Round 5 Project Summary, Publications, aims and objectives

Grant Type	Project Title	Administering Institute	Amount (inc. GST)	Principal Chief Investigator	Project Aims/Objectives	Project Summary	Publications
Patient Blood Management Project Grants	Towards personalised blood product therapy after cardiopulmonary bypass in neonates and infants	Murdoch Children's Research Institute	$485,974.00	Prof Paul Monagle	To reduce bleeding and clotting outcomes caused by coagulopathy during neonatal/infant CPB by optimising replacement therapy after protamine reversal	In Australia, approximately 3000 babies are born with congenital heart disease (CHD). The Royal Children's Hospital (RCH) in Melbourne is the largest paediatric cardiac surgical centre in Australia, where 600 surgeries with CPB are performed each year. Unfortunately, Thrombosis occurs in up to 40% of these cases, significantly increasing the risk of death and poor clinical outcomes, whilst bleeding occurs in more than 20% of all paediatric CPB patients. A recent study at RCH has shown that 70% of patients who bleed are younger than 2 years (RCH data). In this scenario, bleeding is typically treated with broad-based high-volume therapies, primarily blood products. This is problematic because children separating from CPB are particularly sensitive to volume load and are easily pushed into cardiac failure that requires ongoing mechanical circulatory support in the form of Extracorporeal membrane oxygenation (ECMO). The mechanism of bleeding in terms of contribution of factor deficiency, fibrinogen deficiency, acquired von Willebrand disease, hyperfibrinolysis, platelet dysfunction and other potential causes are unknown. This is particularly important because there are now a variety of specific low-volume haemostatic agents available that may provide alternatives to conventional therapies. These include factor VIIa concentrate, fibrinogen concentrate, von Willebrand factor concentrate, Factor XIII concentrate and prothrombinex (3-factor concentrate). To understand the mechanisms of bleeding in order to develop algorithms to determine which therapy to use, the research team will conduct a 3-year prospective study of 150 neonates and infants undergoing CPB at the RCH. Blood samples and detailed clinical data will be collected following our previously published protocol. This detailed study is based on the collection of at least 6 samples from each patient, from post induction of anaesthesia to 12 hours post chest closure. Demographic, clinical data and critical clinical outcomes will be recorded. Once the study samples are collected the team will undertake a comprehensive examination of the plasma coagulation system during paediatric CPB in the context of heparin anticoagulation, to determine the mechanisms that drive bleeding and clotting outcomes associated with CPB and to identify potential therapeutic targets that are best suited to this scenario. This in-depth single-centre pathophysiological examination of a substantial cohort of paediatric patients is the most feasible research in this field, at this time. This study will identify the mechanism of bleeding and clotting and allow us to address some of the most relevant questions that currently	No publication listed yet

						impact on clinical outcome including the appropriate use of specific haematological agents, improved dosing of anticoagulation and, importantly, will provide a platform for future multicentre research. Understanding the mechanisms of bleeding and clotting will not only have the potential to lead to immediate changes in replacement therapy strategies to control bleeding, but also have the potential to lead to new pharmacological therapeutic targets, in this vulnerable population.	
Patient Blood Management Project Grants	Anaemia and transfusion prevalence in Indigenous and non-Indigenous intensive care, pregnant and cardiac patients	Flinders University	$104,956.43	A/Prof David Roxby	To determine prevalence of anaemia, blood groups, alloantibodies and specificities, red cell transfusion rates, and outcomes including mortality and morbidity in three ATSI and non-ATSI patient coho	Aboriginal and Torres Strait Islander (First Nations) people make up 3.3% of the overall Australian population. First nations people attending for hospital care are higher risk compared to non-Indigenous patients. They have both unmet needs relating to underlying health conditions; and a risk of adverse outcomes including disability and death. In certain settings, blood transfusions have the potential to offer benefit to patients. Blood transfusion can assist in correcting anaemia; and may offset adverse events associated with anaemia such as the risk of acute heart events, other body organ dysfunction or failure, and in the emergency acute setting can prevent death. However, transfusion also carries some risk of harm. Recipients of blood transfusions may develop alloantibodies to foreign antigens present in the blood donor but not the recipient of the transfusion. These alloantibodies can affect future pregnancies in women and pose a higher risk for both men and women in finding compatible blood for future blood transfusions. Transfusion also poses a risk of other immune related reactions, and infection, and is associated with increased length of hospital stay. These harms are more likely in patients with pre-existing health conditions. Given the prevalence of pre-existing medical conditions, and the high hazard of alloantibody formation, the harms are potentially higher among First Nations recipients of transfusion. On the other hand, withholding transfusion from those who are likely to benefit may also be harmful, and the risk of this undertreatment is unknown. A systematic approach to determining triggers and harms is needed. Using five-years of retrospective data, a multicentre observational study of transfusion triggers and outcomes in First Nations versus non-Indigenous patients in the Northern Territory and South Australia will be performed. This study will examine three high risk patient groups: - patients admitted to intensive care; - women during pregnancy and childbirth and	A Retrospective Cohort Study of Red Cell Alloimmunisation in Rural, Remote, and Aboriginal and Torres Strait Islander Peoples Admitted to Intensive Care in the Northern Territory, Australia The prevalence of alloantibodies and ABO RhD blood groups in a cohort of Aboriginal and non-Aboriginal cardiac surgery patients from Australia - Transfusion and Apheresis Science

						- patients undergoing heart surgery. The research team will study the baseline demographics, prevalence of anaemia, transfusion of blood, laboratory information on triggers for giving a transfusion, and outcomes including patient survival; women and babies; length of hospital and intensive care stay; and complications such as body organ dysfunction, bleeding, and transfusion reactions including the development of alloantibodies to transfused blood. A comparative analysis of adjusted outcomes by ethnic identification will be performed. This project will inform better clinical decision making and hospital policies regarding care of First Nations patients potentially requiring transfusion. We also aim to improve transfusion related clinical and patient blood management for First Nations patients specifically receiving intensive care, heart surgery, and women and babies during childbirth. Our findings will also provide new evidence which will inform best practice for First Nations patients receiving hospital care more broadly.	
Patient Blood Management Project Grants	International point prevalence study of intensive care unit transfusion practices – the InPUT study	Monash University	$170,616.56	A/Prof Zoe McQuilten	To describe current transfusion practice in ICUs in Australia and benchmark against international practice.	Intensive care unit (ICU) patients commonly develop anaemia, thrombocytopenia, coagulopathy and bleeding – life-threatening issues, associated with morbidity and mortality. Blood transfusions are commonly required interventions in ICU patients, given to correct coagulopathy and/or improve oxygen delivery. Australian patient blood management (PBM) guidelines include a module for critical care; however, for many aspects of transfusion practice, the PBM guidelines could not make evidence-based recommendations for when a blood transfusion may be appropriate due to key evidence gaps. As a result, there exists variation in transfusion practice, both within Australia's ICUs, and internationally. The InPUT study is an international multicentre prospective observational point prevalence study of transfusion practice in ICUs across Australia, Europe, North America and Asia. This project will assess the Australian component and collect data from approximately 47 ICUs around Australia over a one- week period in 2021, and the international collaborators will do similar in their respective countries. The main outcome of the study will be to describe current transfusion practice in ICUs, an area where there is uncertainty. Secondary outcomes will be mortality and length of stay, and differences in transfusion practices between patient subgroups. Using Australian data, we will compare Australian transfusion practice against current Australian PBM guidelines.	[Red Blood Cell Transfusion in the Intensive Care Unit](#)

						All adult patients (18 years and older) admitted to participating ICUs will be included, followed for one week, and then followed up at 28 days. Information collected will include demographics, admission data, types of transfusions and triggers for transfusion, mortality and length of stay. The outcomes of the study will be used to guide future observational and interventional study designs and priorities, and to inform patient blood management guidelines.	
Patient Blood Management Seed Grants	Prehospital plasma for trauma	Monash University	$54,969.00	Prof Biswadev Mitra	The overarching aim of this project is to fill a Patient Blood Management knowledge gap on early and effective management of haemorrhage after trauma.	Haemorrhage is responsible for over 40% of all trauma-related deaths, with nearly half occurring in the pre-hospital setting. In-hospital resuscitation of haemorrhaging injured patients delivers large volumes of blood products, including plasma to combat clotting disorders in the setting of tissue injury and shock. Transfusion of a high ratio of plasma to red cells has been associated with improved outcomes after trauma. But there is limited availability evidence to guide pre-hospital transfusion of plasma. There are approximately 50 episodes of pre-hospital transfusion after trauma among adult patients in Victoria per year. This pilot feasibility trial studied freeze-dried plasma vs standard therapy for patients with haemorrhagic shock receiving pre-hospital blood (Population). The intervention was freeze-dried plasma, obtained for the trial from the German Red Cross (LyoPlas N-w) with a comparator of standard care. The primary outcome investigated the feasibility of implementation, measured by the proportion of randomised patients who complete the intervention. Secondary outcomes will be acceptability of the intervention to pre-hospital staff, demand, practicality, adaptation, integration, expansion and efficacy. Limited data will be available on efficacy, and here the team propose to report mortality at 24 hours, and at hospital discharge, coagulation status on arrival to hospital and blood product use within 24 hours of arrival. This feasibility study aimed to enrol 20 patients over a period of 6-months providing preliminary data and evidence of feasibility for a definitive randomised controlled trial. Assuming effect on mortality at 30-days from pre-hospital freeze-dried plasma, a definitive trial in Australia using a background mortality of 35% and effect size of 9%, using 90% power will require 1100 patients. An Australia-wide trial over 4-5 years will therefore be feasible, with a shorter time period required through our collaborations with overseas centres. This open label, randomised controlled trial was completed in Victoria will include the decision to transfuse pre-hospital red cells requires approval by a clinician at the base at which time Eligible patients will be randomised to receive freeze dried plasma or proceed with standard care.	Pre-hospital freeze-dried plasma for critical bleeding after trauma: A pilot randomized controlled trial Prehospital Blood Transfusion in Helicopter Emergency Medical Services: An Italian Survey

						On completion of this feasibility pilot trial, the team will design and seek funding for the definitive trial. Using the extensive networks and capability in trauma research that has been built through the PATCH-Trauma trial. This trial will provide definitive evidence towards use of pre-hospital plasma to manage critical bleeding after trauma.	
Immunoglobulin Project Grants	OPTIC trial: Intravenous immunoglobulin and intravenous methylprednisolone as optimal induction treatment in CIDP (chronic inflammatory demyelinating polyneuropathy)	ANZAC Health and Medical Research Foundation	$453,238.59	A/Prof Stephen Reddel	To test the combination induction treatment with IVIG and IVMP for 18 weeks in a practical and recruitable randomised double-blind placebo controlled trial.	Induction treatment of CIDP currently consists of either intravenous immunoglobulin (IVIg) infusions or high dose corticosteroids. Both IVIg and intravenous methylprednisolone (IVMP) are recommended as first line treatment, but choice of induction treatment varies. Patients treated with IVIg usually respond fast, but this treatment rarely leads to long term remissions. Patients treated with corticosteroids are more likely to achieve long term remissions so some patients can come off all treatment, but corticosteroids work more slowly and with side-effects if used long-term. Both fast clinical response and long-term remissions may be important for patients, and the combination may also be more effective for CIDP. Long term remissions are important for the patient's return to normal activities and freedom from ongoing healthcare and are also more cost effective for the healthcare system. Pilot data indicates a 59% 1-year remission rate in combination IVIG & IVMP induction treatment for CIDP. This multicentre, randomized, double-blind, placebo-controlled trial (adding sites in Australia to the existing OPTIC trial sites in the Netherlands and the United Kingdom), Will study adult patients with new onset or newly relapsed CIDP. Patients will be treated with IVIG, and either IVMP or placebo, for 18 weeks, then observed off therapy. The primary outcome is whether patients who also receive IVMP achieve long term remission more frequently, at 1 year from treatment initiation. Key secondary outcomes include the extent, rate and time to improvement in CIDP and side effects of therapies. Long term follow-up of clinical outcomes, adverse events and an extended economic evaluation will take place at 104 weeks. The CIDP patient population may benefit if the study demonstrates that a combination of the current standard therapies is more effective or quicker than either alone or achieves more lasting remissions than standard care. The healthcare system benefits particularly if the study demonstrates a higher rate of lasting remission with combination induction therapy for IVIG. CIDP in 2017-18 accounted for 21.2% of all IVIG use and a substantial majority of patients receive IVIG continuously for years. If this study confirms pilot findings of ~60% remission, therefore not requiring years of IVIG (or SCIG), this would	No publication listed yet

						1. Substantially improve the efficiency and sustainability of Ig treatment for CIDP. 2. Identify that intensive induction is a better use of Ig than long-term continuous suppressive Ig therapy 3. Improve outcomes for patients by enabling many to be free of all therapies. 4. Contribute to understanding the different biological effects of Ig and corticosteroids on suppression versus remission of an autoimmune disease, which would have implications for other diseases such as myasthenia gravis. 5. Identify an optimum treatment protocol and time window for Ig in CIDP 6. Explore whether the addition of a cheap alternative treatment for CIDP enables lower long-term Ig requirement.	
Immunoglobulin Project Grants	Evaluating vaccine responses in specific antibody-deficient patients receiving immunoglobulin treatment	Melbourne Health	$163,460.00	Dr Celina Jin	To evaluate Vi-PS vaccine responses in patients with SAD on immunoglobulin replacement to determine if anti-Vi IgG and B cell responses correlate with clinical outcomes, particularly the likelihood of requiring long-term immunoglobulin replacement.	Patients with specific antibody deficiency (SAD) have impaired immune function and suffer from recurrent infections. Some patients are treated with immunoglobulin replacement which involves receiving monthly infusions of pooled protective antibodies from healthy blood donors. In the 2017-2018 National Blood Authority (NBA) report on the issue and use of immunoglobulin, specific antibody deficiency was ranked amongst the top 20 conditions for which immunoglobulin treatment was prescribed in Australia. The current Patient Blood Management Guidelines suggest that after 12 months of immunoglobulin replacement, patients with SAD should be trialled off treatment to assess for immune function recovery. However, these guidelines are based on general recommendations for both children and adults and although children may have some improvement in immune function with time (due to maturation of the immune system with age), this has not been well studied in adults with this condition. SAD is usually diagnosed based on studying responses to vaccines, particularly the pneumococcal polysaccharide vaccine, which is used to prevent pneumonia. This involves vaccinating patients with the pneumococcal vaccine and measuring pneumococcal antibody levels 4-6 weeks later. Unfortunately, this cannot be done while patients are on immunoglobulin replacement, because immunoglobulin products contain pneumococcal antibodies from healthy blood donors. This means that currently we do not have any way of studying immune responses in patients with SAD while they are on immunoglobulin treatment. Our only method is to stop treatment and monitor patients	No publication listed yet

						for infections which can be severe and often require treatment with antibiotics in hospital. A currently available typhoid vaccine (Vi-polysaccharide vaccine) which is routinely given to travellers, could be used as an alternative to the pneumococcal vaccine. This vaccine has been studied in other immunodeficiency conditions and has been shown to be helpful in distinguishing normal immune responses in healthy individuals, from reduced responses in patients with immunodeficiencies. In addition, it appears that immunoglobulin products contain no or little antibodies to this vaccine. This multi-centre trial will evaluate Vi-polysaccharide (Vi-PS) vaccine responses in adult patients with SAD. Patients with SAD will be vaccinated with the Vi-PS vaccine whilst still on immunoglobulin replacement. One-month later bloods will be collected to study vaccine responses and immunoglobulin treatment will be stopped. Patients will be closely monitored over a 12-month period to determine how many are restarted on immunoglobulin replacement. Both patients and treating clinicians will be unaware of the vaccine responses (i.e. blinded). The research team hypothesise that patients with poor vaccine responses are more likely to require long-term immunoglobulin replacement. Results from this study will be used to develop tools to predict which patients with SAD will be able to successfully stop immunoglobulin replacement and which will require long-term treatment. This could be used to rationalise the use of immunoglobulin products and also prevent infectious complications in patients requiring long-term treatment (by avoiding a trial off immunoglobulin replacement).	
Immunoglobulin Seed Grants	A new blood test to guide immunoglobulin replacement therapy in patients with immunodeficiency diseases	The University of Adelaide	$55,000.00	Dr Jovanka King	1. To develop and evaluate the performance of a novel transcriptomic assay assessing expression of the immunoglobulin heavy chain genes. 2. To assess its utility as a biomarker of endogenous immunoglobulin production in patients with primary and secondary immunodeficiencies. 3. To assist in clinical decision-making regarding IRT prescription.	As a result of an underlying disorder, many patients with primary or secondary immunodeficiency diseases produce low levels of immunoglobulin (or antibody). Immunoglobulin is an important part of the immune system, and the immune response to infection. In certain clinical situations, it is not currently possible to accurately determine the amount of immunoglobulin produced. For example, there is no test available to accurately measure immunoglobulin levels in young infants, or in patients who are currently receiving immunoglobulin replacement therapy. It would be advantageous to have a blood test to accurately measure an individual's ability to produce their own immunoglobulin in these contexts, to help guide clinical treatment decisions. This information would help clinicians make important decisions regarding starting or ceasing immunoglobulin therapy.	No publication listed yet

Patients with suspected or confirmed primary or secondary immunodeficiency diseases, and healthy control participants will be invited to participate in this study. Blood will be collected and tested using a new method the research team hasdeveloped for assessing expression of the genes which control production of different types of immunoglobulin (IgG, IgA, IgM and IgG subclasses), to assess how active this process is. This testing method will then be evaluated in these patient groups, and in healthy control participants, to determine whether this is a suitable marker for an individual's immune system ability to produce immunoglobulin.

It is expected that this research will contribute to efficient and effective use of immunoglobulin therapy, and improve the care of patients with immunodeficiency diseases by providing their clinicians with a new tool which can assist with clinical decision-making regarding treatment with immunoglobulin therapy.