomisation will be stratified by site • The study will not be blinded. Infectious outcomes and adverse events will be adjudicated by independent committees
Health Condition(s) or Problem(s) Studied	Patients with acquired hypogammaglobulinemia secondary to haematological malignancies.
Key inclusion and exclusion criteria	Patient inclusion criteria: Patients are eligible for this trial if: • Aged ≥ 18 years of age • Acquired hypogammaglobulinaemia secondary to a haematological malignancy • Meet the Australian National Blood Authority Criteria for the Clinical Use of immunoglobulin (Ig) replacement for secondary hypogammaglobulinaemia (i.e. total IgG below local lower limit of reference range [excluding paraprotein] and history of recurrent or severe bacterial infection(s) OR IgG < 4 g/L [excluding paraprotein]) • Life expectancy > 12 months • Willing and able to attend for monthly IVIg infusion or to self-administer subcutaneous immunoglobulin • Able to give informed consent to participate Patient exclusion criteria: Patients will not be eligible for this study if they fulfil any of the following criteria: • Patient unwilling or unable to give informed consent • Allogeneic haematopoietic stem cell transplantation recipient • Patient has an objection to receiving immunoglobulin • Known severe IgA deficiency • Known allergy or intolerance to both co-trimoxazole and doxycycline History of anaphylactic reaction to human immunoglobulin preparation • Patient already receiving daily antibiotic prophylaxis for the purpose of preventing bacterial infection. Patients receiving dapsone or intermittently-dosed cotrimoxazole for PJP prophylaxis are *not* excluded from the study • Patient has received immunoglobulin replacement in the preceding 3 months • Current active infection requiring systemic antimicrobial agents

	• Anticipated prolonged significant cytopenias, defined by neutrophils < 0.5 x10^9/L or platelets < 50 x10^9/L, precluding regular cotrimoxazole. Temporary cytopenia/s due to therapy are not an exclusion • Pregnant or breastfeeding • Severe renal impairment (creatinine clearance of <30ml/min) • Previous splenectomy
Setting	Coordinating centre: • Monash University Transfusion Research Unit Participating hospitals: • The Canberra Hospital (ACT) • Concord Hospital (NSW) • Monash Health (VIC) • Fiona Stanley Hospital (WA) • Capital & Coast District Health Board, Wellington (NZ) • Royal Hobart Hospital (TAS) • Waikato Hospital (NZ)
Interventions to be compared	Patients will be randomised to one of the two study arms: **1. <u>Prophylactic Immunoglobulin</u>** • IVIg: In accordance with National (Australian) Criteria for the Clinical Use of IVIg in Australia. Monthly (every 4 weeks ± 1 week) dose starting at 0.4g/kg, modified to achieve an IgG trough level of at least lower limit of serum IgG reference range. In the first month of therapy, if IgG < 4g/L then an additional (loading) dose of 0.4g/kg may be given at the clinician's discretion. • SCIg: Subcutaneous immunoglobulin weekly may be used in patients who meet local criteria for home-based self-administration in centres with established SCIg programs. A loading IVIg dose may be given in the first month if required. Thereafter, dosing 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 to or from IVIg to SCIg, 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. **2. <u>Prophylactic oral antibiotics:</u>** Once daily trimethoprim-sulfamethoxazole (co-trimoxazole) 160mg/800mg. For patients with hypersensitivity to co-trimoxazole, doxycycline 100mg daily.
Trial hypothesis	The hypothesis is that in patients with acquired hypogammaglobulinemia secondary to a haematological malignancy, immunoglobulin replacement and oral antibiotics are similarly effective in preventing clinically significant infections.
Primary outcome measure(s)	Proportion of patients alive who remain on assigned treatment arm at 12 months following randomisation.
Secondary outcome measure (s)	• Time to first major infection (Grade 3 or higher according to Common Terminology Criteria for Adverse Events (CTCAE)); all infections • Number of clinically significant infections (defined as presence of symptoms or signs of infection requiring treatment) • Number of microbiologically documented infections • Time to first microbiologically confirmed infection • Susceptibility profile – proportion in each arm with fluoroquinolone

	resistant organisms, co-trimoxazole resistant organisms, extended spectrum beta lactamases or multidrug resistant organisms • All-cause mortality • Infection-related mortality (defined as death within 7 days of diagnosis of infection, confirmed by microbiological means) • Time free from hospitalisation and intravenous antibiotics • Number of treatment-related adverse events • Trough IgG level (or steady state level for SCIg) at 3, 6, 9, 12 months following randomisation • Costs associated with allocated treatment arm and infections during study • Quality of life (QoL) measured at randomisation, 3, 6, 9 and 12 months
Duration of Trial	• The trial will recruit over 24 months • Participants are followed up for 12 months from commencing study treatment • Quality of life data will be collected at baseline then at 3, 6, 9 and 12 months • The planned trial duration is 30 months from initiation of first site to completion of analysis
Countries of recruitment	Australia, New Zealand
Target Sample Size	60 patients at 5 Australian and two New Zealand trial sites 20 subjects will be enrolled to receive Ig (IV or SC) and 40 to receive co-trimoxazole or other antibiotic as appropriate.
Date of first enrolment	December 2016
Recruitment Status	Recruiting
Ancillary Studies/sub-studies	None planned
Contact Details for Public Queries	Neil Waters: neil.waters@monash.edu
Contact Details for Scientific Queries	Dr Zoe McQuilten zoe.mcquilten@monash.edu
Project Manager	Neil Waters
Lay Summary of Trial	The RATIONAL project seeks to understand whether oral antibiotics can be used instead of immunoglobulin (Ig, a blood product made from human plasma) to reduce the risk of infections in people with blood cancers. 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. Over 20% of all Ig issued in Australia is used to try to prevent infections in patients with blood cancers. Even though blood products like Ig used in Australia are very safe, they do still carry some risks and should only be used when really needed. Ig is also expensive and Australia is one of the highest users of Ig in the world, at a cost of hundreds of millions of dollars annually. In some countries, for patients with low immunoglobulin levels, a trial of oral antibiotics is used before commencing Ig, to see whether antibiotics might be enough to reduce the chances of getting an infection. However, we need more information on how these two different interventions compare in terms of benefits, risks and costs. This research aims to improve how we use Ig in Australia by asking: Are prophylactic (preventive) oral antibiotics equivalent to immunoglobulin replacement in reducing the risk of serious infections in adults with blood cancers? The RATIONAL (Role of antibiotic therapy or Ig on infections in haematology) trial is a feasibility study to ask and answer important practical questions before proceeding to a larger clinical trial.

TRIAL SCHEMA



TRIAL SCHEDULE – ASSESSMENTS AND INVESTIGATIONS

Trial assessment	Enrolment	Day 1	3 months	6 months	9 Months	12 months
Eligibility assessment	X					
Informed consent	X					
Demographics and medical history	X					
Quality of life assessment		X	X	X	X	X
Health economic evaluation						X
Baseline investigations						
• IgG Levels	X		X	X	X	X
• Biochemistry (renal function, liver function)	X					
• Full blood count	X					
Review						
• Clinical information (including hospitalisations, prescribed medications, investigations, procedures)			X	X	X	X
• Laboratory tests (including biochemistry, full blood count and microbiological investigations)			X	X	X	X

ABBREVIATIONS AND GLOSSARY

CI	Chief Investigator
CLL	Chronic Lymphocytic Leukaemia
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DEPM	Department of Epidemiology and Preventive Medicine
DSMC	Data Safety Monitoring Committee
eGFR	estimated Glomerular Filtration Rate
FBC	Full blood count
GCP	Good Clinical Practice
HR	Human Resources
HREC	Human Research Ethics Committee
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
Ig	Immunoglobulin
IVIg	Intravenous immunoglobulin
MBS	Medicare Benefits Schedule (Australia)
MM	Multiple Myeloma
MMC	Monash Medical Centre Clayton, Monash Health
NBA	National Blood Authority (Australia)
NHL	Non-Hodgkin Lymphoma
NHMRC	National Health and Medical Research Council (Australia)
OAC	Outcome Adjudication Committee
QoL	Quality of Life
RBC	Red Blood Cell
SAE	Serious Adverse Event
SCIg	Subcutaneous immunoglobulin
SPHPM	School of Public Health and Preventive Medicine
TMC	Trial Management Committee

BACKGROUND AND RATIONALE

Australia has one of the highest uses per capita of intravenous immunoglobulin (IVIg) in the world. Patients with acquired hypogammaglobulinaemia due to haematological malignancies are the largest single group for whom IVIg is issued in Australia, accounting for 21.5% of all IVIg issued in 2013-14, with a 1.6 fold increase since 2009, with a conservative estimated product cost of approximately $40 million.[1]

Evidence for Ig replacement in acquired hypogammaglobulinemia

Acquired hypogammaglobulinaemia is common in haematological malignancies including non-Hodgkin lymphoma (NHL), chronic lymphocytic leukaemia (CLL) and multiple myeloma (MM), and is associated with reduced ability to mount antibody responses to a range of infectious agents and vaccinations.[2, 3] Consequences include increased susceptibility to infections, particularly caused by encapsulated bacteria, which contribute to morbidity, mortality and healthcare resource use. Bacterial infections have been shown to be the most common infections in CLL and MM.[4, 5]

Immunoglobulin replacement is frequently used to reduce the likelihood, frequency and/or severity of infections, based on randomised controlled trials (RCTs) that demonstrated reduction in major infections necessitating inpatient treatment and intravenous antibiotics or clinically documented infections.[6, 7] The most recent Cochrane systematic review on the efficacy of IVIg for this indication identified 10 trials and demonstrated a significant decrease in occurrence of major infections, but no change in survival.[8] However, only 2 studies examined mortality at 12-months and only 3 trials included clinically and microbiologically documented infections. Therefore, the meta-analysis for efficacy in prevention of infection included only 205 patients.[8] There were also insufficient numbers for subgroup analyses (including IgG levels or past history of infection) to investigate whether there are patients more or less likely to benefit from IVIg. In addition, all of these trials were published in the 1980s and 1990s, with major changes in treatment of both underlying diseases and infection having occurred since these trials were undertaken. An updated systematic review, published in 2009, did not identify any new trials and concluded that “contemporary RCTs on IVIg prophylaxis are needed to assess the effect of IVIg on infectious morbidity and overall survival at present. Physicians caring for these patients should be encourage to include them in such trials”.[9]

Therefore, the available evidence of efficacy of prophylactic Ig (either given IV or subcutaneous) pre-dates modern treatment for haematological malignancies, which limits applicability to current practice, including which patients are most likely to benefit. Important changes that limit the applicability of these findings include major changes in the therapies used and overall survival for CLL, MM and NHL, differences in Ig preparation and route of administration and management of infections, including hospitalisation days and antibiotic therapy, all of which may alter the costs and benefits of Ig.

Patients are living longer due to availability and widespread use of newer therapeutics[10], which may have effects on risk of infection over time. In addition, introduction of newer therapies may change the severity and frequency of infections, in unpredictable ways.[7, 9, 11, 12] For example, ibrutinib, a Bruton tyrosine kinase [BTK] inhibitor) used for CLL, has been shown to lead to overall decrease in IgG at 24 months of treatment (median 23% reduction, IQR 9-37%); however this is associated with a reduction in infection rate over time on ibrutinib with evidence of recovery of normal B cells and increase in IgA.[12] A recent Australian review of infection in patients undergoing treatment for MM identified a bimodal distribution of peak infections, with a late risk in incidence of bacterial and viral infections coinciding with end-stage disease, likely due to cumulative effects of multiple treatments on the immune system.[4] Therefore, risk of infection over the course of disease for patients with MM, CLL and NHL has likely changed substantially since the previous studies examining the efficacy of IVIg. Supportive care and antimicrobial treatments have also improved since the original IVIg studies were performed. Therefore, new studies are required to re-evaluate which patients are most likely to benefit from Ig (either IV or SC) prophylaxis, and at which time point.

Although Ig is a pathogen-reduced fractionated plasma product with very low infectious risks, other serious side-effects can occur.[9, 13] These include allergic reactions, haemolysis (due to passive anti-A, anti-B and occasionally anti-D), aseptic meningitis syndrome, renal dysfunction and acute renal failure and thromboembolic events.[14] A recent study of over 20 years of Medicare claims data linked with cancer registry data from the United States reported an increased risk of acute myocardial infarction and ischemic stroke during the first 24 hours after IVIg infusion in CLL and MM patients with acquired hypogammaglobulinaemia.[15] The authors recommended that these possible risks should be considered when weighing the possible risks of IVIg against its therapeutic benefit in this patient population.

No new studies have been published, nor are there any ongoing trials registered on the use of prophylactic Ig.

Variation in practice – nationally and internationally

Substantial variation exists in the approach to immunoglobulin replacement, both internationally and within Australia,[6, 16] in relation to indications for commencing therapy and requirements for prior, adjunctive or alternative therapies.

In the UK, access to IVIg for patients with secondary hypogammaglobulinaemia requires recurrent infections despite continuous oral antibiotic therapy for 3 months. In Australia, based on national criteria, patients with EITHER IgG <4g/L, OR hypogammaglobulinemia and recurrent infections, are eligible for IVIg prophylaxis.[17]

Prophylactic oral antibiotics -- an alternative to immunoglobulin for initial therapy for some patients?

As noted above, international guidelines recommend a trial of prophylactic antibiotics prior to Ig, and only commence immunoglobulin replacement if the patient experiences a major or recurrent minor bacterial infections.[18] However, no studies have reported results directly comparing the efficacy of antibiotics to Ig prophylaxis in terms of infection prevention. Prophylactic oral antibiotics have been shown to reduce infections by 30-50% in neutropenic haematology patients following chemotherapy[19], and in non-haematologic malignancy patients with bronchiectasis,[20] supporting the rationale for their use in acquired hypogammaglobulinaemia. Bacterial infections have been shown to be the most common infections in acquired hypogammaglobulinaemia, however no studies have evaluated the efficacy of prophylactic antibiotics in this patient group. In addition, no studies have directly compared the efficacy of antibiotics to immunoglobulin prophylaxis in terms of infection prevention.

Potential advantages include reduced total healthcare costs, possible improvements to quality of life (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,[20, 21] and clinical interactions that might improve care by providing early opportunities to proactively manage infection may be reduced if patients attend day treatment centres less frequently. Therefore, their use should be properly evaluated with respect to efficacy, safety, QoL, and healthcare costs.[22]

Potential cost savings:

Around 3700 patients with haematologic malignancies received 862,898g of IVIg across Australia in 2013-14.[1] If all patients had received imported IVIg, costs would conservatively be in the order of $40 million for that period. Hospital direct (e.g. product administration) and indirect (inventory management, adverse events) costs are poorly documented but undoubtedly add to overall costs.

If antibiotic prophylaxis (e.g, co-trimoxazole, annual cost $464.00 per person) were equivalent in preventing infection, and some current or future patients received antibiotics instead of IVIg or SCIg for even a proportion of their treatment period, millions of dollars could be saved annually.

The need for a trial comparing prophylactic immunoglobulin with antibiotics

Immunoglobulin replacement is effective at reducing infection in this setting, BUT:

- 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 and SCIg carries 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.
- IVIg and SCIg costs continue to increase, and haematological malignancies are a growing indication.
- Changes in practice may bring unforeseen and unintended consequences.

Therefore, clinical equipoise exists.[22] Careful studies with local data are required to inform Australian policy and healthcare resource allocation, and guide day-to-day patient management and efficient use of Ig.

Before we can embark on a definitive, phase III RCT powered for clinical outcomes, we must first demonstrate the feasibility of randomising patients with acquired hypogammaglobulinaemia to prophylactic antibiotics or Ig (IVIg and SCIg) and determine the rates and outcomes of all infections.

AIMS AND OUTCOMES

Aims

The aims of this study are to:

- Determine the feasibility of delivering prophylactic antibiotics as an alternative to Ig (IVIg or SCIg) in patients with haematological malignancies and acquired hypogammaglobulinaemia
- Determine the incidence of clinically important (Grade 3 or higher – see below) infections to inform sample size calculations for a larger future trial
- Compare costs of Ig with prophylactic antibiotics in this setting

Primary outcome

Proportion of participants alive who remain on assigned treatment arm at 12 months following randomisation.

Secondary outcomes

- Time to first major infection (Grade 3 or higher according to CTCAE)
- Number of infections (defined as presence of symptoms or signs of infection requiring treatment
- Number of microbiologically documented infections
- Time to first microbiologically confirmed infection
- Susceptibility profile – proportion in each arm with fluoroquinolone resistant organisms, co-trimoxazole resistant organisms, extended spectrum beta lactamases or multidrug resistant organisms
- All-cause mortality
- Infection related mortality (defined as death within 7 days of diagnosis of infection by microbiological means)
- Time free from hospitalisation and intravenous antibiotics
- Number of treatment-related adverse events
- Trough IgG level (or steady state level for SCIg) at 3, 6, 9, 12 months following randomisation.
- Costs associated with allocated treatment arm and infections during study
- Quality of life (QoL) measured at randomisation, 3, 6, 9 and 12 months

Setting

This trial will be conducted in seven participating hospitals:

- The Canberra Hospital (ACT)

- Concord Hospital (NSW)
- Monash Medical Centre (VIC)
- Fiona Stanley Hospital (WA)
- Capital & Coast District Health Board (NZ)
- Royal Hobart Hospital (TAS)
- Waikato Hospital (NZ)

And coordinated from:

- Monash University Transfusion Research Unit

SELECTION OF PARTICIPANTS

Eligibility

Patients will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria detailed below.

Patient inclusion criteria

Patients are eligible for this trial if:

- Aged ≥ 18 years of age
- Acquired hypogammaglobulinaemia secondary to a haematological malignancy
- Meet the Australian National Blood Authority Criteria for the Clinical Use of IVIg for secondary hypogammaglobulinaemia (i.e. total IgG below local lower limit of reference range [excluding paraprotein] and history of recurrent or severe bacterial infection(s) OR IgG < 4 g/L [excluding paraprotein])
- Life expectancy > 12 months
- Willing and able to attend for monthly IVIg infusion or to self-administer subcutaneous immunoglobulin
- Able to give informed consent to participate

Patient exclusion criteria

Patients will not be eligible for this study if they fulfil any of the following criteria:

- Patient unwilling or unable to give informed consent
- Allogeneic haematopoietic stem cell transplantation recipient
- Patient has an objection to receiving immunoglobulin
- Known severe IgA deficiency.
- Patients with allergy or intolerance to both co-trimoxazole and doxycycline;
- History of anaphylactic reaction to human immunoglobulin preparation
- Patient already receiving daily antibiotic prophylaxis for the purpose of preventing bacterial infection.
- Patients receiving dapsone or intermittently-dosed cotrimoxazole for PJP prophylaxis are not excluded from the study
- Patient has received immunoglobulin replacement in the preceding 3 months
- Current active infection requiring systemic antimicrobial agents
- Anticipated prolonged (4 weeks or more) significant cytopenias, defined by neutrophils < 0.5 x10^9/L or platelets < 50 x10^9/L, precluding regular cotrimoxazole. Temporary cytopenia/s due to therapy are not an exclusion
- Pregnant or breastfeeding
- Severe renal impairment (creatinine clearance of <30ml/min)
- Previous splenectomy

Screening and Recruitment

A screening log will be completed on all patients admitted to the participating units with a diagnosis of acquired hypogammaglobulinaemia secondary to haematological malignancy. The log will include age, and main diagnosis. It will include patients approached but in whom consent was not obtained for the trial (with reasons) and therefore will define how representative randomised patients are as a group relative to the group of eligible patients who were not randomised.

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

Each participant will be assigned a unique trial number consisting of 6 digits, the first 3 digits denoting the site number and the remaining 2 the patient number from 01 to 99. The trial number will be recorded on the screening log.

RANDOMISATION

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.

Randomisation will be stratified by site and balanced within blocks of varying, undisclosed sizes.

Patients who are assessed by their clinician as requiring commencement of IVIg and meeting inclusion and exclusion criteria will be enrolled and randomised into one of the two intervention arms, either Ig (IVIg/SCIg) or prophylactic antibiotics.
The study research personnel will allocate participants to the intervention arms using randomisation schedules. These schedules will be held in a locked area in the Transfusion Research Unit in Monash University. The randomisation schedule will be prepared centrally by the study statistician.
There is a schedule for each individual research site.
Each randomisation code will be numbered with a 6-character randomisation number in the format Rssspp where Rss is the site number and ppp is a three digit number for the participant.
The schedule will contain the randomisation number and which arm of the trial the participant is randomised to.
Schedules must be followed in sequential number order.
The randomisation number must be recorded on the case report form (CRF) where indicated.
The date and time of randomisation and the trial number of the participant will be entered on a list of randomisation numbers on the randomisation schedule to act as a check that the randomisation is sequential.

The local PI/delegate is responsible for informing the patient's consultant/physician of the patient's participation in the trial, and for placing a label indicating trial participation on the cover of the patient's medical notes or as a note in the electronic notes.

The study will not be blinded. Infectious outcomes and adverse events will be adjudicated by independent committees.

TREATMENT OF PATIENTS

The trial has an Ig arm (IVIg/ SCIg) and a prophylactic antibiotic arm.

Interventions

Prophylactic immunoglobulin

IVIg:
Participants will be treated in accordance with national Criteria:[17]
Monthly (every 4 weeks ± 1 week) dose of 0.4g/kg, modified to achieve an IgG trough level of at least lower limit of age-specific serum IgG reference range. In the first month of therapy, if IgG <4g/L then an additional (loading) dose of 0.4g/kg may be given at the clinician's discretion.

SCIg:
Subcutaneous immunoglobulin weekly may be used in patients who meet local criteria for home based self-administration in centres with established SCIg programs. A loading IVIg dose may be given in the first month if required. Thereafter, dosing 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, 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.

Prophylactic oral antibiotics:

Participants will be treated with once daily trimethoprim-sulfamethoxazole (cotrimoxazole) 160mg/800mg, with dose adjustments as listed below. For patients with hypersensitivity to co-trimoxazole, 100mg doxycycline daily will be permitted as an alternative prophylactic antibiotic. Participants must be able to tolerate at least one of the study antibiotics to be eligible for entry into the study.

If participants encounter cytopenias which are exacerbated by the study antibiotics, participants can be switched to the other antibiotic or to IVIg.

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	Action
more than 50 mL/Min	Full dose (160/800mg)
25 to 50 mL/Min	50% dose reduction to 80/400mg)
< 25 mL/Min	Discuss with TMC, then consider switching to doxycycline, or withdraw from study

Other 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 on low-dose co-trimoxazole for Pneumocystis jiroveci pneumonia prophylaxis will continue if allocated to Ig, or have the dose increased if allocated to the antibiotic arm of the study.

It is recommended that all participants receive routine vaccinations, including pneumococcal vaccine, as part of their usual care and have measurement of pre- and post-vaccination pneumococcal responses.

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

Discontinuation

If a participant on the antibiotic arm has a Grade 3 or higher infectious complication, he/she will be discontinued on the treatment arm and be allowed to cross-over into the Ig (IVIg/SCIg) arm. Patients will not come off study. Data about such an event will be collected using a specific case report form. For patients on Ig who have a Grade 3 or higher infectious complication, their treatment will be according to usual standard care. If patients have a grade 3-4 adverse event on either treatment, they will be discontinued on allocated treatment. Patients will not come off study and will continue to have data collected.

ASSESSMENTS AND REVIEW

Assessments

Demographics and medical history

- Date of birth
- Gender
- Weight
- Height
- Diagnosis
- Disease stage
- Performance status
- Previous treatment for primary disease (CLL, MM or NHL) including cumulative steroid dose
- Current therapy for primary disease (CLL, MM or NHL)
- Co-morbidities
- Pneumococcal vaccination status

Laboratory results

- Immunoglobulin levels at baseline
- Renal function
- Full blood count (FBC)
- Liver function
- Pneumococcal antibody response

Review at 3, 6, 9 and 12 months:

- Infectious events in preceding three months – date of onset, radiological and microbiological investigation results, admission to hospital, treatment received (antibiotics, antiviral, antifungal therapy), interventions required (surgery, endoscopy, etc), hospital admission and length of stay, ICU admission and length of stay
- Hospital admissions in preceding three months
- Date and dose of IVIg and SCIg infusions in preceding three months
- Antibiotic, antifungal and antiviral use in preceding three months
- Granulocyte colony stimulating factor (G-CSF) use (including pegylated GCSF)
- Treatment received for primary disease in preceding three months
- Quality of life assessment (EQ-5D-5L, EORTC QLQ-C30 & FACT-N) at randomisation, and at 3, 6, 9 and 12 month
- Laboratory results (FBC, renal function, IgG level)
- Death – date and cause

Outcome adjudication committee (OAC)

An outcome adjudication committee, comprising of three infectious disease experts, will be established prior to patient enrolment. The OAC will be responsible for reviewing and adjudicating on: time to first major infection; clinically significant infections; microbiologically documented infection; susceptibility profile of microbiologically documented infections, infection-related mortality and treatment-related adverse events.

The OAC will be provided with the details of infectious events collected at 3, 6, 9 and 12 months. Details will be provided in a blinded fashion, to ensure that the OAC are not aware of which treatment arm the participant was receiving. No data on IVIG or antibiotics will be provided. All committee members will review the events individually and determine whether they meet one or more of the secondary outcomes as outlined above. All members will subsequently convene several teleconferences for final consensus decision on the secondary end-points for each trial patient.

SAFETY

Data Safety Monitoring Committee

An independent Data Safety and Monitoring Committee (DSMC), comprising experts in haematology, infectious diseases and a statistician will be established before patient enrolment. The DSMC will be responsible for safeguarding the interests of trial participants and assessing the safety during the trial. The DSMC will monitor evidence for treatment harm (e.g. SAEs, deaths) and compliance with the protocol and with previous DSMC recommendations. The DSMC will also review enrolment rates and failure rates. The DSMC will be advisory to the Trial Management Committee (TMC). The TMC will be responsible for promptly reviewing the DSMC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in study 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 clinical investigators, trial data coordinating centre, and Monash University.

Adverse events

Defined adverse events will be collected. Any undefined adverse events will be collected as free text bearing in mind that it is recognised that the patient population will experience a number of common aberrations in laboratory values, signs and symptoms due to the severity of the underlying disease and the impact of standard therapies. These will not necessarily constitute adverse events unless they are considered to be causally related to the study intervention or are otherwise considered to be of concern in the investigator's judgement.

Serious adverse events

Defined serious adverse events (SAE) will be collected. These include allergic reactions, new onset haemolysis, aseptic meningitis, renal failure (CTCAE 3 or higher), liver failure (CTCAE 3 or higher), Stevens-Johnson syndrome or other severe skin reaction, bone marrow suppression (CTCAE 3 or higher), thromboembolic event, unplanned hospitalisation or death. A SAE can be considered unexpected when the adverse reaction, the nature or severity of which is not consistent with the applicable product information or expected serious adverse events listed above.

Reporting

SAEs will be recorded on separate case report forms. SAEs which occur from the time of commencement of study treatment to 28 days post study treatment completion will be reported to the coordinating centre (Transfusion Research Unit, Monash University) by emailing the provided SAE form. A copy of the report will be forwarded to the site Pharmacy as well as to the relevant Health Research Ethics Committee (HREC). SAEs should be reported within 24 hours of study staff becoming aware of the event. Minimum information to report will include:

- Patient initials and study number
- Nature of the event
- Commencement and cessation of the event
- An investigator's opinion of the relationship between study involvement and the event (unrelated, possibly, probably or definitely related)
- Whether treatment was required for the event and what treatment was administered.

SAEs must be reported via email. Follow up reporting may be required. The SAE reports will then be forwarded to the DSMC for review and will also be forwarded to all sites for reporting to their HRECs in accordance with local requirements. Sites must also report suspected IVIg and SCIg reactions to their national/regional haemovigilance system or blood authority, as per usual reporting requirements.

STATISTICAL CONSIDERATIONS

Sample size

Our chosen sample size (n=60) is based on primary outcome of proportion of participants (alive) who remain on assigned treatment arm at 12 months following randomisation.

With a sample size of 60 patients (40 in the antibiotic arm and 20 in the IVIg arm), we will be able to estimate an adherence rate to the protocol of 80% to within a 95% confidence interval of ± 10%.

Our cautious estimate is for 1-2 patients/month per site, allowing recruitment of 60 participants over 12-18 months.

Analysis plan

All data will be initially assessed for normality. Group comparisons will be performed using chi-square tests for equal proportion, student t-tests or ANOVA for continuously normally distributed variables and Kruskal Wallis and Wilcoxon rank sum tests otherwise. Results will be reported as proportions (95% CI), means (standard deviations) or medians (interquartile range) in accordance with the underlying distribution. All analysis will be performed using STATA version 14 (StataCorp, Texas, US) and a two sided p-value of 0.05 will be used to indicate statistical significance. No adjustment for multiple comparison will be performed. All analyses will be performed according to the intention-to-treat principle and will include all enrolled patients. Sensitivity to missing data for primary outcomes will be assessed. Missing data for secondary or safety outcomes will be assumed to be missing-at-random.

ETHICS AND REGULATORY

Compliance

This study is to be performed in accordance with the ethical principles of the Declaration of Helsinki (June 1964 and amended 1975, 1983, 1989, 1996, 2000, 2008 and Note of Clarification 2002 and 2004), ICH GCP Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with Therapeutic Goods Administration comments, NHMRC National Statement on Ethical Conduct in Research Involving Humans (March 2007); the New Zealand Interim Good Clinical Research Practice Guidelines (Volume 2 1998 and Volume 3 2000) and ICH GCP Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95).

In the interests of protecting the trial participants' privacy and confidentiality of health information, the project will be conducted in compliance with the Health Records Act 2001 (Vic) Health Privacy Principles and the Information Privacy Act 2000 (Vic) Information Privacy Principles and the NHMRC Australian Code for the Responsible Conduct of Research.

Data collection, retention and access

Data will initially be handwritten onto a case report form and will subsequently entered onto a Microsoft Excel

spreadsheet and saved to the Monash University computer system which is backed up daily.

Following completion of analysis, the trial database will be archived in accordance with Monash University's policies.

The sites must keep the signed Informed Consent forms, all trial documentation and source documents collected during the trial in a secure location (e.g. locked filing cabinets in a room with restricted access). All data must be accessible to the competent authorities and the Sponsor with suitable notice for inspection. All trial documentation must be retained for at least 5 years after trial completion or termination. In addition, the Investigator must not discard or destroy any trial specific materials unless otherwise instructed by Monash University.

Ethics committee approval

This protocol will be submitted to a Human Research and Ethics Committee constituted according to the NHMRC National Statement on Ethical Conduct in Research Involving Humans (March 2007) for each Australian institution. For the New Zealand site, approval will be required from the Health and Disability Ethics Committee, in accordance with the National Ethics Guidelines for Interventional Studies for New Zealand (Ministry of Health, July 2012). Approval of the protocol and related documents will be obtained prior to the start of the study.

It is the Principal Investigator's responsibility to ensure that all conditions for approval of the study are met and that amendments to the protocol are reported to the HREC as required by that Committee.

The Principal Investigator will be responsible for obtaining ethics approval at their site. During the study, any amendment or modification to the study protocol will be notified to the independent Ethics Committee by the Principal Investigator and approved by the independent Ethics Committee before implementation.

The Coordinating Principal Investigator will produce progress reports, and any other required documentation for the local independent Ethics Committee in accordance with their guidelines. Any amendments or additions to the study protocol and material must be notified to the independent Ethics Committee by the Coordinating Principal Investigator and approved by the Ethics Committee.

It is the responsibility of the Principal Investigator at each participating hospital to keep an up to date record of all correspondence and applicable documentation with the local Independent Ethics Committee.

Consent

Informed consent will be sought by the Principal Investigators or appropriately trained delegate. At this point the patient will receive a written information sheet (Patient Information Sheet) about the study, to keep, as well as a further verbal explanation to address any questions they may have.

Each patient will be asked to sign the consent form before study participation. Patients will not be allowed to take part in the study unless fully-informed consent has been obtained.

The patients will also be informed that they have the right to withdraw from the study at any time and this will not affect their future treatment in any way. Any samples collected up until the time of withdrawal will be retained and included in the analysis.

Confidentiality of data

Data will be anonymised as soon as it is practical to do so.

FINANCE

FUNDING

The study is funded by a three-year grant from the commonwealth of Australia represented by the National Blood Authority, under the National Blood Sector Research and Development Pilot. Grant number ID124: Oral antibiotics or intravenous immunoglobulin to reduce infections in patients with blood cancers.

Declaration of interests

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

OVERSIGHT AND GOVERNANCE

Trial Management Committee (TMC)

The Trial Management Committee (TMC) will oversee the overall conduct of the trial. The list of responsibilities are given above (page 6).

Role of trial sponsor

Monash University is the sponsor for this trial. Monash University will have ultimate authority over the study design; collection, management, analysis, and interpretation of data; writing of the report; or the decision to submit the report for publication.

Role of trial funder

The National Blood Authority is the funder of this trial. The National Blood Authority has had no role in the design of the study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results for presentation or publication.

PUBLICATION

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 Trial Management Group has published its report. The Trial Management Group will form the basis of the Writing Committee and will advise on the nature of publications.

Authorship

Authorship of all publications associated with this trial will be compliant with the International Committee of Medical Journal Editors criteria for authorship.

Approvals

The TMC will see and approve the final trial publication. The Co-ordinating Investigators will see and approve any supplementary publications.

Identification

A trial identifier will be included on all presentations and publications (e.g. the ISCRTN).

Timing

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

Acknowledgements

All professionals/sites who have participated in the RATIONAL trial for a minimum of one year will be listed in the acknowledgements section of the final trial report.

PROTOCOL AMENDMENTS

Any modifications of 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 amendments will be agreed upon by the TMG and approved by the Ethics Committee prior to implementation.

Administrative changes of the protocol are minor amendments that have no effect on the way that the study is conducted. These administrative changes will be agreed by the TMC and the Ethics Committee will be informed of the minor amendment.

Revision History:

Version	Author	Date	Reason for revision
0.01	Various.	20 October 2016	Draft for review
1.2	Various	03 January 2017	Approval changes for HREC Clarifications/corrections
2.0	Various	22 August 2018	Clarifications/corrections

REFERENCES

1. National Blood Authority: **National Report on the issue and use of immunoglobulin, 2013-2014**. In.; 2014.
2. Pasiarski M, Rolinski J, Grywalska E, Stelmach-Goldys A, Korona-Glowniak I, Gozdz S, Hus I, Malm A: **Antibody and plasmablast response to 13-valent pneumococcal conjugate vaccine in chronic lymphocytic leukemia patients--preliminary report**. *PloS one* 2014, **9**(12):e114966.
3. Karlsson J, Roalfe L, Hogevik H, Zancolli M, Andreasson B, Goldblatt D, Wenneras C: **Poor Correlation between Pneumococcal IgG and IgM Titers and Opsonophagocytic Activity in Vaccinated Patients with Multiple Myeloma and Waldenstrom's Macroglobulinemia**. *Clin Vaccine Immunol* 2016, **23**(4):379-385.
4. Teh BW, Harrison SJ, Worth LJ, Spelman T, Thursky KA, Slavin MA: **Risks, severity and timing of infections in patients with multiple myeloma: a longitudinal cohort study in the era of immunomodulatory drug therapy**. *Br J Haematol* 2015, **171**(1):100-108.
5. Morrison VA: **Infectious complications of chronic lymphocytic leukaemia: pathogenesis, spectrum of infection, preventive approaches**. *Best practice & research Clinical haematology* 2010, **23**(1):145-153.
6. Paxton L, Hawkins C, Crispin P: **Selecting haematological malignancy patients for intravenous immunoglobulin**. *Intern Med J* 2016, **46**(10):1216-1218.
7. Lachance S, Christofides AL, Lee JK, Sehn LH, Ritchie BC, Shustik C, Stewart DA, Toze CL, Haddad E, Vinh DC: **A Canadian perspective on the use of immunoglobulin therapy to reduce infectious complications in chronic lymphocytic leukemia**. *Curr Oncol* 2016, **23**(1):42-51.
8. Raanani P, Gafter-Gvili A, Paul M, Ben-Bassat I, Leibovici L, Shpilberg O: **Immunoglobulin prophylaxis in hematological malignancies and hematopoietic stem cell transplantation**. *Cochrane Database Syst Rev* 2008(4):CD006501.
9. Raanani P, Gafter-Gvili A, Paul M, Ben-Bassat I, Leibovici L, Shpilberg O: **Immunoglobulin prophylaxis in chronic lymphocytic leukemia and multiple myeloma: systematic review and meta-analysis**. *Leukemia & lymphoma* 2009, **50**(5):764-772.
10. Casulo C, Maragulia J, Zelenetz AD: **Incidence of hypogammaglobulinemia in patients receiving rituximab and the use of intravenous immunoglobulin for recurrent infections**. *Clin Lymphoma Myeloma Leuk* 2013, **13**(2):106-111.
11. Byrd JC, Furman RR, Coutre SE, Burger JA, Blum KA, Coleman M, Wierda WG, Jones JA, Zhao W, Heerema NA *et al*: **Three-year follow-up of treatment-naive and previously treated patients with CLL and SLL receiving single-agent ibrutinib**. *Blood* 2015, **125**(16):2497-2506.
12. Sun C, Tian X, Lee YS, Gunti S, Lipsky A, Herman SE, Salem D, Stetler-Stevenson M, Yuan C, Kardava L *et al*: **Partial reconstitution of humoral immunity and fewer infections in patients with chronic lymphocytic leukemia treated with ibrutinib**. *Blood* 2015, **126**(19):2213-2219.
13. Gunther G, Dreger B: **Post-marketing observational study on 5% intravenous immunoglobulin therapy in patients with secondary immunodeficiency and recurrent serious bacterial infections**. *Microbiol Immunol* 2013, **57**(7):527-535.
14. CSL Behring Pty Ltd: **Product Information Intragam® P Australia**. 2014.
15. Ammann EM, Jones MP, Link BK, Carnahan RM, Winiecki SK, Torner JC, McDowell BD, Fireman BH, Chrischilles EA: **Intravenous immune globulin and thromboembolic adverse events in patients with hematologic malignancy**. *Blood* 2016, **127**(2):200-207.
16. Keegan A: **Australian trends in the distribution of intravenous immunoglobulin to chronic lymphocytic leukaemia patients with acquired hypogammaglobulinaemia and severe and/or recurrent infections from 2008-2013**. In: *International Workshop on CLL.* Sydney, Australia; 2014.
17. National Blood Authority: **Criteria for the clinical use of intravenous immunoglobulin in Australia, 2nd Edition**, vol. 2nd. Canberra: National Blood Authority; 2012.
18. Oscier D, Dearden C, Eren E, Fegan C, Follows G, Hillmen P, Illidge T, Matutes E, Milligan DW, Pettitt A *et al*: **Guidelines on the diagnosis, investigation and management of chronic lymphocytic leukaemia**. *Br J Haematol* 2012, **159**(5):541-564.
19. Gafter-Gvili A, Fraser A, Paul M, Vidal L, Lawrie TA, van de Wetering MD, Kremer LC, Leibovici L: **Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy**. *Cochrane Database Syst Rev* 2012, **1**:CD004386.
20. Wong C, Jayaram L, Karalus N, Eaton T, Tong C, Hockey H, Milne D, Fergusson W, Tuffery C, Sexton P *et al*: **Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial**. *Lancet* 2012, **380**(9842):660-667.
21. Fennelly KP, Griffith DE: **Azithromycin in non-cystic-fibrosis bronchiectasis**. *Lancet* 2013, **381**(9860):27.

22. Dhalla F, Lucas M, Schuh A, Bhole M, Jain R, Patel SY, Misbah S, Chapel H: **Antibody deficiency secondary to chronic lymphocytic leukemia: Should patients be treated with prophylactic replacement immunoglobulin?** *J Clin Immunol* 2014, **34**(3):277-282.