Review Article

# Peri-operative blood management

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## ABSTRACT

Anaemia and allogeneic blood transfusions in surgical patients are associated with poor outcomes. Patient blood management (PBM) has been developed as an evidence-based clinical tool, by which clinicians can optimise anaemia, manage peri-operative bleeding, avoid unnecessary blood transfusion and improve patient outcome. This article aims to highlight the recent updates regarding evidence-based PBM in the perioperative period, following a thorough literature review involving original research articles, published guidelines and consensus documents discovered through an extensive PubMed and Medline search. PBM addresses three main pillars of the patient's journey through the pre-operative, intra-operative and post-operative periods. PBM encourages a restrictive approach to transfusion of blood products and promotes alternatives to blood transfusion to maximise clinical efficacy while minimising risks. Anaemia has been identified as an independent risk factor for poor outcomes. PBM highlights the importance of treating anaemia in the pre-operative period. Major elective surgery may be postponed until anaemia is corrected preoperatively. The intra-operative approach to PBM is a collaborative effort between the anaesthesia, surgery and transfusion laboratory teams. Use of tranexamic acid, meticulous haemostasis and cell salvage techniques play an important role during the intra-operative management of surgical and traumatic haemorrhage. Point-of-care coagulation tests with visco-elastographic methods and haemoglobin measurement ensure that the transfusion prescription is tailored to a patient. In the post-operative period, PBM highlights the need for patients to be optimised before discharge from the hospital. Implementation of the PBM has been shown to have individual health as well as economic benefits.

**Key words:** Anaemia, iron deficiency, patient blood management, peri-operative

## INTRODUCTION

Pre-operative anaemia is an independent risk factor for increased hospital stay, post-operative complications, need for blood transfusion and increased mortality.[1] The clinical risks and financial costs involved in blood transfusion have long been appreciated by healthcare providers and managers. As a result, an evidence-based, multi-disciplinary and patient-centred programme for the rationalisation of the use of this limited and potentially harmful resource was devised. This is known as patient blood management (PBM). The PBM strategy was first endorsed in 2010 by the World Health Organization (WHO) that presented some guidelines and praised the programme for its potential to 'promote the availability of transfusion alternatives'.[2]

The PBM model divides the patient's clinical journey into three chronological 'pillars' of pre-operative preparation, intra-operative techniques and post-operative periods. In essence, the concept encourages healthcare providers to give the right blood product to the right patient, at the right dose, at the right time for the right reason [Figure 1].

Advances in surgical techniques including minimally invasive surgery, use of haemostatic agents and meticulous haemostasis have facilitated reduction in blood loss in the peri-operative period.

The advantages of PBM have been demonstrated by numerous trials around the world. In Europe, the PREPARE study concluded that transfusion rates and outcomes among elective orthopaedic patients were



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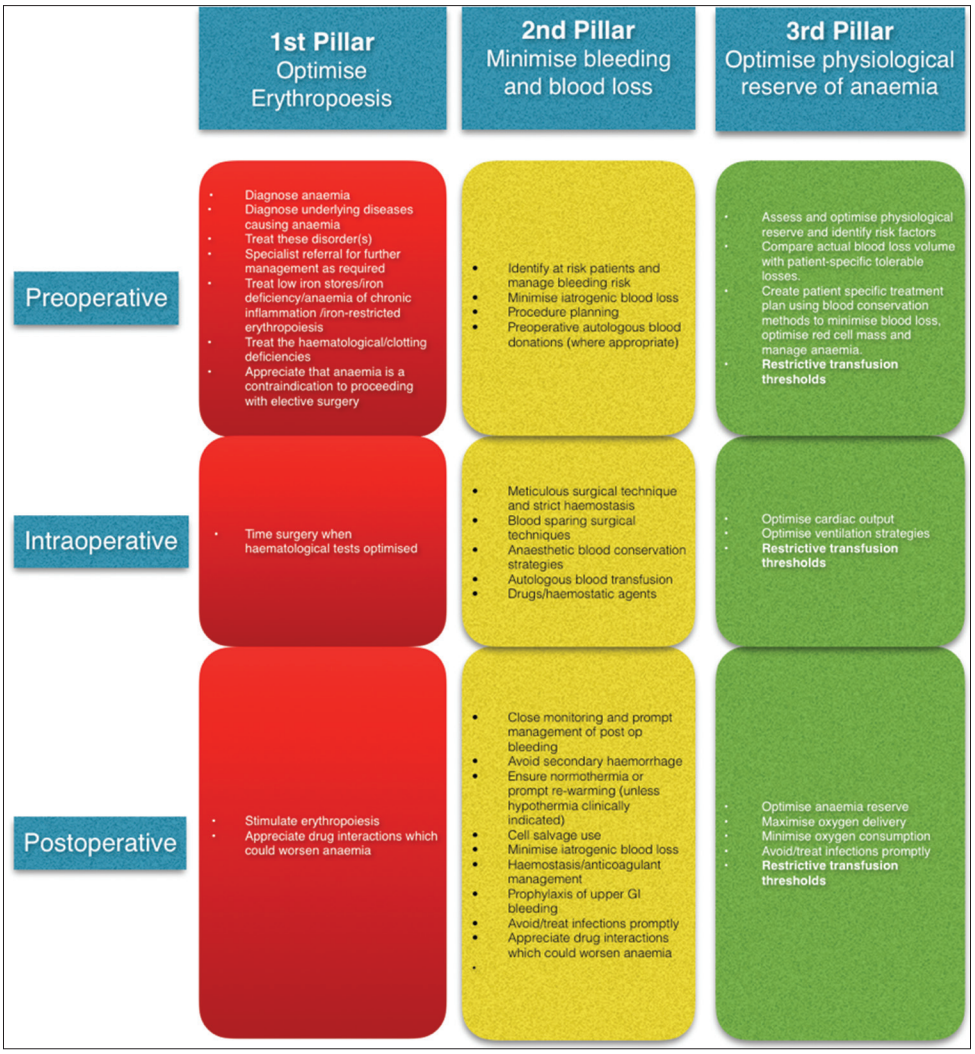


**Figure 1:** The three-pillar matrix of the peri-operative patient blood management. Initially developed by the Western Australia Patient Blood Management Program, this table displays the multiple patient blood management strategies that may be considered in the peri-operative period (from Reference 20)

improved in hospitals that had adopted PBM pathways.[3] Over a 5-year period from 2008, after adoption of the PBM programme, the healthcare authorities of Western Australia were able to reduce the rate of transfusion from 30.47 to 27.54 red cell units per 1000 population. Specifically, fewer patients were transfused perioperatively (3% vs. 2.5%), and when they were transfused, less blood was administered (3.5 vs. 3.0 units of blood). The PBM system was also credited with direct and indirect cost savings in the form of reduced length of hospital stay and spared potential complications.[4]

## PRE-OPERATIVE

### Identification of anaemia

The WHO defines anaemia as a haemoglobin concentration of <13.0 g/dL for men, <12.0 g/dL for non-pregnant women and <11.0 g/L for pregnant.[5] However, it must be considered that women have a lower total blood volume than men, and for a similar volume of blood loss during surgery, women lose more blood as a percentage of total blood volume than men and are thus more likely to need a blood transfusion. It has therefore been postulated by recent consensus guidelines that clinicians should aim for preoperative haemoglobin of 13.0 g/dL in patients of either sex.[5]

It has been found that about one-third of patients presenting for intermediate grade and major surgery are anaemic in the pre-operative period and this figure increases to 40%–60% when cardiac surgical patients are included.[5,6] It has also been demonstrated in large clinical trials that anaemia is an independent risk factor for poor outcome, in both cardiac and non-cardiac surgery.[1,6] Mild anaemia is associated with an increased risk of peri-operative complications

by 30%–40%, and this figure increases as the severity of anaemia worsens.[6] However, despite this evidence, the diagnosis and treatment of anaemia preoperatively are frequently sub-optimal.

For decades, transfusion of blood has been the practice to raise low haemoglobin levels in the pre-operative period. However, it has been postulated that because the transfusion does not address the issue that is causing anaemia, it should not be seen as a treatment modality. Packed red blood cell (PRBC) transfusions continue to be associated with a variety of risks. A recent audit by the NHS Blood and Transfusion group (NHSBT) in the United Kingdom calculated that 0.6% of all transfusions were stopped due to an adverse event.[7] These risks include febrile and anaphylactoid reactions, fluid overload, haemolytic reactions, graft versus host disease, lung injury and transmission of viral and bacterial infections. Although the incidence of transfusion mismatch and infectious disease transmissions is ever decreasing, other risks such as immunosuppression have also been recognised.[1,7]

## Optimisation of clotting function

Patients may be anaemic or at risk of coagulopathy either due to disease or use of pharmacological agents. It is very important to identify these patients and optimise their coagulation profile before subjecting them to surgery to minimise intraoperative blood loss. At the same time, care should be taken to weigh the risks of inducing a relatively hypercoagulable state in an individual patient. Guidelines have been developed and regularly updated to help clinicians manage their patients who require both surgery and anticoagulant therapy.[8] Despite all these measures, a recent audit by the NHSBT showed that one-third of patients were operated with an international normalised ratio >1.4[7,8] due to erroneous timings for omissions of warfarin and issues with low molecular weight heparin bridging regimens.

## Investigations

It is recommended that patients should have a full assessment of their haematological function 30 days before the planned date of any elective major surgery so that there is adequate time to optimise the patient preoperatively and reduce the need for potentially unnecessary intra-operative blood transfusions. A full blood count test will help diagnose anaemia. For anaemic patients, additional blood tests including iron studies, a marker of inflammation such as C-reactive protein (CRP), Vitamin B12 and folate levels will help differentiate the type of anaemia and facilitate therapy.[5] The most common causes of anaemia include deficiencies of iron, Vitamin B12 and folate, disease-specific bleeding episodes, renal failure, gastrointestinal disease and haemoglobinopathies.[5,6]

Ordinarily, patients with a serum ferritin <30 ng/mL are diagnosed as having an absolute iron deficiency (AID) and this is due to either lack of intake of dietary iron or continued loss of blood.[5] Much research has been undertaken recently in the area of iron metabolism, and recent advances have improved our understanding with respect to the process of inflammation [Figure 2]. It is believed that inflammation directly affects the function of hepcidin, the protein involved in iron regulation.[9] Many conditions such as infection and inflammation increase hepcidin synthesis. It has been postulated that even with a CRP >10 mg/dL, patients will have notably raised hepcidin levels.[9] Hepcidin acts to inhibit the intestinal absorption of iron and the release of iron from macrophages. It is now understood that patients with normal iron levels may suffer from functional iron deficiency (FID) as they are unable to utilise their iron. At this time, clinical implications of manipulating hepcidin levels are unclear, and more research is required in the area.

## Iron supplementation

Iron deficiency (both AID and FID) can be treated by administering iron orally or intravenously (IV) depending on patient factors and time available. Oral iron supplements require that at least 4–6 weeks are available preoperatively for optimal efficacy. A significant number of patients (approximately 25%–30%) are unable to tolerate oral iron due to gastrointestinal side effects.[5] Furthermore, most oral iron supplements have a poor oral bioavailability (10%–15%) which further reduces their usefulness.[5] Despite these limitations, the oral route is considered the first line of treatment of iron deficiency anaemia due to low-cost and easy availability.

IV iron infusions are the preferred route of administration when time for optimisation is limited. It has been suggested that a response is noted if the infusion is administered at least 5 days preoperatively, and the peak efficacy is thought to be at 2–4 weeks after infusion.[5] The IV approach is also beneficial as it negates the effect of the hepcidin on intestinal absorption. Modern formulations such as ferric carboxymaltose and iron isomaltoside allow for the complete replacement of a patient's iron stores in a

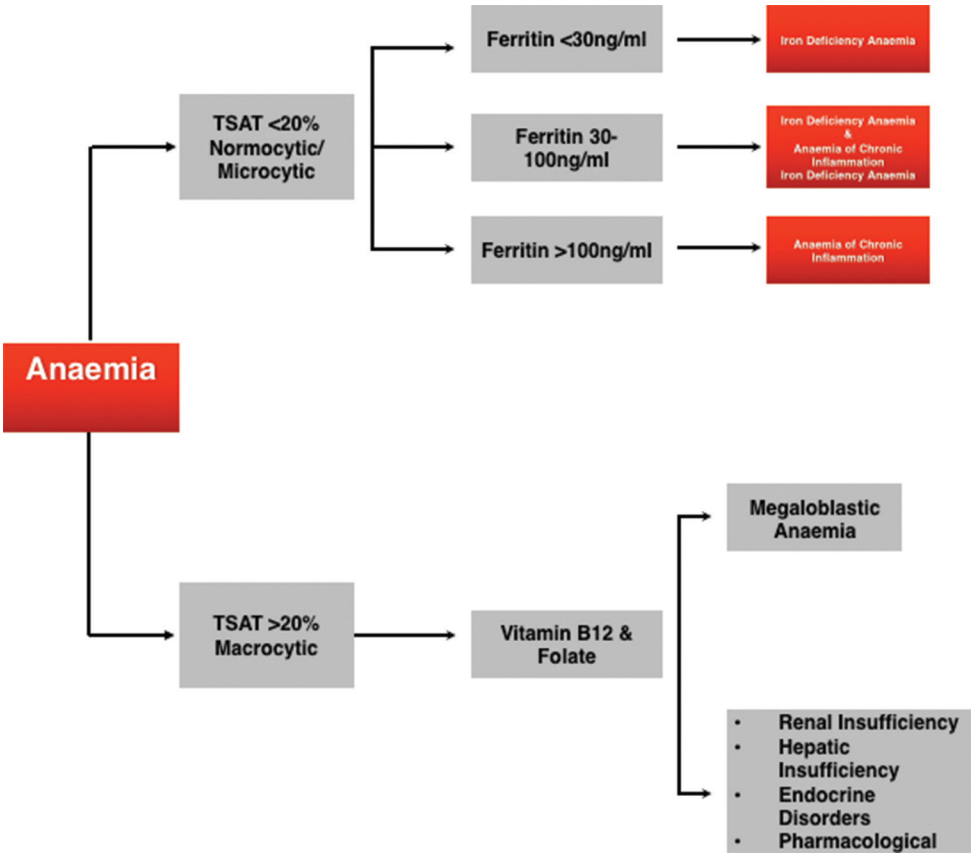


**Figure 2:** A flowchart showing the classifications of anaemia. TSAT = Transferrin saturation (From Reference 21)

single dose which takes approximately 15–30 min to administer.[5] Current data estimate that serious adverse events occur in <1 in 200,000 patients.[7] A single-centre clinical trial in Australia has highlighted the efficacy of IV iron perioperatively, and currently, a few multicentre randomised clinical trials are in progress to address the use of IV iron in the pre-operative period.[5,10] An international consensus statement has been published recently to highlight the benefits of iron supplementation in peri-operative period.[5]

Recombinant human erythropoietin (EPO) is licensed for use in Europe in an attempt to reduce blood transfusion rates in patients with adequate iron stores and haemoglobin levels of 100–130 g/L who are scheduled to undergo orthopaedic surgery where a moderate blood loss is expected.[5,7] Recent National Institute for Health and Care Excellence (NICE) guidelines however warn against routine use of EPO, except in patients who decline blood transfusion or if a particular blood group is unavailable due to the presence of red cell antibodies.[11] EPO is not only expensive but has also been linked to increased risks of thromboembolic events and tumour growth through the promotion of angiogenesis.[8,11]

It is becoming apparent that in the elective setting, surgery should be postponed or cancelled when untreated anaemia is identified preoperatively so that effective treatment can be instituted, and the patient is not exposed to unnecessary risk. Pre-operative blood transfusion is recommended only in patients with persistent bleeding, urgent or emergency surgery and in cancer-related surgery where operations cannot be delayed.

## INTRA-OPERATIVE MEASURES

The maintenance of normal physiology throughout the operative period is integral to optimising coagulation parameters and minimising the need for blood transfusions. Anaesthetic strategies include careful patient positioning and appropriate haemodynamic monitoring. Strict temperature control by the use of fluid warmers, warm air blanket devices, heated mattresses and limited exposure of the patient prevents hypothermia-induced platelet dysfunction and coagulopathy. When appropriate, blood gasses should be assessed so that any acidosis and hypocalcaemia can be identified and treated as this can also affect coagulation. During major haemorrhage management,

the aim is to maintain minimally acceptable preload and blood pressure (permissive hypotension) with volume resuscitation alone.[8] This may need to be modified in the presence of head and spinal injuries. The administration of fluids must be judicious and guided by goal-directed fluid therapy using cardiac output monitors. Careful fluid resuscitation helps avoid dilutional coagulopathy and maintain acceptable blood pressure. The use of vasopressors should be avoided during active haemorrhage.[8] Over-resuscitation and fluid overload must be avoided with careful monitoring of IV fluid and blood product administration. Invasive monitoring such as central venous pressure, continuous arterial blood pressure and cardiac output monitoring will facilitate optimisation of fluid balance.

In the last decade, publication of two large multicentre clinical trials on trauma and post-partum haemorrhage have created immense interest in the utility of tranexamic acid (TA) in surgical bleeding.[12] TA has been extensively researched and is a cheap and widely available anti-fibrinolytic drug. TA is a synthetic lysine derivative that blocks the lysine binding site on the plasminogen molecule, rendering it inactive and thus inhibiting fibrinolysis. TA acts by preventing clot breakdown without inducing clotting. The largest trial to date on use of anti-fibrinolytics the Clinical Randomisation of Antifibrinolytics in Significant Haemorrhage (CRASH-2) trial concluded that in the presence of trauma, the prompt administration (<3 h after trauma) of TA reduced mortality and was 'highly cost-effective'.[13] The 2017 WOMAN trial showed that TA successfully reduced the risk of death by bleeding in women suffering from post-partum haemorrhage.[14] The recent AAGBI guidelines propose use of TA in all surgical patients where more than 500 ml blood loss is anticipated.[8] The recommended IV dose is 10 mg/kg body weight as bolus followed by 1 mg/kg/h infusion if bleeding continues.[12] The CRASH-2 trial adopted dose of 1 g IV bolus followed by 1 g infusion over 8 h.[13]

In the intra-operative setting, transfusion should ideally be guided by accurate clinical assessment and point-of-care testing of blood. This includes haemoglobin testing via HemoCue monitor, point-of-care prothrombin time and activated clotting time testing and complex visco-elastography methods such as coagulation assessments with rotational thromboelastometry (ROTEM®), thromboelastography (TEG®) and platelet function assay. These point-of-care tests allow for the quick and accurate selection of specific blood products as required. The timely administration of clotting factors and pharmacological agents leads to optimised coagulation and a potential reduction in bleeding risk. Evidence validating the use of these devices in cardiac and transplant surgery has been published and clinical trials for guided therapy in trauma and obstetrics are on-going.[7,8,11]

Transfusion thresholds and haemoglobin targets have been debated recently, and currently, the NICE in the UK suggests that physicians should consider transfusing when the haemoglobin drops below 7.0 g/dL and the blood transfusion should be titrated to a target haemoglobin of 7.0–9.0 g/dL after transfusion. These values are patient and clinical situation specific. It is understood that patients with a history of ischaemic heart disease would benefit from maintaining a haemoglobin of 9.0–10.0 g/dL.[11] The most recent NICE guidelines also suggest that when blood transfusion is required, single unit transfusions should be considered for patients who are not actively bleeding in an attempt to encourage the practice of restrictive transfusion.[11]

For circumstances where there is major unanticipated haemorrhage, hospitals should have protocols to standardise care and ensure optimal management. The pathways should duplicate some of the suggestions included in the broader PBM plan and aim to minimise blood loss as well as maximise efficacy of blood product transfusion when it is required. Knowledge from the resuscitation of patients in the military setting has led to the formulation of the golden ratio by which fresh frozen plasma PRBCs should be administered. The PROPPR trial recently attempted to compare the administration of 1:1:1 blood products to 1:1:2 products (PRBCS, FFP, platelets); however, there was no statistical difference in mortality between the two groups at the endpoints of 24 h and 30 days.[15] However, fewer patients receiving blood products in a 1:1:1 ratio died due to exsanguination. The trial has helped reinforce the need for standardised transfusion protocols and protocolised care in the setting of major trauma and surgery-induced haemorrhage.

## Surgical strategies

Surgical technique is the key factor in determining peri-operative blood loss. Use of minimally invasive techniques such as laparoscopic, robot-assisted and endovascular techniques helps in minimising tissue trauma and thus surgical stress to the patient and

helps in reducing blood loss. Advances in technology have also ensured that meticulous haemostasis can be achieved by the use of diathermy, laser cautery, tourniquets, topical agents such as glues and local vasoconstriction induced by the injection of adrenaline containing local anaesthetic agents.

Blood loss can be pre-empted, and when it does occur, the blood can be collected, cleaned and re-administered to the patient during the operation through the use of cell salvage machines. These machines have become highly advanced, and with the introduction of leucocyte filters, unwanted materials such as cancer cells are prevented from being transfused.[16] Cell salvage devices are also available in continuous circuit form and thus may also be appropriate for use in Jehovah's Witness patients. Cell salvage devices are indicated in operations where the blood loss is expected to exceed 500 ml.[8,11]

Acute normovolaemic haemodilution (ANH) is a blood conservation technique which may be considered for patients undergoing surgery, in which substantial blood loss is anticipated. Whole blood is drained by gravity into blood collection bags containing anticoagulant before surgery. As blood is collected, haemodynamic optimisation is achieved by administration of either crystalloid or colloid fluid. Collected blood is transfused before the end of surgery, thus reducing the need for allogeneic blood transfusion. A recent meta-analysis has shown that ANH reduces the number of allogeneic RBCs transfused in the cardiac surgery setting.[17] ANH can also be practised in neurosurgery, spine surgery and orthopaedic surgery. It is also accepted by most of the Jehovah's Witness subjects.

## POST-OPERATIVE MEASURES

PBM strategies in the post-operative period further highlight the need for individualised care tailored to the patient. If diagnosed, anaemia needs to be treated and appropriate transfusion targets need to be set depending on the comorbidities of the patient. The same restrictive transfusion measures need to be adhered to throughout patient's journey. We need to challenge the culture of 2-unit blood transfusions in non-bleeding patients. Single-unit blood transfusions are now recommended in stable patients without active bleeding as they provide both patient safety and economic benefits.[11] After each single-unit RBC transfusion, full clinical assessment must be undertaken with haemoglobin check and further transfusions given only if needed. Clinicians are encouraged to understand the need for adequate nutrition, iron and vitamin supplementation to ensure good bone marrow function.

Intensive Care Units (ICUs) provide much of the post-operative support and monitoring required after major surgery. However, with this high level of monitoring and care, there are several disadvantages.

Numerous studies have been published to highlight the phenomenon of iatrogenic anaemia in the critical care setting. One recent publication revealed that on average 52.4 ml of blood is withdrawn from each patient every day that they spend on the ICU.[18] Avoiding unindicated, unnecessary routine investigations and doing only targeted investigations help in avoiding this iatrogenic anaemia. Optimisation of oxygen delivery and cardiac output is also essential in the ICU so that the detrimental sequelae of anaemia are minimised.[19] There are currently on-going clinical trials assessing the benefits of post-surgery IV iron infusions in the management of peri-operative anaemia.[5,20,21]

### The future of peri-operative blood management

The benefit of establishing PBM in peri-operative pathways is clear. As clinicians become more familiar with the theory, technology and research advances, the PBM system will be able to evolve into more of an individualised blood management system. These bespoke strategies of the future will allow further reduction of unnecessary transfusions and help reduce the number of adverse events. The accuracy of point-of-care testing will improve and the availability of in-line, *in vivo* testing will obviate the need for blood sampling, rendering iatrogenic anaemia a thing of the past. The availability of blood products produced from the patient's own stem cells may become a possibility and will help reduce the risks associated with the transfusion of donated products. Surgical techniques will no doubt improve with robotic 'bloodless' surgery minimising the amount of blood lost during the intra-operative period and cell salvage technologies ensuring that any blood that is shed is not wasted.

These postulated future advances will no doubt reduce the importance of the PBM system as we know it; however, by developing vigilant, structured and respectful practices in the present day, we will be able to ensure optimal patient care in the future.

## CONCLUSION

The PBM strategy is the simplification of a complex process, and to date, over 100 measures have been described. The PBM contains many concepts that are already commonly understood and its existence merely helps amalgamate numerous ideas into one body of work. The system is based on the patient journey through the peri-operative period, and by understanding the chronological events, clinicians are reminded of the importance of each step during their journey. The implementation of PBM in the peri-operative period has been shown to have both individual patient and economic benefits.

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### Conflicts of interest

There are no conflicts of interest.

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