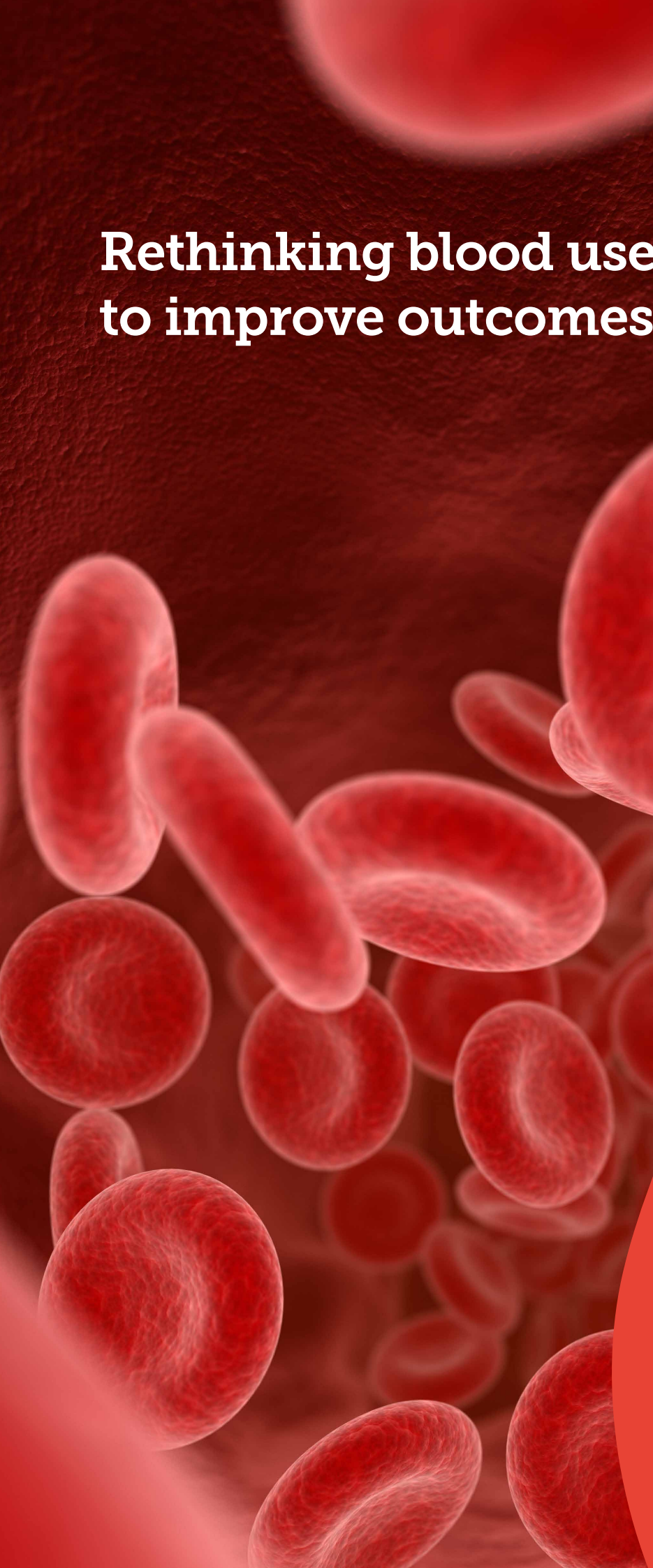
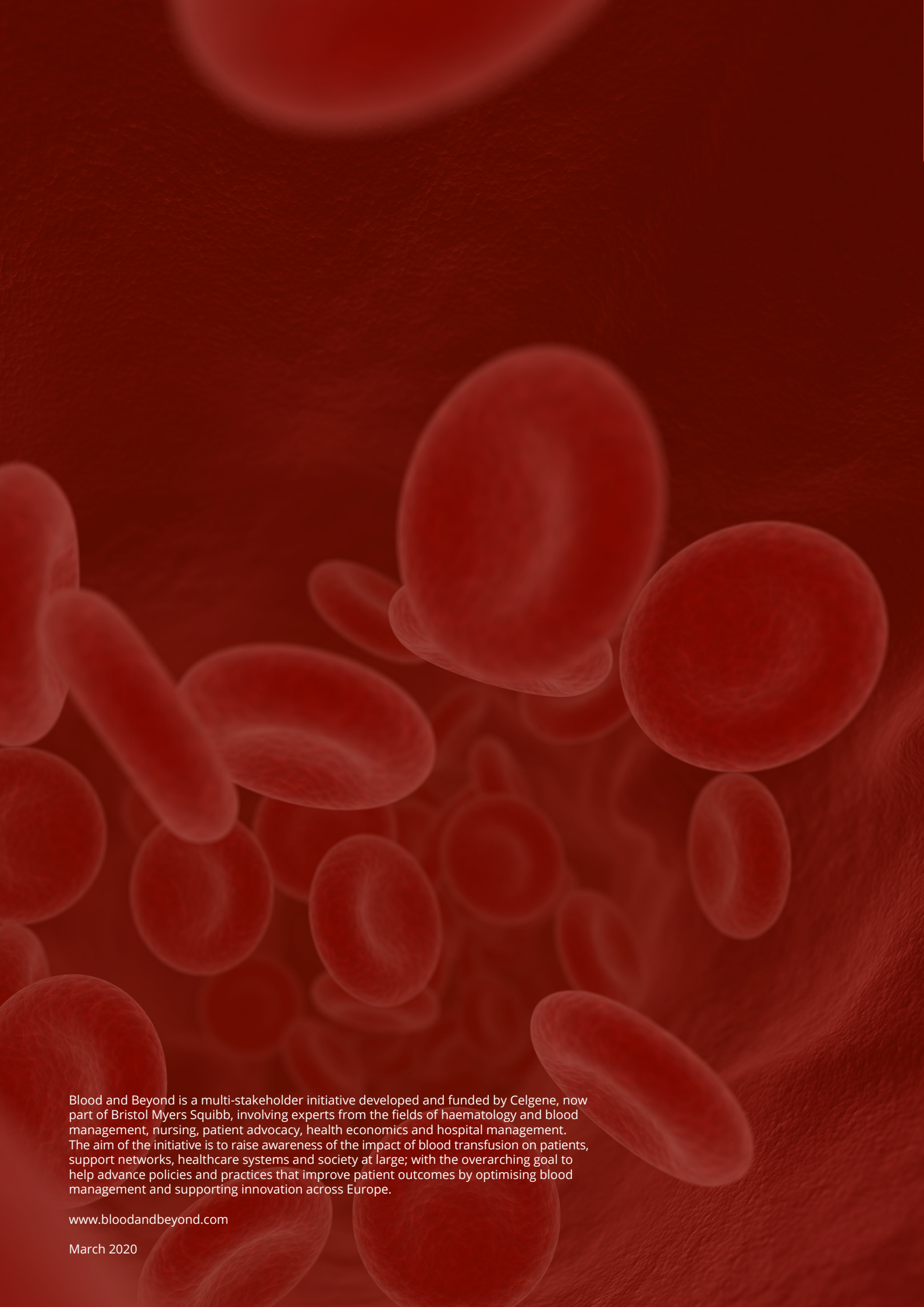
Rethinking blood use in Europe to improve outcomes for patients



Blood and Beyond

Rethinking Blood Use



Blood and Beyond is a multi-stakeholder initiative developed and funded by Celgene, now part of Bristol Myers Squibb, involving experts from the fields of haematology and blood management, nursing, patient advocacy, health economics and hospital management. The aim of the initiative is to raise awareness of the impact of blood transfusion on patients, support networks, healthcare systems and society at large; with the overarching goal to help advance policies and practices that improve patient outcomes by optimising blood management and supporting innovation across Europe.

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European Union of Private Hospitals (UEHP)

Haematology Nurses and Healthcare Professionals Group

MDS Alliance

Swedish Blood Cancer Association (Blodcancerförbundet)

Thalassaemia International Federation (TIF)

Contents

Foreword

Dr Cristian-Silviu Buşoi

Member of the European Parliament
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A well-functioning blood system is a vital component of every health system. A report published by the Directorate for the Quality of Medicines & HealthCare (EDQM) of the Council of Europe in 2015 showed there is a considerable variation across Europe in the per capita numbers of blood units donated and used. However, on average, the numbers of blood units donated and used are very similar. This illustrates the fine balance between blood demand and supply that is expected to come under increased pressure in the coming years. While blood service provision is a national competence, the EU can play a pivotal role in identifying and sharing good practices, and in regulating blood safety and quality.

Blood transfusion is a common clinical procedure that plays an important role in the treatment of anaemia associated with many chronic diseases, complications during pregnancy and childbirth, severe trauma due to accidents, and surgical procedures. In some cases, patients' lives depend on regular transfusions. However, transfusions come with various challenges for patients and carers – including significant risks and negative effects on their quality of life. They also require a complex supply system and entail considerable costs for healthcare systems. Meanwhile, ensuring the sustainability of the blood supply in Europe is a key priority.

I welcome this forward-thinking report as it recommends various policy actions to help address these challenges, in part learning from lessons from the 'patient blood management' approaches that have already been of benefit in surgery. The need for harmonised, evidence-based guidelines for patient blood management (including transfusions) in patients with chronic diseases should be developed in collaboration with all relevant stakeholders (including patients) and coupled with continuous professional education in relevant specialties.

There is a clear need for collaborative research to support all of these aspects and clearly the EU has a role here. Such research should not only be about excellence but should also focus on improving the lives of patients and their caregivers.

This report is particularly timely with respect to the EU Evaluation of the Blood, Tissue and Cells Directives. EU regulation of blood has been of proven value over the last two decades. However, the Blood Directive must now be updated to reflect the developments in the field and to address gaps and shortcomings, and this Report represents a valuable contribution to this process.

Executive summary

Introduction

A collaborative, patient-centred approach is needed to rethink and optimise blood management in chronic diseases in Europe. There are many aspects to optimising blood management. This report focuses on the need to: 1) reduce the negative impact that blood transfusion dependency has on the lives of patients and carers and thus improve patient outcomes, including quality of life (QoL); 2) reduce the potential risks of transfusions; and 3) avoid blood wastage, thereby safeguarding supplies for patients who genuinely need blood and reducing the costs of transfusions.

This report, developed as part of the multi-stakeholder Blood and Beyond initiative, outlines the important challenges that transfusion presents and offers a shared vision of participating stakeholders on the future of blood management in Europe, with policy-focused recommendations to overcome unmet needs.

Blood transfusion in Europe: an overview

Red blood cell (RBC) transfusions are currently a cornerstone of treatment for anaemia caused by various chronic diseases, with some patients being dependent on regular, life-long transfusions. Blood is a finite, perishable resource requiring a complex and highly specialised supply chain. European Union (EU)-level regulation has been beneficial, but needs updating to reflect new realities and address gaps and divergencies identified between member states.

Priority challenges and unmet needs

Transfusions play an important role in therapy for many patients, and improvements in the safety and use of blood have benefited patients in recent years. However, blood transfusions – especially transfusion dependence – still present important challenges. These include:

- *Transfusion dependence can contribute to increased morbidity and impaired health-related QoL among patients. Regular transfusions are inconvenient and burdensome for patients and their families, and come with important risks such as iron overload and immune reactions.*
- *Variations exist in transfusion practices for treating anaemia, related in part to a multiplicity of transfusion guidelines and to non-adherence to guidelines. Systems for the oversight of blood quality also vary across Europe.*
- *Transfusion dependence contributes to a substantial increase in the costs of care for chronic diseases that cause anaemia.*
- *Reducing blood demand and wastage will be key to ensuring the future sustainability of blood supplies, which are expected to come under increased pressure, as well as improving patient outcomes.*
- *There is a pressing unmet need for alternatives to blood transfusion for the treatment of anaemia in chronic diseases.*

Rethinking blood use – a shared vision

Policy-focused recommendations are offered to help: 1) optimise patient blood management to improve outcomes for patients with chronic diseases while reducing the demand for donor blood and thereby safeguarding blood supplies for patients who need them; and 2) promote access to timely, high-quality and safe blood transfusion therapy for all patients with chronic diseases who genuinely require transfusions.

At EU level, the following recommendations should be taken forward via the following mechanisms: 1) An EU Action Plan to strengthen member states' cooperation in the blood sector; 2) an EU Joint Action or a series of EU-funded projects; and 3) EU health research funding support. The recommendations are also intended to help inform future EU legislation on blood.

Supporting patient-centred transfusion services

- *EU-funded actions should be established to help identify and share good practices with respect to: 1) improving access to transfusion services and lessening the impact of treatment on patients; 2) educating and empowering patients and families with respect to transfusions and other forms of patient blood management; and 3) assessing QoL in clinical practice in patients with chronic anaemia.*

Supporting harmonised guidelines and professional education

- *Clinical guideline developers from relevant specialties (e.g. scientific/professional societies) should collaborate to develop, disseminate and implement harmonised, evidence-based, European-level guidelines for patient blood management, including transfusions, in chronic diseases.*
- *Clinical guidelines should be developed in collaboration with patient advocacy organisations.*
- *The EU should support best practice sharing on guideline implementation and audit with respect to transfusions and other aspects of patient blood management in chronic diseases.*
- *All stakeholders in health professional education (including professional societies, universities, hospitals, authorities governing professional education, health ministries and the EU) should promote and facilitate continuous education on patient blood management in chronic diseases.*

Supporting research

- *At EU and national level, health research funding should be directed to priority research topics to better understand and address the health and societal impact of anaemia and transfusions in chronic diseases, with research findings being systematically translated into policy design and used to update good practice.*
- *Hospitals, insurers and health ministries should collaborate to develop suitable patient-level data collection and benchmarking systems.*
- *National health ministries should provide suitable and long-term funding for disease registries.*
- *The EU should support collaborative research in this field, including via the harmonisation of disease registries, and support research into unmet clinical and scientific needs.*

Supporting innovation

- *Stakeholders should collaborate in the development, evaluation and implementation of innovative approaches to optimise transfusion use and blood management in chronic diseases.*
- *Future EU legislation on blood should be designed and harmonised to help foster innovation and its uptake.*

Raising public awareness

- *EU and national-level policymakers should collaborate with all relevant stakeholders to boost public awareness of anaemia requiring regular blood transfusion, including blood donation, and to support existing or forthcoming initiatives in the field with funding, participation and/or endorsement.*

Conclusions and call to action

We call on the EU and national decision-makers and other stakeholders to act on these recommendations to help improve patient outcomes, reduce the potential risks of transfusions, and avoid blood wastage to help safeguard supplies and reduce the costs of transfusions.

At EU level, the Evaluation of the Blood, Tissue and Cells Directives (Directives 2002/98/EC and 2004/23/EC) should prompt revision of legislation regarding blood, taking this report into account.

1. Introduction

A collaborative, patient-centred approach is needed to rethink and optimise blood management in chronic diseases in Europe. There are many aspects to optimising blood management. This report focuses primarily on blood transfusion. For many healthcare professionals, blood transfusion remains the first-line treatment for patients with chronic anaemia (i.e. a lack of red blood cells or haemoglobin in the blood) caused by malignant and non-malignant blood diseases, solid cancers and various other chronic diseases.

Blood transfusion is one of the most commonly used procedures in hospitals.[1] Across the European Union (EU), 1400 blood establishments collect and process 20 million blood donations every year, enabling around 25 million transfusions to patients.[2] However, while blood transfusion can help to save, extend and improve lives, it also has inherent risks and negative effects on patients, both in the acute care setting and in chronically ill patients. In surgery, transfusion rates are already falling. This is as a result of changes in clinical practice (known as Patient Blood Management) implemented to manage and preserve the patient's own blood to improve patient outcomes, rather than resorting to blood transfusion in the first place. This helps to safeguard finite supplies of blood for use in situations where transfusions are the only option.[3] Optimising blood use is also likely to become increasingly important to ensure the sustainability of blood supplies, which are expected to come under increasing pressure owing to societal ageing[4] and migration,[5] and because donation awareness campaigns are no longer high on the healthcare agenda in some countries.[6]

The majority of blood transfusions are now used in medical care for chronic diseases, rather than in surgery.[7,8] Accordingly, optimising blood management in chronic diseases in Europe should in part aim to: 1) reduce the negative impact of blood transfusions on the lives of patients and carers and thus improve patient outcomes, including quality of life (QoL); 2) reduce the potential risks of transfusions – recognising that the risks of clinically significant pathogen-borne and other unwanted reactions have been dramatically reduced (and indeed nearly eliminated in some EU countries); and 3) avoid blood wastage, thereby safeguarding supplies for patients who genuinely need blood and reducing the costs of transfusions.

"A targeted and careful administration of blood and blood components can be expected to lead to a significant reduction in the use of allogeneic blood products, and at the same time significantly improve patient safety and outcomes."[9]

This report has been developed as part of the collaborative, multi-stakeholder Blood and Beyond initiative (see Panel). It was developed based on a roundtable meeting that brought stakeholders together to gather insights and exchange perspectives on blood transfusion and anaemia care across Europe, focusing on chronic diseases. Specifically, this report:

- *provides an overview of how blood transfusions (especially red blood cells) are used, supplied and regulated in Europe*
- *outlines the important challenges that transfusion presents from the perspective of patients, families, hospitals and healthcare systems, and societies*
- *presents a shared vision of participating stakeholders on the future of blood management in Europe and policy-focused recommendations to overcome unmet needs.*

Blood and Beyond is a multi-stakeholder initiative developed and funded by Celgene, now part of Bristol-Myers Squibb, involving experts from the fields of haematology and blood management, nursing, patient advocacy, health economics and hospital management. The aim of the initiative is to raise awareness of the impact of blood transfusion on patients, support networks, healthcare systems and society at large; with the overarching goal to help advance policies and practices that improve patient outcomes by optimising blood management and supporting innovation across Europe.

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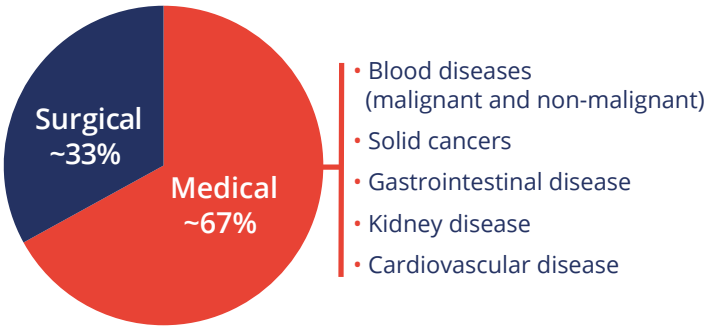
2. Blood transfusion in Europe: an overview

Key points

- *Red blood cell (RBC) transfusion is currently a cornerstone of treatment for anaemia caused by various chronic diseases. Some patients are currently dependent on regular, life-long transfusions while others receive transfusions intermittently.*
- *Blood is a finite, perishable resource requiring a complex and highly specialised supply chain spanning donation to transfusion, and involving multiple actors.*
- *European (EU)-level regulation has been beneficial, but now needs updating to reflect new realities and address gaps and divergencies identified between member states.*

Fig. 1. Most RBCs are used for medical (rather than surgical) indications.[1,8]



Introduction: why is blood transfusion considered so important?

RBC transfusions are by far the most common type of transfusion given to patients.[1] RBCs transport oxygen from the lungs to other parts of the body, and from there they carry carbon dioxide back to the lungs.

Regular RBC transfusions are currently regarded as a cornerstone of treatment for severe anaemia caused by several chronic diseases that impair the production of normal RBCs, including various malignant and non-malignant diseases of the blood (Table 1).[2–7] Together, patients with these haematological diseases account for approximately one in four RBC transfusions.[1,8] Some patients with these conditions are currently dependent on regular, lifelong blood transfusions. Others may require transfusions intermittently, depending on their level of anaemia.

RBC transfusions are also commonly used in the treatment of patients with anaemia associated with solid cancers, chronic kidney disease, gastrointestinal disease and cardiovascular disease (Fig. 1).[1,8,9]

"The daily challenges for dealing with the disease from day to day are plentiful. There's fatigue, which means exhaustion and tiredness, which follows me and that's a constant challenge, to deal with the exhaustion and tiredness."
Bergit, living with myelodysplastic syndrome

By reducing the amount of oxygen reaching the muscles and brain, anaemia commonly causes fatigue, dizziness, inability to concentrate, and palpitations. Anaemia can impair functioning and worsen patients' quality of life (QoL). The associated reduction in oxygen transportation can also cause long-term damage to organs, including the heart. Generally, anaemia management (for instance through RBC transfusions), aims to reduce or resolve the symptoms and associated organ damage, and improve the patient's QoL.[2,5]

Blood supply ecosystem

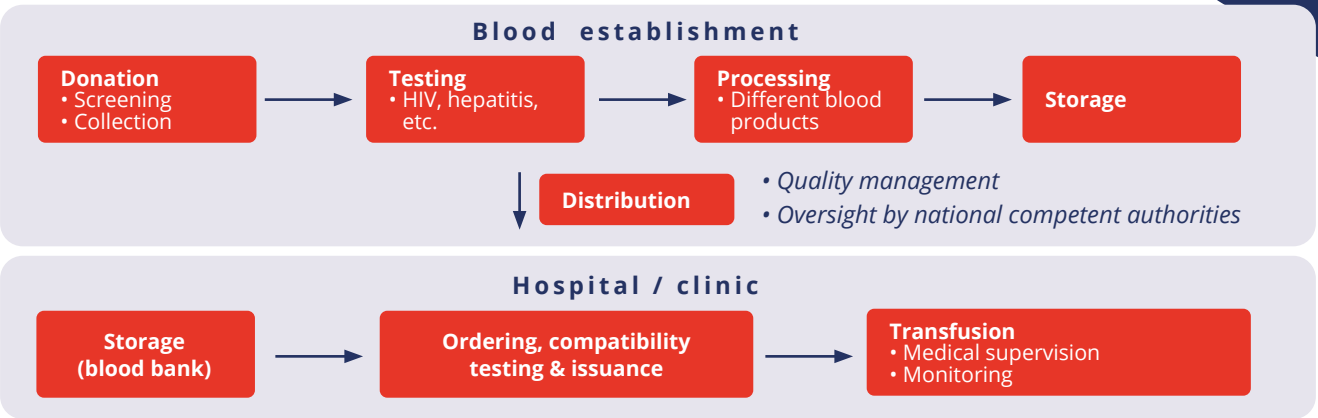
Blood is a finite natural resource that the EU encourages member states to obtain by voluntary, unpaid donation by the public (whereas donors are paid in some countries, such as in the USA). It requires a complex and highly specialised supply chain and ecosystem involving many different actors (Fig. 2). This system encompasses the recruitment and screening of potential donors, blood collection, testing and processing to produce different blood products. Moreover, specialised storage and distribution systems are necessary because blood products are perishable and have limited shelf-lives. According to national data in England and Wales, around 2% of issued RBC units are wasted, representing tens of thousands of units each year.[10]

Blood products are ordered from hospital blood banks by clinicians for issuance and transfusion to patients, after testing to avoid incompatibilities between the donor and recipient. The specific organisation and funding of the blood supply system varies between countries.[11]

Table 1. Examples of blood diseases associated with impaired RBC production and anaemia currently treated using transfusion.[2–7]

Malignancies	Inherited non-malignant conditions
• Myelodysplastic syndrome	• Thalassaemia syndromes
• Acute myeloid leukaemia	• Sickle cell disease
• Chronic myelomonocytic leukaemia	• Congenital dyserythropoietic anaemia
• Myelofibrosis	• Hereditary spherocytosis

Fig. 2. Steps in the blood supply chain



Policy and regulation

European Commission

Blood Directive: The Treaty on the Functioning of the EU (Article 168 4[a]) gives a clear mandate to the EU to take action to improve the quality and safety of substances of human origin. Blood transfusion is currently regulated at EU level by the European Blood Directive (2002/98/EC). Adopted in 2002, the Directive lays down standards of quality and safety of human blood and blood components, in order to ensure a high level of human health protection. It provides legally binding common (minimum) quality and safety standards within the EU spanning the collection and testing of human blood and blood components, and their processing, storage, and distribution when intended for transfusion.

A recent review of the Blood, Tissues and Cells Directives by DG SANTE concluded that the legislation has been beneficial in all member states. However, it acknowledges that: 1) the legislation is not up to date with scientific, technological, epidemiological and societal developments; 2) gaps and divergences now exist at national level; and 3) further measures are needed to ensure sufficiency and sustainability in the supply of blood.[11]

EU Health Programme: EU-funded actions on blood include two guidelines to help hospitals and health authorities establish Patient Blood Management as a standard to improve quality and safety of patient care.[12,13] Amongst other EU-funded initiatives, the Optimal Blood Use project generated a Manual of Optimal Blood Use to support safe, clinically effective and efficient use of blood in Europe and improve the quality of clinical transfusion processes.[14]

Council of Europe/EDQM

The European Directorate for the Quality of Medicines and HealthCare (EDQM), a directorate of the Council of Europe, publishes harmonised standards and recommendations on the collection, preparation, use and quality assurance of blood components, aiming to ensure their safety, efficacy, quality and appropriate use across Europe[15] together with annual data reports.

National Competent Authorities

The management of healthcare itself, i.e. the clinical use of blood, remains under the responsibility of the member states. All EU member states have designated National Competent Authorities that authorise and inspect blood establishments, verify compliance with quality criteria, and undertake vigilance (e.g. adverse event reporting) and traceability functions. Most member states have national blood policies and a national council or expert committee to advise the Ministry of Health on transfusion-related policy issues.[16]

World Health Organization (WHO): The WHO provides guidance and advice to member states on aspects including blood donation and use, strengthening national blood systems, quality assurance and safety, and haemovigilance. It also has roles in monitoring national blood policy and organisation, including collecting data on blood safety and availability via the WHO Global Database on Blood Safety (GDBS), and in public awareness.

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3. Priority challenges and unmet needs

Key points

- *Transfusion dependence can contribute to increased morbidity and impaired health-related quality of life (QoL) among patients. Although transfusions play an important role in therapy for many patients, regular transfusions are inconvenient and burdensome for patients and their families, and come with important risks such as iron overload and immune reactions.*
- *Transfusion dependence contributes to a substantial increase in the costs of care for chronic diseases that cause anaemia.*
- *Variations exist in transfusion practices for treating anaemia, related in part to a multiplicity of transfusion guidelines and to non-adherence to guidelines. Systems for the oversight of blood quality also vary across Europe.*
- *Optimising blood use to reduce demand and wastage will be key to ensuring the future sustainability of blood supplies, as well as improving patient outcomes.*
- *There is a pressing unmet need for alternatives to blood transfusion for the treatment of anaemia in chronic diseases.*

Introduction

Improvements in the safety and use of blood have benefited patients in recent years. However, blood transfusion – especially transfusion dependence – still comes with important challenges from the perspective of patients, families, hospitals and healthcare systems, and societies.

Impact on patients' lives

Transfusions provide short-term relief from the debilitating symptoms of anaemia in patients with chronic diseases. However, this benefit often wears off, leaving patients with symptoms while waiting for their haemoglobin level to fall below the threshold level that has been chosen to trigger their transfusion therapy.

Indeed, transfusion dependence, higher transfusion frequency, and transfusion-related iron overload and its treatment, are all associated with worse health-related QoL compared with patients with the same disease who are transfusion-independent.[1–8] Transfusion therapy can be debilitating for patients, and burdensome both for them and their caregivers and families. Blood transfusions are normally given in hospital or clinic settings. Patients may receive transfusions as often as every 1–5 weeks.[9–11] Each transfusion visit can take a full day, given the need for travel to the clinic, blood tests (including compatibility tests), obtainment of suitable blood from the blood bank, followed by the transfusion procedure itself and the subsequent monitoring for any adverse reactions. This is inconvenient and disruptive to normal activities and, depending on the patient's situation, can often negatively affect employment or school performance,[12,13] as well as family and social life.

"No transfusion has had the same impact on me as the first one. I felt I could jump off of the roof, like I was healthy again. It made a world of difference. Now my strength is leaving me after 8 or 9 days following a transfusion. This means I am short of breath – I have an even harder time climbing stairs than when I've had a transfusion ... Concentration is a problem ... I have a hard time with the fact that I can't focus for more than three hours, that's why I was not able to work anymore very quickly."
Bergit, living with myelodysplastic syndrome

"Having thalassaemia and having regular blood transfusions has affected my life in many different ways. First of all, you have all the social issues. When I was younger, every 3 weeks I was not in school for 3 days. This is quite a lot."
Stella, living with β-thalassaemia

"It adds up to about 6 to 8 hours, depending on how long the tests at the blood bank take. It's a working day. I usually get there at 8am and usually get home by 3pm ... Whenever I need a transfusion, any other appointment gets cancelled – no matter how important it is to me. My friends and family all know that. They know that I'm quite unreliable ..."
Bergit, living with myelodysplastic syndrome

Accessing hospital transfusion services can be particularly onerous for certain patients (e.g. the elderly, those on low incomes and those living in rural communities).

Hospital visits can also involve significant out-of-pocket costs for patients and families. According to one survey, 31% and 21% of transfusion-dependent patients with myelodysplastic syndrome reported that the costs of travelling to hospital and of car parking, respectively, had an impact on their household budget.[14]

Transfusion risks

Current technologies and policies for testing for known pathogens and donor-recipient incompatibilities have made blood transfusion very safe in terms of transfusion-related infections and immediate transfusion reactions.

Nevertheless, blood transfusion is a medical procedure, with potentially life-threatening complications, that needs to be delivered by well-educated healthcare providers following strict guidelines and standard operating procedures. Furthermore, liberal blood transfusion policies are independently associated with increased morbidity (including hospital-acquired infections, ischaemic events and other complications and sequelae), length of hospital stay and mortality in various clinical settings – giving rise to the approach of Patient Blood Management (PBM; Section 4).[15–19]

Transfusion-dependent patients with haematological diseases have a worse prognosis (including a higher risk of death) than those with the same disease who are transfusion-independent.[20–22] While this reflects the greater severity of underlying disease among transfusion-dependent patients, long-term transfusion therapy can also contribute to poor clinical outcomes.[23]

Key risks of long-term transfusion therapy include:

- ***Iron overload:*** *Each red blood cell (RBC) transfusion contains iron. As the human body cannot excrete excess iron, regular transfusion therapy invariably causes iron to accumulate and exceed normal levels. Known as iron overload, this damages many organs (including the heart and liver) and worsens survival.[10,23] Iron overload can occur after as few as 10–20 transfusions.[9] Iron chelating therapy is used to reduce transfusion-related iron overload.[9,23] However, patients may not receive optimal treatment since this additional therapy requires careful dosage adjustment, can also cause significant adverse effects and adherence can be poor.*
- ***Immune-mediated reactions:*** *Alloimmunisation (i.e. an immune response due to genetic differences between the donor and recipient RBCs) is a major complication of chronic transfusions that can cause delayed transfusion reactions and difficulties in finding compatible blood for patients. In β-thalassaemia, alloimmunisation is particularly common in patients with thalassaemia intermedia who start transfusions after the age of 3 years.[9] Other immune-mediated reactions include acute reactions and a severe reaction known as transfusion-related acute lung injury (TRALI). Adverse transfusion reactions and alloimmunisation may occur in around 50% and 10–20% of patients, respectively.[10]*
- ***Infections:*** *Donor and blood testing by blood establishments have reduced the risk of transfusion-transmitted infections to low or negligible levels.[24] Systems are in place at national and European levels to monitor epidemiological risks or the emergence of new transmittable diseases. Nevertheless, there remains a risk of infection transmission by unknown or emerging pathogens and an increased risk of infections due to transfusion-related suppression of the immune system.[25]*

Clinical practice variations and education

The inter- and intra-institutional variability in anaemia treatment and transfusion practices, including in chronic diseases, underlines the need to improve the quality of care and thereby reduce blood demand while improving patient outcomes.[26–32]

"One bag of blood contains as much iron as one person normally ingests through nutrition during the course of half a year. That means, with a double blood transfusion, your intake is a year's worth of iron. Therefore, there is a severe risk of iron overload, especially since the body has no capacity to get rid of excess iron."
Prof. Norbert Gattermann, University Cancer Center, Heinrich Heine University, Düsseldorf, Germany

These variations may be related to different clinical and biological characteristics between patients with different diseases. This is compounded by the multiplicity of transfusion guidelines that exists across the various medical specialties involved, e.g. haematology, oncology, cardiology and nephrology. Moreover, evidence suggests that national transfusion guidelines may often not be followed[31,32] and may be difficult to apply in patients with multiple comorbidities, each of which contributes to the underlying anaemia (e.g. chronic blood disease in conjunction with chronic kidney failure).

Generally, a holistic and patient-centred approach beyond transfusion therapy – based on the principles of PBM (Section 4) – has yet to be widely applied to the treatment of anaemia in patients with chronic diseases.

Ensuring the quality of blood transfusion

The quality of transfusion products is a key concern for patients and families, as well as healthcare professionals. Being a biological product, blood quality is affected by donor-to-donor variation, as well as the integrity of each step in the supply chain (Section 2), underscoring the importance of quality management throughout.[24]

One important issue is the potential for "storage lesions".[33] Storage lesions include a variety of biochemical changes that can damage stored RBCs, including changes in oxygen affinity, metabolic alterations like glutathione depletion, oxidative damage to lipids and proteins, as well as morphological abnormalities. Storage lesions also include the formation of erythrocyte-derived extracellular vesicles, which can interfere with blood coagulation and induce a pro-inflammatory host response. Collectively, storage lesions may aggravate the bone marrow dysfunction that causes chronic transfusion-dependent anaemia in the first place, e.g. in patients with myelodysplastic syndrome.

Some experts recommend that patients who require frequent transfusions (e.g. those with chronic blood diseases) should be given 'young' (i.e. fresh) RBC units, as these allow for less frequent transfusions and hence reduce transfusion-related risks.[34] However, specific policies are lacking and variable across the EU and within member states, and are tempered by limitations in blood supplies. Moreover, the prioritisation of fresh units for chronic care patients raises ethical questions because the use of older RBC units might worsen outcomes in adult acute care patients.

Although EU-wide quality oversight provisions are seen as a major achievement of the Blood Directive, the Evaluation of the Blood, Tissues and Cells Directives concluded that the independence and technical expertise of national competent authorities is not fully ensured. The evaluation points to significant variation in the authorities themselves, the associated inspection systems, authorisation of product preparation processes, and procedures for reporting of adverse reactions.[24]

Healthcare costs of transfusions

Blood may often be taken for granted as inexpensive, but in fact it entails substantial costs when considering the:

- *complex, specialised supply chain (Section 2)*
- *healthcare costs, i.e. products, tests, transfusion procedure and management of any associated complications*

- *costs incurred by donors and recipients (travel, time, absenteeism).*

For example, a pooled estimate from studies in Austria, France, Sweden, Switzerland and the UK put the cost of transfusing two units of RBCs at €878.[35] This is more or less consistent with an estimate of €772 by the Swedish Institute for Health Economics. Assuming patients received two units every 2 weeks, this Swedish estimate translates into €20,072 per patient each year and an annual cost of €154.4 million/year for a country with a total population of 10 million.[36] However, this does not include all the indirect costs (e.g. through lost productivity) and hence underestimates the total cost associated with transfusion. Indeed, the full cost impact of transfusion therapy in chronic diseases has not been well studied to date.

Long-term transfusion and iron chelation therapy together contribute substantially to the costs of care for chronic diseases that cause anaemia. For example, in myelodysplastic syndrome, transfusion-dependence more than doubles the cost of care compared with non-dependent patients.[2,37–40] In β-thalassaemia, transfusions reportedly account for 31–38% of care costs, while iron chelation therapy accounts for an additional 45–48%.[41,42] Transfusions are also one of the major cost drivers in acute myeloid leukaemia care.[43]

Negotiating adequate reimbursement for transfusions is also a major concern for hospitals. Reimbursement for blood transfusions can be complex and problematic. Depending on the clinical situation and the healthcare system, blood transfusion costs may or may not be fully included in applicable Diagnosis Related Groups (DRG) systems, and may depend on multiple reimbursement mechanisms.[44]

Transfusion demand and supply

Demand

There is a large variation between EU countries in the number of blood transfusions used per capita.[45] While the demand for blood has fallen in recent years in Europe owing to PBM initiatives, demographic changes threaten to increase future demands and put pressure on supplies.[46,47] As European populations age (owing to increased life expectancy and decreased birth rates), there will be a greater need for complex surgery and cancer therapy where blood transfusion is used, together with an increased prevalence of chronic diseases causing anaemia. In addition, demand for transfusion may be affected by increased migration of people to Europe from areas where haemoglobinopathies such as β-thalassaemia are endemic.[48]

"There are some areas of blood transfusion which could be improved. For example, the first thing is accessibility. [...] I think this must be solved in Europe because we're living in 2020 and it's not possible that patients go to the hospital and they are sent home again because there is no blood. This would also improve the quality of life, because when it's not possible for me to get blood, it's not possible for me to stand up, to go to my work, to live a normal life, when my body cannot support this. So, I'm tired and I cannot just live normally. [...] Not only there should be blood available, but there should be blood available at any time, so you don't have to not go to work or not go to school."
Stella, living with β-thalassaemia

"In most cases, no alternative treatments exist to save or enhance human lives."
European Commission Evaluation of the Blood, Tissues and Cells Directives, 2019[23]

"Patients who depend on blood transfusions to manage β-thalassaemia ... have an unmet medical need for new treatments."
European Medicines Agency, 2019[51]

"Efforts to develop new scientific discoveries and therapeutics can have a major impact on the growing and aging population in Europe at many different levels. Elucidation of normal erythropoiesis is ... essential to develop new strategies for treating the wide variety of conditions affecting the erythroid system. ... Identifying drugs that ... may inhibit ineffective erythropoiesis and improve anemia in those with low-risk myelodysplastic syndrome represents a priority."
European Haematology Association Roadmap for European Hematology Research[49]

"Anaemia thus remains a conspicuous unmet need in the management of myelofibrosis."
Naymagon et al.[20]

"I should expect that the major burden is a daily iron chelation, but that is not what I experience when I ask the patients. They are much more concerned about blood transfusions. So it remains an unmet need to find an alternative treatment."
Prof. Maria-Domenica Cappellini, University of Milan, Italy

Supply

At present, the supply of blood generally meets demand in the EU. However, as the Evaluation of the Blood, Tissues and Cells Directives recently acknowledged,[24] seasonal shortages can occur in some member states and affect patients' access to transfusion. Delays in the transfusion protocol can be particularly harmful for patients whose lives depend on transfusion. In particular, the development of alloimmunisation among patients who are chronically transfused can make it difficult to find supplies of suitable blood. RBCs are rarely exchanged between member states, except in emergency or humanitarian situations or in difficult cases with very rare blood types.[24] Countries with a large population of patients with chronic anaemias have greater difficulties in establishing adequate supplies. For example, Greece still imports blood mainly from Switzerland to overcome seasonal shortfall from local donation, which is more apparent during the summer vacation period. Even where overt shortages may not be present, stocks in some countries may be low and placed under unprecedented pressure at times, as recently reported in France and the UK.[49,50]

Meeting any increase in future demands will be challenging because the population of suitable blood donors, as a proportion of the ageing population, is shrinking. The Evaluation of the Blood, Tissues and Cells Directives concluded that the current provisions are insufficient to support an adequate and sustainable supply for blood. It warned of a lack of provisions and actions to ensure continuity of supply, and of variations in preparedness between countries.[24] The Evaluation also noted the lack of EU-level mandatory provisions for monitoring of supply, demand, import/export and inter-Member State exchanges. In 2010, a World Health Assembly Resolution also urged member states "to take all necessary steps to establish, implement and support nationally-coordinated, efficiently-managed and sustainable blood and plasma programmes according to the availability of resources, with the aim of achieving self-sufficiency".[51]

In sum, optimising blood usage to reduce demand and avoid wastage is key to ensuring the sustainability of blood supplies, as well as improving patient outcomes.

Lack of treatment options other than transfusion

Treatment recommendations and available therapies for chronic forms of anaemia depend on the underlying disease. However, there are few alternative options to treat severe anaemia once patients require transfusions. Stem cell transplantation offers the potential of a cure for some chronic blood diseases, but also entails significant risks and is not suitable or available for all patients.

Many experts and stakeholders have therefore drawn attention to the unmet need for alternatives to blood transfusion for the treatment of anaemia in chronic diseases.[21,24,52–55]

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4. Rethinking blood use – a shared vision

Introduction

This section presents a shared vision and policy-focused recommendations to help:

- *optimise blood management to improve outcomes for patients with chronic diseases while reducing the demand for donor blood and thereby safeguarding blood supplies for patients who need them; and*
- *promote access to timely, high-quality and safe blood transfusion therapy for all patients with chronic diseases who genuinely require transfusions. We focus on clinical transfusion aspects, as a detailed consideration of the upstream supply chain is beyond the scope of this group.*

At European Union (EU) level, the recommendations in this section should be taken forward via the following overarching mechanisms:

- *An EU Action Plan should be developed to strengthen member states' cooperation in the blood sector – similar to the EU action plan on organ donation and transplantation (2009–2015).*[1]
- *An EU Joint Action or a series of EU-funded projects should be established to identify and share good practices, educate and empower patients and families, and facilitate healthcare professionals' education on blood transfusion and Patient Blood Management (PBM) more broadly.*
- *EU health research funding support is necessary to address priority research topics.*

The recommendations in this section are also intended to help inform the development of future EU legislation on blood.

Supporting patient-centred services

Several approaches can be used to improve the patient-centredness of transfusion therapy, where this is necessary.

Improving accessibility

Research and innovation should be directed toward improving access to transfusion service delivery and modalities to make chronic transfusion therapy less burdensome for patients and caregivers.

What can we learn from patient blood management?

A shift is underway in many areas of the world to optimise patient outcomes while reducing perioperative blood use based on the concept of patient blood management. This is an evidence-based bundle of care to optimise patient outcomes by managing and preserving a patient's blood.[2,3] *PBM is based on three pillars: optimising the patient's own blood volume, minimising blood loss and bleeding, and harnessing and optimising the physiological reserve of anaemia.*[4,5]

Patient blood management reduces the need for transfusions, together with complication and mortality rates, length of hospital stay, and costs.[2,6,7,8] *Endorsed by the World Health Organization, it has been led by Australia, USA and within Europe in the Netherlands and Austria. Further efforts are underway to widen its implementation.*[2,3,6,9] *We would argue that approaches to optimising blood use in chronic diseases warrant similar policy attention.*

EU guidance recommends that initiatives should increasingly focus on PBM in medical patients, especially haematology patients. It encourages transfusion stakeholders "to take a fresh look at their professional fields and discover new opportunities for safely reducing the transfusion rate in their hospitals".[10]

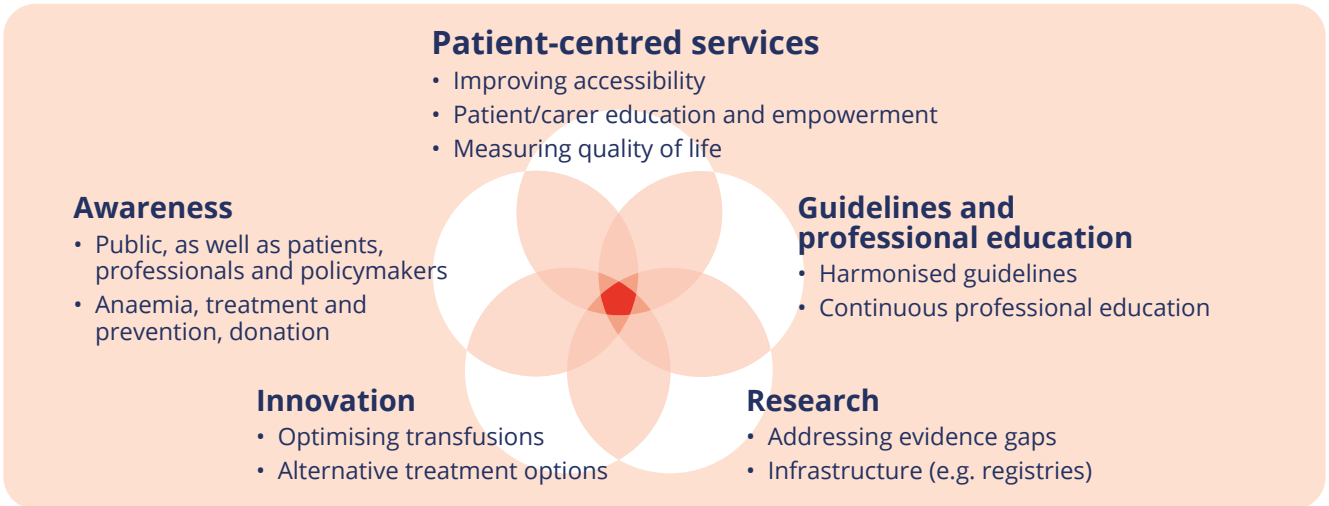
Empowering patients and caregivers

High-quality education and support are required for chronic disease patients with anaemia (and their caregivers) regarding the role and impact of transfusions and other forms of PBM to allow patients to participate in decision-making and to improve quality of life (QoL).[11–13]

Hospitals and health departments should also collaborate with national and EU-level organisations representing patients and all relevant healthcare professionals in the development of support materials and programmes. These should include appropriate information on the patient's disease and respective primary and alternative treatment, together with the value of proper adherence to therapeutic plans. These programmes should be updated according to scientific developments.

Other forms of holistic and social support for patients and caregivers may also be of benefit to help manage the impact of chronic transfusions.[14,15] This may include access to mental health or counselling services, integrated health and social care services, and

Fig. 3: Schematic summary of recommendations to help optimise transfusion and patient blood management in chronic diseases.



employment or welfare policies that allow working time arrangements and reimbursement to caregivers for time taken off work for hospital or clinic visits.

Measuring QoL

Physicians may underestimate the impact of chronic conditions and the associated anaemia on QoL[16]. Patient-reported outcomes (PRO) should be assessed in routine clinical care to help to better evaluate the symptom burden and to improve patient-centredness, quality of care and QoL.[16,17] Disease-specific QoL measures may exist for many conditions.[16–19] Notably, the EU-funded MDS-Right project is currently evaluating the impact of myelodysplastic syndrome and therapeutic interventions on health-related QoL, together with treatment costs, in elderly patients.

***Recommendation:** EU-funded actions should be established to help identify and share good practices with respect to 1) improving access to transfusion services and lessening the impact of treatment on patients; 2) educating and empowering patients and families with respect to transfusions and other forms of patient blood management; and 3) assessing QoL in clinical practice in patients with chronic anaemia.*

Supporting harmonised guidelines and professional education

Guidelines

In order to ensure appropriate anaemia management and optimal use of blood, transfusion decisions should always adhere to current evidence-based guidelines and a patient-specific evaluation.[10] European-level guidelines are important to support good clinical practice and drive common standards of care. At present there are multiple guidelines for transfusion practices developed by and for different medical specialties, which hampers a common approach. In contrast, there are relatively few guidelines for anaemia management, more broadly. Moreover, many of the transfusion guidelines have been developed based on expert opinions due to paucity of available data. For example, the time of initiation of chronic transfusion and the levels of pre-transfusion haemoglobin for transfusion-dependent thalassaemia were based on scarce paediatric data on the improvement of growth in these patients with transfusion implementation and indirect measures of the suppression of RBC production.

There is a pressing need for a multidisciplinary, harmonised guideline that takes account of multiple co-morbidities. This should be patient-centred, aiming to optimising QoL rather than haemoglobin levels and clinical outcomes alone, and considering the individualised needs of patients. Guidelines should be updated to take account of the developing evidence base.

***Recommendations:** Clinical guideline developers from relevant specialties (e.g. scientific/professional societies) should collaborate to develop, disseminate and implement harmonised, evidence-based European-level guidelines for patient blood management, including transfusion, in chronic diseases.*

Clinical guidelines should be developed in collaboration with patient advocacy organisations.

Measures are required to better implement and audit clinical guidelines to ensure all patients have access to a high standard of care. The development of reference centres to guide and supervise the appropriate management of regularly transfused patients is essential for proper healthcare provision. Approaches to improving compliance with transfusion guidelines include: integration in clinical decision support tools; ordering systems; regular audits of transfusion practices and feedback; or automated continuous data capture and analysis.[13]

***Recommendation:** The EU should support best practice sharing on guideline implementation and audit with respect to transfusion and other aspects of patient blood management in chronic diseases.*

Education of healthcare professionals

Undergraduate and post-graduate clinical training and education of healthcare professionals on blood management in chronic diseases is centrally important. This training should be continuous and based on evidence-based guidelines, taking into account developments in the available evidence and technologies. It applies to all staff involved in patient care, but is particularly relevant to specialist clinicians (e.g. haematologists, oncologists, paediatricians, geriatricians, gastroenterologists and cardiologists), together with primary care doctors, specialist nurses, clinical pharmacists and quality and safety managers.[13] Continuous education should be supported and motivated by hospital administrators, professional societies and other actors.

***Recommendation:** All stakeholders in health professional education (including professional societies, universities, hospitals, authorities governing professional education, health ministries and the EU) should promote and facilitate continuous education on patient blood management in chronic diseases.*

Supporting research

At a European level, current public spending on haematology research does not match the vast medical need in this field.[20] Research is vital to address the deficit of evidence on transfusion and other aspects of PBM in chronic diseases and to develop new approaches to prevention and treatment of anaemia. The panel below summarises key priorities for research.

Recommendations for the continuous collection of patient-level data on anaemia, transfusion and outcome, coupled with benchmarking and reporting systems,[10,13]

Research priorities regarding anaemia, transfusion and broader patient blood management in chronic diseases

- *Disease epidemiology and course in relation to anaemia*
- *Contribution that blood transfusion therapy makes to the clinical, societal and economic impact of chronic diseases (national or international level)*
- *Evaluation of biological markers assessing the impact of anaemia and redefining the goals of transfusion therapy based on these markers*
- *Patient-reported impact and outcomes (including QoL) of anaemia, blood transfusion and other modes of blood management*
- *Service delivery approaches to make chronic transfusion therapy less burdensome for patients and caregivers*
- *Clinical and cost-effectiveness outcomes from transfusion and other means of patient blood management, especially long-term morbidity, mortality, and cost-effectiveness*
- *International comparison between health systems in blood transfusion reimbursement*

should be applied in chronic disease settings to guide the implementation of new standards of care that reduce transfusion exposure and improve patient outcomes.

EU and national-level funding are necessary to support infrastructures (e.g. disease registries) to facilitate real-world evidence collection to inform optimisation of transfusion and innovation in PBM in chronic diseases. Registries may be either disease- or treatment- (i.e. transfusion) specific. The latter supports better health system planning and the inclusion of very rare diseases. Many registries are supported by the scientific community and are not organised by governmental initiatives. In these cases, appropriate public funding must be secured to support maintenance and improvements of the registries to ensure their sustainability and the generation of reliable and comparable data that can guide clinical decisions and policy making.

***Recommendations:** At EU and national level, health research funding should be directed to priority research topics to better understand and address the health impact of anaemia and transfusions in chronic diseases, with research findings being systematically translated into policy design and used to update good practice.*

Hospitals, insurers and health ministries should collaborate to develop suitable patient-level data collection and benchmarking systems.

National health ministries and the EU should provide suitable and long-term funding for disease registries.

The EU should support collaborative research in this field, including via the harmonisation of disease registries, and support research into unmet clinical and scientific needs.

Supporting innovation

Innovation in various aspects of care will be key to optimising transfusion use and PBM more broadly to improve patient outcomes and limit unnecessary transfusions and the associated impacts.

Optimising blood use

Innovation should be supported to help ensure that blood transfusions are used in optimal ways and with reduced risks. Areas where innovation is required include:

- *continued innovation in blood processing, pathogen testing, storage compatibility testing to help improve supply and safety*
- *improved transfusion service delivery, transfusion protocols, and decision support systems that optimise blood use based on the evolving evidence base*
- *novel treatments for iron overload due to chronic transfusion.*

Alternatives to blood use

Crucially, in light of the well-established unmet need (Section 3), all stakeholders should support the development, availability and access to novel, evidence-based treatment options for anaemia that reduce the need for transfusions. These include:

- *alternative treatment options to manage anaemia and reduce transfusion dependency in chronic diseases*
- *development of alternatives to blood, such as synthetic oxygen carriers*
- *gene therapy or bone marrow transplantation for inherited diseases.*

Haemophilia: a case study of innovation

Haemophilias are inherited bleeding disorders caused by a deficiency in certain blood factors involved in blood clotting. The last decade has seen a revolution in haemophilia therapy, providing a timely example of the impact of accelerated innovation towards patient benefit. New and emerging approaches to haemophilia treatment include new types of replacement blood factors, non-factor therapies with novel modes of action, and the potential of a cure via gene therapy.[23]

- ***Recommendation:** Stakeholders should collaborate in the development, evaluation and implementation of innovative approaches to optimise transfusion use and blood management in chronic diseases.*

EU policy and legislation

The Evaluation of the Blood, Tissues and Cells Directives concluded that a high level of innovation in the sector had occurred and is likely to continue or increase. It is also acknowledged that new ways to collect, prepare, store and apply blood, tissues and cells to patients can bring significant health benefits, usually in a cost-effective manner that achieves wide patient access. However, it is recognised that legislation has not kept up with innovation. For example, it pointed to gaps and divergencies in provisions for authorisation of novel processing methods and some lack of coherence between applicable frameworks and communication between relevant authorities.[21] Thus, outdated legislation may hamper investment in the uptake of innovation.[21]

***Recommendation:** Future EU legislation on blood should be designed and harmonised to help foster innovation and its uptake.*

One suggestion to this end would be to have the legislation itself be "light" on technical points, and instead reference the Council of Europe/EDQM blood guide[22] to allow regular updates on technical aspects based on an annual review.

Raising public awareness

Fundamentally, there is a need for national and/or EU initiatives to improve public awareness about anaemia requiring regular blood transfusions,[13] including its causes and consequences, current approaches to treatment (including the impact of transfusions), and prevention (e.g. via screening for haemoglobinopathies during pregnancy).

New approaches are also necessary to recruit and retain blood donors among the public. Better communication of the pressures facing blood supplies, and the role of blood in the lifelong treatment of patients with some chronic diseases, might help to promote regular donations. By highlighting the number of annual blood donations needed to treat different patients with various diseases who require frequent transfusions, the general public can be educated on blood donation needs.

A collaborative international/EU "Anaemia Day" co-ordinated by WHO or the EU for national roll-out could be an important vehicle to build awareness.[13]

Hospital communications departments have a role in educating the public, as well as patients.[10]

***Recommendation:** EU and national-level policymakers should collaborate with all relevant stakeholders to boost public awareness of anaemia requiring regular blood transfusion, including blood donation, and to support existing or forthcoming initiatives in the field with funding, participation and/or endorsement.*

Conclusions and call to action

Optimising blood management in chronic diseases in Europe will involve consideration of many topics. This report, a part of the Blood and Beyond initiative, focuses primarily on blood transfusion. It represents a unique collaboration between stakeholders concerned with optimising blood transfusion and broader patient blood management in chronic diseases.

We call on the EU and national decision-makers and other stakeholders to act on the recommendations in Section 4 to help improve patient outcomes, reduce the potential risks of transfusions, and avoid blood wastage to help safeguard supplies and reduce the costs of transfusions. In particular, at EU level, the Evaluation of the Blood, Tissues and Cells Directives should prompt revision of legislation regarding blood, taking this report into account.

The contributors to this report stand ready to support these efforts. Updates on further activities of the Blood and Beyond initiative can be found at www.bloodandbeyond.com.

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This report was informed by discussions at a multi-stakeholder roundtable held in Brussels on 26 September 2019, attended by the following individuals:

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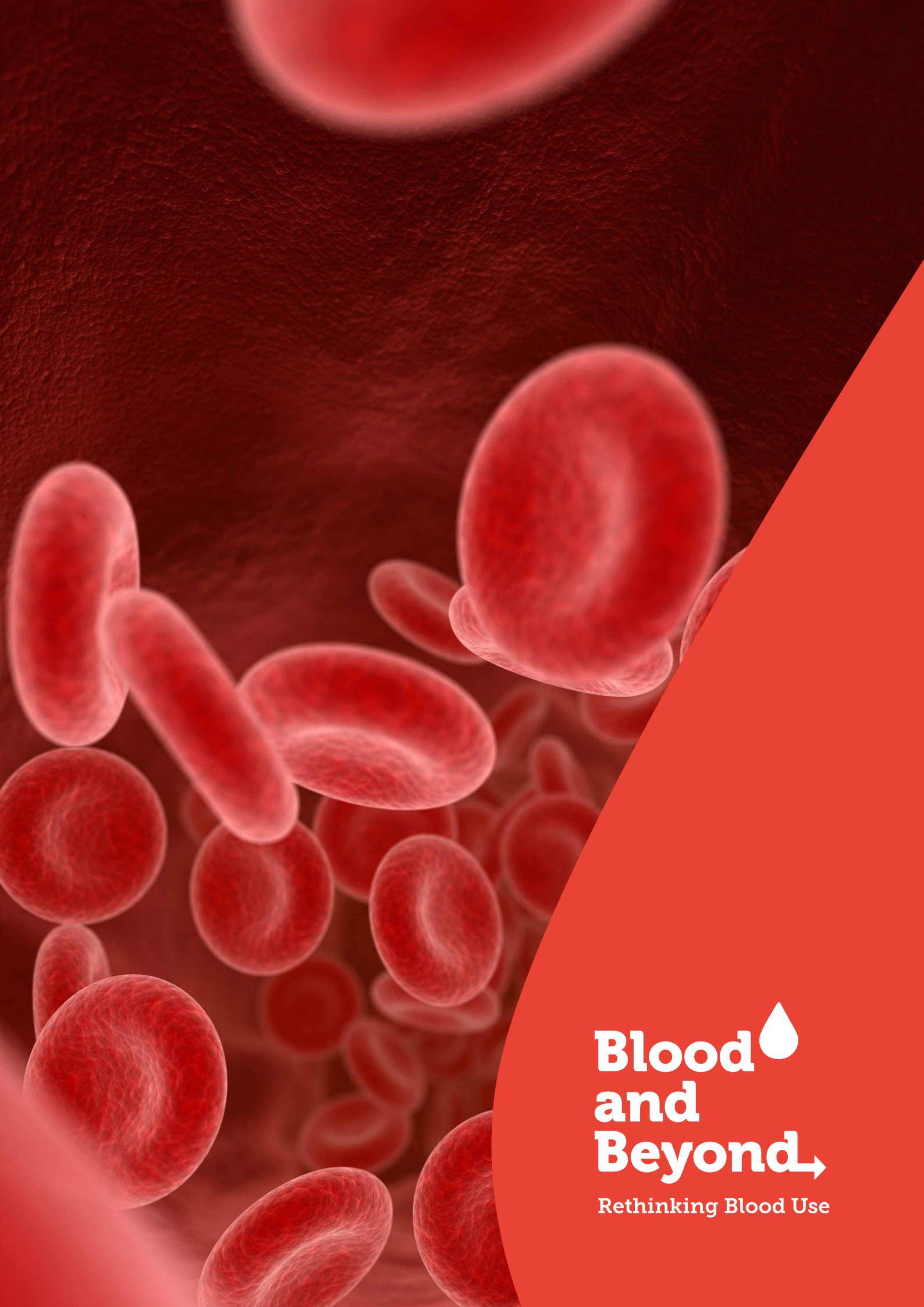
Only participants listed on page 3 contributed to the report.
Other individuals did not review the present report and are not responsible for its content.



Blood and Beyond

Rethinking Blood Use