Institution: University of Cambridge		
Unit of Assessment: 2 Public Health, Health Services and Primary Care		
Title of case study: Improving the safety and efficiency of blood donation and transfusion		
Period when the underpinning research was undertaken: 2012-2018		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Emanuele Di Angelantonio	Professor	2005-current
John Danesh	Professor	2001-current
Stephen Kaptoge	Principal Research Associate	2005-current
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Simon Thompson	Director of Research	2011-2018
Period when the claimed impact occurred: 2018-present		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact (indicative maximum 100 words)

Blood transfusions save millions of lives every year around the world. But the evidence-base for the safety and efficiency of blood donation and transfusion has remained weak and underdeveloped, risking harm and waste. University of Cambridge collaborative research has addressed this challenge through innovative studies identifying how frequently blood can safely be given, how to ensure people do not proceed to give blood when their iron stores are too low, how to improve organisation of blood donation services, and how to avoid adverse events associated with transfusion. Findings have changed policies and practices in the UK, USA, Canada, and the Netherlands, contributing to improvements in blood supply, prevention of anaemia, and efficiency of blood services. The research has also enabled more personalised matching of donated blood with recipients' immune profiles to find more and better matches and reduce serious reactions. By decreasing harms and risks, and by improving services, this research has delivered benefits for donors, patients, blood services, and health systems on a large scale.

2. Underpinning research (indicative maximum 500 words)

Blood donation and transfusion: life-saving interventions

Globally, around 100 million blood transfusions happen every year, saving many lives and promoting recovery from trauma, surgery, cancer, anaemia, haemophilia and many other conditions (WHO statistics). Although blood donation and transfusion have been practised for more than a century, a weak evidence base has led to major uncertainties and variations in key practices around the world. Specific uncertainties have persisted about how frequently donors can safely give blood, how to ensure donors are not bled when they are at risk of anaemia, how to encourage people to keep donation appointments, and how to avoid harmful sensitisation of recipients to donor blood.

Cambridge-led collaborative research has addressed these and other important practical issues, often for the first time, in rigorous large-scale studies. It has done this in close partnership with NHS Blood and Transplant (NHSBT, the national blood service of England), other national blood services, blood donors and recipients, and other researchers.

How often can people safely give blood? The INTERVAL trial and extension study

The Cambridge-led INTERVAL study, undertaken with NHSBT and Oxford University researchers, was the first-ever individually randomised controlled trial to examine the frequency of blood donation on donor health and blood supply [1]. Between 2012 and 2014, INTERVAL recruited around 45,000 blood donors in England. Men were randomly assigned to give blood at three different intervals of frequency: 8, 10 or 12 weeks between each donation. Women were randomly allocated to give blood at 12-, 14- or 16-week intervals. All participants were initially followed up for two years. An extension study, involving participants who agreed to continue trial participation on their originally allocated intervals for four years of follow-up, allowed assessment of the longer-term effects [2].

The trial found that the most frequent interval (every eight weeks for men and every 12 weeks

for women) was associated with more blood being donated: 33% more for men and 24% more for women, compared with the least frequent interval. Increasing blood supply through more frequent donation did not appear to have any major negative effects for donors. But there were some minor unwanted consequences, with increased frequency of donation associated with increased feelings of faintness and tiredness [1]. An important finding of the trial was that **donating blood more frequently was more likely to deplete donors' iron stores and to result in more deferrals of donation for low haemoglobin** (where donors show up to give blood but cannot do so because their iron stores are too low) [1].

The extension study confirmed that more frequent donation can be maintained over a four-year period without causing major harm to donor health, but it **also showed iron depletion became more pronounced over time** [2]. The study included an evaluation of an intensive reminder approach, finding that it encourages donors to keep blood donation appointments and results in more blood being collected [2].

Identifying the best way to do pre-donation screening to prevent inappropriate bleeding of people with low iron stores: the COMPARE study

INTERVAL showed that **around 10% of blood donors were being inappropriately bled**: they were found to have a haemoglobin concentration (an indicator of iron stores) below the legal requirements specified by the Blood Safety Quality Regulations. This was happening even though these donors had passed in-session pre-donation screening tests [1,2]. It meant that then-current screening processes were not good enough at detecting low iron stores, increasing the risks that some donors might develop anaemia after giving blood.

To address this problem, the Cambridge-led COMPARE study (2016-2017) was undertaken with NHSBT and others. The largest-ever diagnostic accuracy study in blood donation, it compared four rapid field methods to test for haemoglobin levels with a gold standard laboratory method in over 21,000 donors [3]. Using a scorecard of outcomes that assessed accuracy, feasibility, donor acceptability, and cost, the study judged the best approach to be **a simple finger-prick method**. It outperformed newer (and more costly) methods, including a non-invasive light-shining spectrometry method that was being adopted at that time by several European countries [3].

Enhancing compatibility between recipient blood and donor blood to prevent serious reactions through low-cost, scalable genotype matching

Ensuring immuno-compatibility between recipient and donor is essential to prevent serious reactions after blood transfusions, including sensitisation. It is, however, typically done using crude methods based on simple blood-type matching, with the result that around 500,000 recipients annually experience harm through sensitisation. Sensitisation results in a lifetime risk of haemolytic transfusion reactions, responsible for about 15% of deaths associated with blood transfusions, and renders transfusion-dependent patients un-transfusable.

Cambridge researchers, working with Dutch and American blood services, have developed and validated a novel genotyping platform for blood donors [4,5]. A pragmatic low-cost technology (<GBP20 per sample), it enables large-scale screening of dozens of red blood cell and other antigens to match donations with the immune profiles of recipients. The research found **that the likelihood of finding a compatible donor is substantially increased when genotyping is used**, compared with standard methods [4,5].

3. References to the research (indicative maximum of six references)

1. **Di Angelantonio E**, **Thompson SG**, **Kaptoge S**, **Moore C**, Walker M, …**Danesh J**. Efficiency and safety of varying the frequency of whole blood donation (INTERVAL): a randomised trial of 45 000 donors. *Lancet* 2017;390:2360-2371.*
2. **Kaptoge S**, **Di Angelantonio E**, …**Danesh J**, Thompson S. Longer-term efficiency and safety of increasing the frequency of whole blood donation (INTERVAL): extension study of a randomised trial of 20 757 blood donors. *Lancet Haematol* 2019;6(10):e510-e520.*
3. Bell S, Sweeting M, … **Kaptoge S**, … Moore C, …**Danesh J**, **Di Angelantonio E**. Comparison of four methods to measure haemoglobin concentrations in whole blood

donors (COMPARE): A diagnostic accuracy study. *Transfusion Medicine*. 2020; 1–10. https://doi.org/10.1111/tme.12750
4. Lane WJ, Westhoff CM, Gleadall NS, … Soranzo N, **Di Angelantonio E**, **Danesh J**, …Green RC; MedSeq Project. Automated typing of red blood cell and platelet antigens: a whole-genome sequencing study. *Lancet Haematol* 2018;5:e241-e251.*
5. Gleadall NS, Veldhuisen B, … **Danesh J**, …**Di Angelantonio E**, van der Schoot CE, Astle WJ, Watkins N, Lane WJ. Development and validation of a universal blood donor genotyping platform: a multinational prospective study. *Blood Adv* 2020;4(15):3495-3506.*

*These publications have been peer reviewed, providing evidence of research quality.

Competitive funding received

NHS Blood and Transplant. INTERVAL trial. GBP2,800,000, 2012-2014 (PI: **Danesh J**).
National Institute for Health Research (NIHR) Blood and Transplant Research Unit in Donor Health and Genomics. GBP5,300,000, 2015-2022 (PIs: **Di Angelantonio E**, **Danesh J**).
NHSBT. COMPARE diagnostic study. GBP300,000, 2015-2017 (PI: **Di Angelantonio E**)
NIHR BioResource. Genotyping in INTERVAL. GBP1,500,000 (PI: **Danesh J**).

4. Details of the impact (indicative maximum 750 words)

Improving the safety and efficiency of blood donation and transfusion: a global challenge

Donated blood is a crucial resource for healthcare systems, enabling life-saving transfusions. Though blood donation has been practised for over a century, and takes place on a massive scale – over 100 million donations annually worldwide, including 1.4 million in the UK (NHSBT statistics) – many basic questions relevant to safety and efficiency have not been answered. This has resulted in unwarranted variation in policies and practices that pose potential threats to people's health and to the sustainability of blood services (*Lancet* 2013). Noting this deficit in knowledge, the National Institute for Health Research (NIHR) wrote in 2014: "*Donor health is a new area of research […] that has been neglected by the international research community"* [A].

New evidence-base and long-term infrastructures to inform life-saving blood donation and transfusion practices

University of Cambridge-led collaborative efforts to address the problems of the weak evidence-base for blood donation safety and efficiency have powerfully influenced blood donation services in the UK and internationally. In 2015, the UK's first standalone research unit on blood donation was established at Cambridge, in partnership with NHSBT, Oxford University and the Wellcome Sanger Institute: the NIHR Blood and Transplant Research Unit in Donor Health and Genomics [B]. In 2017, the UK's first-ever Professorship of Blood Donor Health was established at the University of Cambridge (with Professor Di Angelantonio appointed the Foundation Chair), in partnership with NHSBT [C].

These novel infrastructures have enabled rapid translation of Cambridge-led research into new policies and practices through close collaboration with NHSBT, active engagement with policy-makers, and focus on coproducing studies to answer the most pressing questions and achieve shared goals. Studies are developed and delivered jointly to provide actionable, practical findings that directly benefit donors, recipients, blood services, and health systems. Research findings are presented regularly to NHSBT's senior leadership team and the **UK Blood Services Standing Advisory Committee on the Care and Selection of Donors**, which advises the Joint United Kingdom Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee on guidelines for the care and selection of whole blood and component donors [D]. This close relationship ensures that the research rapidly effects change on a large scale.

Impact on improving the safety of blood donation

Awarded 'Best Publication of the Year' in 2018 by the NHSBT Research & Development Awards [E], the INTERVAL trial [1,2] resolved longstanding policy debates about how frequently blood can safely be given. Recognising that more frequent donation can have unwanted effects, **Cambridge evidence now underpins NHSBT's policy of a normal**

maximum donation frequency of every 12 weeks for men and every 16 weeks for women [D].

Evidence from the INTERVAL studies has also encouraged adoption of new safety-oriented policies internationally. For example, supported by the findings of INTERVAL, **Canadian Blood Services have now increased the minimum inter-donation interval in females from 8 to 12 weeks and require donors to have higher haemoglobin before donation** to prevent inappropriate bleeding of people with low iron stores [F]. These changes reflect recognition of the INTERVAL studies as providing *"very convincing data about the importance of the minimum inter donation interval on donor iron status and Hb levels"* [F].

The Canadian Blood Services Chief Scientist reports that such policy changes resulted *"in cost savings for the organization and a better donation experience for female donors"*, and *"[are] our first steps toward helping our donors do a better job of iron maintenance"* [F]. The number of people attending donation sessions in Canada and found to have low iron stores has **decreased by over a quarter (27%)** in both women and men since 2017 [G], indicating improved safety.

Evidence from the COMPARE study has been key to reducing rates of anaemia among blood donors by convincing NHSBT to introduce a new approach to pre-donation screening of donor haemoglobin across the entire English national blood service in 2018 [H]. Following presentations and written submissions to the NHSBT Board by Professor Di Angelantonio in 2017 (later published in a scientific paper [3]), NHSBT acted swiftly on the study's key recommendation to replace the existing venous blood test with the finger-prick test that the study found to be more accurate [I]. As a direct result of this change, about 100 blood donors each day – around 30,000 every year – are estimated to be saved from avoidable anaemia and potential iron deficiency [D]. As iron deficiency can cause symptoms such as tiredness, shortness of breath, and palpitations, these are significant benefits for donors – who generously give blood to help others.

A further related impact of this research has been **avoiding potential reputational and financial damage to blood services in England**. This could have arisen if NHSBT had gone ahead, without evaluation, with adopting non-invasive light-shining methods to screen haemoglobin levels of donors. These methods were introduced in blood services in countries including Ireland, Spain, and Bavaria. But they were later found to perform poorly, leading hundreds of donors to develop avoidable anaemia by being bled when their iron stores were low. The Irish Blood Transfusion Service, for example, had to suspend blood donations for a period. The service had to pay for affected donors' medical tests and treatment, faced legal action, and provided financial compensation [J]. Its medical and scientific director described the situation as "*a 'never event' and we were very distressed by it*" [J].

The evidence from COMPARE guided NHSBT to avoid spectrometry methods, showing that these methods did not offer sufficient accuracy, especially for people of different ethnicities and skin colour types, and were unsuitable for blood services in countries with a large and ethnically diverse pool of donors such as the UK [3].

Impact on the efficiency of blood collection

The INTERVAL extension study [2] showed that an intensive, pragmatic approach combining text and telephone messages to remind donors of their appointments improved the efficiency of blood collection compared with the then-standard NHSBT protocol. Because people were more likely to keep their appointments, this strategy led to a mean increase of 0.11 units of blood collected per year from men, and 0.06 units from women. At scale, these improvements translate into around 40,000 extra litres – or 75,000 extra potential units (a unit of blood costs about GBP120) – collected from the current donor base in England of approximately 900,000 people [1,2], with associated benefits for NHSBT and the economy.

The findings led NHSBT to adopt, in 2016, the trial's comprehensive multi-modal reminder process to help donors make and keep appointments. It has been well received by donors, whose ratings of their experience are at their highest level for five years [D].

Impact on the safety of blood transfusion

Global common practice is to match blood only for the ABO and RhD blood groups, even though the imprecision in this approach results each year in an estimated 500,000 patients worldwide becoming sensitised by forming antibodies. Sensitisation is a very bad outcome: it can mean transfusion-dependent people cannot be transfused, and it increases risks of haemolytic transfusion reactions, which are responsible for about 15% of deaths associated with blood transfusions (US Food and Drug Administration statistics). In pregnancy, sensitisation may lead to potentially life-threatening haemolytic disease of the fetus or newborn infant. Until now, however, better matching has been challenging due to the cost and difficulty of more precise donor typing.

Cambridge's work with blood services in the Netherlands and USA has resulted in a validated, low-cost genotyping technology for blood groups that can be used routinely [4,5]. Its distinctive strength is that it enables more precise, reliable and personalised matching of the available blood to the immune profile of the recipient. This application of genomics-based transfusion medicine [5] **reduces risk to donation recipients, allows patients at risk of adverse reactions to be transfused, and increases the likelihood of finding suitable donor blood**.

Using this approach, blood services have identified two-to-three times more compatible donors for particularly at-risk patients, and have been able to identify at least one match for hundreds of individuals for whom previously no match could be found from the same donors using cruder methods [5]. The New York Blood Center, which serves communities of more than 75 million people and over 500 hospitals across the United States, has changed its investment decisions and strategy accordingly. *"Because we are the leader in the U.S. of genomic testing for transfusion offering testing for other blood centers across the country, your studies impact practice in all of the U.S to provide immediate clinical benefit. You have shown that genomic approaches will fundamentally change the way donors are recruited, units are stored, and products are selected for transfusion"* [K].

Already, lives are being saved as a consequence of the platform's development, with even greater potential to make transfusion safer in the future. For example, the Cambridge-devised technology was used to provide life-saving transfusion to a 24-year old Dutch patient with a serious condition who required blood with a rare profile possessed by only 1 in 400 donors. By using genotyping results generated by the platform, five compatible active donors were identified [L].

5. Sources to corroborate the impact (indicative maximum of ten references)

A. NIHR Blood & Transplant Research Units Application Guidance, p. 9.
B. NIHR Blood & Transplant Research Units Award Letter, p. 1.
C. University of Cambridge NHSBT Professorship in Donor Health.
D. Testimony from NHS Blood and Transplant, December 2020.
E. Best Publication of the Year award, 2018, NHSBT Research & Development Awards
F. Testimony from Canadian Blood Services, p. 1
G. Goldman M, Yi QL, Steed T, O'Brien SF. Changes in minimum hemoglobin and interdonation interval: impact on donor hemoglobin and donation frequency. *Transfusion*. 2019;59(5):1734–1741. doi:10.1111/trf.15155. pp. 1, 4.
H. NHSBT practice documents, pp. 5, 7.
I. Evidence of finger-prick test introduction **(i)** implications of the INTERVAL and COMPARE studies, pp. 1, 3; **(ii)** Give Blood website, 'New haemoglobin test' accessed 08/01/2021 https://www.blood.co.uk/news-and-campaigns/the-donor-autumn-2018/new-haemoglobin-test/
J. The Irish Times, 18/11/2015 https://www.irishtimes.com/news/health/blood-service-not-told-about-problems-with-testing-device-1.2433719
K. Testimony from NY Blood Center
L. Testimony from Dutch Blood Service