THINK FLT3 ONE MORE TIME

AML: DEVASTATING

WITH A FLT3 MUTATION: DISASTROUS

IN PATIENTS WITH AML,

A *FLT3-ITD* mutation drives progression and may lead to lower patient survival.[1-3]

Explore the clinical impact of FLT3 at

thinkflt3.co.uk

Prescribing information for: XOSPATA™ ▼ 40 mg film coated tablets (gilteritinib). **Indications:** Gilteritinib is indicated as monotherapy for the treatment of adult patients who have relapsed or refractory acute myeloid leukaemia (AML) with a FLT3 mutation. **Posology and administration:** Treatment with gilteritinib should be initiated and supervised by a physician experienced in the use of anti-cancer therapies. Before taking gilteritinib, relapsed or refractory AML patients must have confirmation of FMS-like tyrosine kinase 3 (FLT3) mutation (internal tandem duplication [ITD] or tyrosine kinase domain [TKD]) using a validated test. The recommended starting dose is 120 mg gilteritinib (three 40 mg tablets) orally once daily, with or without food, swallowed whole with water and should not be broken or crushed. Gilteritinib should be administered at about the same time each day. See *Special warnings and precautions for use* section on tests to be conducted prior to initiation e.g. blood chemistries, ECG & pregnancy test. Treatment should continue until the patient is no longer clinically benefiting from gilteritinib or until unacceptable toxicity occurs. Response may be delayed; therefore, continuation of treatment at the prescribed dose for up to 6 months should be considered to allow time for a clinical response. In the absence of a response (patient did not achieve a composite complete remission (CRc) after 4 weeks of treatment), the dose can be increased to 200 mg (five 40 mg tablets) once daily, if tolerated or clinically warranted. Gilteritinib may be re-initiated in patients following haematopoietic stem cell transplantation (HSCT), Planned HSCT: Interrupt treatment one week prior to administration of the conditioning regimen for HSCT. Treatment can be resumed 30 days after HSCT if engraftment was successful, the patient did not have grade ≥2 acute graft versus host disease and was in CRc. Elderly: No dose adjustment is required in patients ≥65 years of age. Gilteritinib is not recommended for use in patients with severe (Child-Pugh Class C) hepatic impairment. Please refer to SPC, section 4.2 for full instructions for use in hepatic & renal impairment. Paediatric population: The safety and efficacy of gilteritinib in children aged below 18 years has not yet been established. No data are available. Due to in vitro binding to $5HT_{2B}$, there is a potential impact on cardiac development in patients less than 6 months of age. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SPC. **Special warnings and precautions for use:** Differentiation syndrome: Gilteritinib has been associated with differentiation syndrome. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms and clinical findings of differentiation syndrome include fever, dyspnoea, pleural effusion, pericardial effusion, pulmonary oedema, hypotension, rapid weight gain, peripheral oedema, rash, and renal dysfunction. If differentiation syndrome is suspected, corticosteroid therapy should be initiated along with haemodynamic monitoring until symptom resolution. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, gilteritinib should be interrupted until signs and symptoms are no longer severe. Corticosteroids can be tapered after resolution of symptoms and should be administered for a minimum of 3 days. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid treatment. Resume gilteritinib at the same dose when signs and symptoms improve to Grade 2 or lower. Posterior reversible encephalopathy syndrome: There have been reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving gilteritinib. PRES is a rare, reversible, neurological disorder which can present with rapidly evolving symptoms including seizure, headache, confusion, visual and neurological disturbances, with or without associated hypertension and altered mental status. If PRES is suspected, it should be confirmed by brain imaging, preferably magnetic resonance imaging (MRI). Discontinuation of gilteritinib in patients who develop PRES is recommended. Prolonged QT interval: Gilteritinib has been associated with prolonged cardiac ventricular repolarisation (QT interval). QT prolongation can be observed in the first three months of treatment with gilteritinib. Therefore, ECG should be performed prior to initiation of treatment, on day 8 and 15 of cycle 1, and prior to the start of the next three subsequent months of treatment. Caution is warranted in patients with relevant cardiac history. Hypokalaemia or hypomagnesaemia may increase the QT prolongation risk. Hypokalaemia or hypomagnesaemia should therefore be corrected prior to and during gilteritinib treatment. Gilteritinib should be interrupted in patients who have a QTcF >500 msec.The decision to re-introduce gilteritinib treatment after an event of QT prolongation should be based on careful consideration of benefits and risks. Resume gilteritinib at a reduced dose (from 120 mg to 80 mg or from 200 mg to 120 mg) when QTcF interval returns to within 30 msec of baseline or ≤480 msec. Patients with QTcF interval increase by >30 msec on day 8 of cycle 1 should have a further ECG on day 9; if QTcF increase is confirmed gilteritinib dose should be reduced to 80 mg. If gilteritinib is re-introduced at a reduced dose, ECG should be performed after 15 days of dosing, and prior to the start of the next three subsequent months of treatment. In clinical studies, 12 patients had QTcF >500 msec. Three patients interrupted and re-initiated treatment without recurrence of QT prolongation. Pancreatitis: There have been reports of pancreatitis. Patients who develop signs and symptoms suggestive of pancreatitis should be evaluated and monitored. Gilteritinib should be interrupted and can be resumed at a reduced dose (reduced from 120 mg to 80 mg or from 200 mg to 120 mg) when the signs and symptoms of pancreatitis have resolved. Toxicity: If the patient experiences other Grade 3 or higher toxicity considered related to treatment, interrupt treatment until the toxicity resolves or improves to Grade 1. If deemed clinically appropriate gilteritinib can be resumed at a reduced dose (reduced from 120 mg to 80 mg or from 200 mg to 120 mg). Interactions: Co-administration of CYP3A/P-gp inducers may lead to decreased gilteritinib exposure and consequently a risk for lack of efficacy. Therefore, concomitant use of gilteritinib with strong CYP3A4/P-gp inducers should be avoided. Caution is required when concomitantly prescribing gilteritinib with medicinal products that are strong inhibitors of CYP3A,P-gp and/or breast cancer resistant protein (BCRP) (such as, but not limited to, voriconazole, itraconazole, posaconazole and clarithromycin) because they can increase gilteritinib exposure. Alternative medicinal products that do not strongly inhibit CYP3A, P-gp and/or BCRP activity should be considered. In situations where satisfactory therapeutic alternatives do not exist, patients should be closely monitored for toxicities during administration of gilteritinib. Gilteritinib may reduce the effects of medicinal products that target $5HT_{2B}$ receptor or sigma nonspecific receptors. Therefore, concomitant use of gilteritinib with these products should be avoided unless use is considered essential for the care of the patient. Embryofoetal toxicity and contraception: Pregnant women should be informed of the potential risk to a foetus. Females of reproductive potential should be advised to have a pregnancy test within seven days prior to starting treatment with gilteritinib and to use effective contraception during treatment with gilteritinib and for at least 6 months after stopping treatment. Women using hormonal contraceptives should add a barrier method of contraception. Males with female partners of reproductive potential should be advised to use effective contraception during treatment and for at least 4 months after the last dose of gilteritinib. **Interactions:** Gilteritinib is primarily metabolised by CYP3A enzymes, which can be induced or inhibited by a number of concomitant medicinal products. See Special Warnings and Precautions for Use section above for further information on this and the effects of gilteritinib on products that target $5HT_{2B}$ receptor or sigma nonspecific receptors. *Gilteritinib as an inhibitor or inducer:* gilteritinib is not an inhibitor or inducer of CYP3A4 or an inhibitor of MATE1 *in vivo*. Gilteritinib is an inhibitor of P-gp, BCRP and OCT1 (organic cation transporter 1) *in vitro*. As no clinical data is available, it cannot be excluded that gilteritinib could inhibit these transporters at a therapeutic dose. Caution is advised during co-administration of gilteritinib with substrates of P-gp (e.g., digoxin, dabigatran etexilate), BCRP (e.g., mitoxantrone, methotrexate, rosuvastatin) and OCT1 (e.g., metformin). **Fertility, pregnancy and lactation:** Pregnancy: Gilteritinib is not recommended during pregnancy and in women of childbearing potential not using effective contraception. See Special Warnings and Precautions for Use section above for information on pregnancy testing and contraception. Breastfeeding: Breastfeeding should be discontinued during treatment with gilteritinib and for at least two months after the last dose. Fertility: There are no data on the effect of gilterinitib on human fertility. **List of adverse reactions:** *Prescribers should consult the SPC for full information on adverse events* **List of adverse reactions:** Very common (≥1/10): Dizziness, Hypotension, Cough, Dyspnoea, Diarrhoea, Nausea, Constipation, Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood creatine phosphokinase increased, Blood alkaline phosphatase increased, Pain in extremity, Arthralgia, Myalgia, Fatigue, Peripheral oedema and Asthenia. Common (≥1/100 to <1/10): Anaphylactic reaction, Electrocardiogram QT prolonged, Pericardial effusion, Pericarditis, Cardiac failure, Differentiation syndrome, Musculoskeletal pain, Acute kidney injury and Malaise. Serious adverse reactions: The most frequent serious adverse reactions noted from evaluation of 319 patients with relapsed or refractory AML who have received at least one dose of 120 mg gilteritinib were acute kidney injury, diarrhoea, ALT increased, dyspnea, AST increased and hypotension. Other clinically significant serious adverse reactions included differentiation syndrome, electrocardiogram QT prolonged and posterior reversible encephalopathy syndrome. **Overdose:** There is no known specific antidote for gilteritinib. In the event of an overdose, treatment should be stopped. Patients must be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic and supportive treatment initiated, taking into consideration the long half-life estimated at 113 hours. **Cost (excluding VAT):** United Kingdom (UK): XOSPATA 40 mg film-coated tablets x 84: £14,188.00. **Legal classification:** POM. **Marketing authorisation number:** Great Britain (GB): PLGB 00166/0425. Northern Ireland NI: EU/1/19/1399/001. **Marketing authorisation holder:** GB: Astellas Pharma Ltd., 300 Dashwood Lang Road, Bourne Business Park, Addlestone, United Kingdom, KT15 2NX. NI: Astellas Pharma Europe B.V. Sylviusweg 62, 2333 BE Leiden, The Netherlands. **Date of preparation:** March 2023. **Document number:** MAT_UK_XOS_2023_00039. **Further information available from:** Astellas Pharma Ltd., Medical Information: 0800 783 5018.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Astellas Pharma Ltd. on 0800 783 5018.

AML=acute myeloid leukemia; FLT3=FMS-like tyrosine kinase 3; ITD=internal tandem duplication.

References: 1. Chevallier P, et al. Leukemia 2011;25(6):939-44. **2.** Gale RE, et al. Blood 2008;111(5):2776-84. **3.** Smith CC, et al. Nature 2012;485(7397):260-3.

astellas

MAT-UK-XOS-2023-00023 | March 2023

Received: 5 August 2023 | Accepted: 3 October 2023

DOI: 10.1111/bjh.19158

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

WIDER PERSPECTIVES

Harnessing the potential of data-driven strategies to optimise transfusion practice

H. G. Evans[1] | M. F. Murphy[1,2,3] | R. Foy[4] | P. Dhiman[5] | L. Green[6,7,8] | A. Kotze[9] | L. von Neree[10] | A. J. Palmer[11] | S. E. Robinson[12] | A. Shah[13] | F. Tomini[14] | S. Trompeter[10,15] | S. Warnakulasuriya[10,15] | W. K. Wong[16] | S. J. Stanworth[1,2,3]

[1]NIHR Blood and Transplant Research Unit in Data Driven Transfusion Practice, Radcliffe Department of Medicine, University of Oxford, Oxford, UK

[2]Oxford University Hospitals NHS Foundation Trust, John Radcliffe Hospital, Oxford, UK

[3]NHS Blood and Transplant, John Radcliffe Hospital, Oxford, UK

[4]Leeds Institute of Health Sciences, University of Leeds, Leeds, UK

[5]Centre for Statistics in Medicine, Botnar Research Centre, Oxford, UK

[6]Blizard Institute, Queen Mary University of London, London, UK

[7]Barts Health NHS Trust, London, UK

[8]NHS Blood and Transplant, London, UK

[9]Leeds Teaching Hospitals, Leeds, UK

[10]University College London Hospitals NHS Foundation Trust, London, UK

[11]Nuffield Orthopaedic Centre, Oxford University NHS Foundation Trust, Oxford, UK

[12]Guy's and St Thomas' NHS Foundation Trust, London, UK

[13]Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK

[14]Queen Mary University of London, London, UK

[15]University College London, London, UK

[16]Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

Correspondence
S. J. Stanworth, NHS Blood and Transplant, John Radcliffe Hospital, Headley Way, Headington, Oxford OX3 9DU, UK.
Email: simon.stanworth@nhsbt.nhs.uk

Funding information
National Institute for Health and Care Research, Grant/Award Number: NIHR203334

Summary

No one doubts the significant variation in the practice of transfusion medicine. Common examples are the variability in transfusion thresholds and the use of tranexamic acid for surgery with likely high blood loss despite evidence-based standards. There is a long history of applying different strategies to address this variation, including education, clinical guidelines, audit and feedback, but the effectiveness and cost-effectiveness of these initiatives remains unclear. Advances in computerised decision support systems and the application of novel electronic capabilities offer alternative approaches to improving transfusion practice. In England, the National Institute for Health and Care Research funded a Blood and Transplant Research Unit (BTRU) programme focussing on 'A data-enabled programme of research to improve transfusion practices'. The overarching aim of the BTRU is to accelerate the development of data-driven methods to optimise the use of blood and transfusion alternatives, and to integrate them within routine practice to improve patient outcomes. One particular area of focus is implementation science to address variation in practice.

KEYWORDS
audit and feedback, blood transfusion, changing practice, electronic data capture

INTRODUCTION

Variation in clinical practice is a widely recognised phenomenon and to a degree, this is an inevitable feature of healthcare systems, including the National Health Service (NHS). Documentation of variation in practice does however serve a critical purpose in informing major national initiatives. In England, for example, the Getting it Right First Time (GIRFT) programme, is a NHS programme looking to improve the quality of care and reduce cost by reducing variation.[1] While some variability in transfusion practice is to be expected due to individual differences in patient care and preferences, deviating too far from evidence-based recommendations can be detrimental to patient and healthcare outcomes and is associated with higher healthcare costs.[2] Much of the work to date in healthcare has been focussed on describing and visualising variation but with arguably less research aimed at addressing why variation in practice occurs and how to reduce it.[3–5] In all clinical specialities including transfusion medicine, there is unpredictability in how research evidence is adopted into clinical practice.

The general aim of this article is to provide a background to the work of the 'Blood and Transplant Research Unit' (BTRU) research programme funded by the NIHR on 'A data-enabled programme of research to improve transfusion practices'. Specific objectives of this article were to highlight the variation in transfusion practice and the use of transfusion alternatives commonly seen in medicine, and to provide an overview of strategies to improve uptake of evidence-based practice, including newer approaches based on electronic systems such as computerised decision support systems (CDSS).

VARIATION IN TRANSFUSION CARE

There are many examples of the complexity and variation in the practice of transfusion medicine: the many types of components that differ in their degree of matching requirements, the blood count and haemostasis test thresholds that trigger their use, the storage age, the volume that is prescribed and the additional specifications that may be applied. Any literature search readily identifies multiple publications to this effect.[6–9] Slightly under 2.2 million blood components were issued in 2022 in the UK,[10] yet data from successive audits of practice suggest that as many as 20% of transfused blood components may have been given outside national standards and recommendations (Table 1).[2] A national audit in 2016 of the use of red cells showed that 16% of all red blood cell transfusions were considered inappropriate across 170 sites with 4328 participants.[11] The national audit of blood transfusion programme also found inappropriate use of prophylactic platelets (37% of all transfusions) and preprocedure transfusions (19%). A further audit in 2019 (110 sites with 5155 participants) reported that 30% of patients with a pretransfusion Hb of >70 g/L were transfused without adequate clinical reason. This was even higher in patients with acute coronary syndrome or cardiorespiratory disease, where 61% had a pretransfusion Hb of >80 g/L. We have estimated that the number of unnecessary transfusions could be as many as 300–400 000 across the UK costing over £60 M per year. Of note, estimates of purchase costs of blood often do not fully consider the added costs of storage, testing and safe administration in hospitals.[12] The importance of addressing inappropriate transfusions is highlighted by real concerns in the most recent Serious Hazards of Transfusion (SHOT) annual report describing cases of two preventable patient deaths and one major morbidity following ABO-incompatible red blood cell transfusion.[10]

These national audits indicate limited compliance with guideline recommendations of strategies to promote alternatives or measures to minimise the use of blood. This is a serious concern given that blood is a limited resource.[13] Preoperative anaemia has been identified as a risk factor for the need for transfusion and for increased morbidity and mortality following surgery. Yet, audits continue to

TABLE 1 Results of three recent national transfusion audits.

Audit	Finding
2021 National Comparative Audit of NICE Quality Standard of Blood Transfusion QS138 (153 sites, 4679 participants)	59% of the patients who were known to have iron deficiency anaemia prior to being admitted for surgery were treated with iron before surgery
	67% of patients undergoing surgery with expected moderate blood loss received tranexamic acid
	58% of patients receiving elective red blood cell transfusions had both their Hb checked and a clinical re-assessment after a unit of red cells was transfused
2019 Medical Use of Red Cells (110 sites, 5155 participants)	30% of patients with a pretransfusion Hb of >70 mg/L were transfused without adequate clinical reason
	61% of patients with acute coronary syndrome or cardiorespiratory disease were transfused despite having a pretransfusion Hb of >80 mg/L
2016 Use of Red Cells and Platelet Transfusion in Adult Haematology (170 sites, 4328 participants)	16% of all red blood cell transfusions given were considered inappropriate
	37% of prophylactic platelet transfusions were inappropriate
	19% of transfusions carried out preprocedure were inappropriate
	6% of therapeutic platelet transfusions were inappropriate

Note: National Comparative Audit of Blood Transfusion. https://hospital.blood.co.uk/audits/national-comparative-audit/. Accessed 31.7.2023.[11]

demonstrate suboptimal identification and management of preoperative anaemia. For example, the 2021 National Audit of the National Institute for Health and Care Excellence (NICE) Quality Standard of Blood Transfusion found that only 58% of elective surgical patients were treated with iron preoperatively (Table 1).[11] Effective patient blood management (PBM) is recommended[14] and yet there is inconsistency in its implementation. A recent French cross-sectional study highlighted many deficiencies in perioperative anaemia management and correction of iron deficiency was poorly implemented.[15] Yet data increasingly support the effectiveness of PBM. For example, a recent study in Germany used the records of 1.2 million patients to report a reduction in transfusion rate of 13.7% in the group who underwent active PBM.[16]

There is an accumulating body of evidence demonstrating the benefits of tranexamic acid (TXA) in surgical patients reducing the risk of major surgical bleeding and transfusion by 25% with no increased risk of thrombosis.[17,18] Indeed, Roman et al. concluded that TXA is the single most effective PBM intervention.[19] NICE recommended that adults having surgery where blood loss is expected to be moderate (>500 mL) should be offered TXA (NICE NG24)[20] and in 2016 this recommendation became a NICE Quality Standard (NICE QS138).[21] Yet the 2021 National Comparative Audit found that only 67% of potentially eligible surgical patients were given TXA (Table 1).[11] This means of the 1.5 million major surgeries each year, around 500 000 people do not benefit from TXA, leading to approximately 15 000 otherwise avoidable major bleeding events.[22] Correct compliance with this quality standard alone could decrease the demand for blood by 33 000 units per year and save over £5 M in transfusion costs without considering the added benefits to patients. A recent national survey of anaesthetic trainees indicated that the use of TXA varies considerably between surgical specialities as does the availability of policies or the use of checklists to promote its use.[23]

Equally concerning are lower levels of compliance with the NICE quality standard for patient information and education. A national audit found that only 26% of people who received a blood transfusion were given verbal and written information about blood transfusion.[11] Another national study found this increases to only 50% in patients who may lack capacity, for example critically ill patients.[24] Comparable data exist across other clinical settings; in maternity care, only 1.6% of women were offered full written information on the correct administration of iron and how to maximise absorption.[25] There is also a lack of compliance to guidance for pretransfusion testing. A national audit demonstrated that only half of eligible patients with sickle cell disease had received the correct pretransfusion testing indicated in the guidance.[26]

The slow uptake of evidence-based recommendations is costly, both to patients and the healthcare system alike, with studies showing that PBM interventions can reduce the requirement for blood components translating into important potential cost and resource savings.[19] As such, this represents a strategically important issue for service providers, policymakers, healthcare systems and funders. It is a major challenge for transfusion medicine because of its ubiquity throughout almost all areas of hospital practice.

RECENT BLOOD SHORTAGES HIGHLIGHT THE NEED TO REDUCE UNNECESSARY BLOOD USAGE

The occurrence of serious transfusion-transmitted infections since the 1970s and the recent blood shortages in England highlight the importance of only using blood appropriately. Indeed, many countries are experiencing persistent challenges in providing an adequate and timely blood supply after the COVID-19 pandemic.[13] The reasons are complex but include changing patterns of blood donation, and modified donor behaviour.[27,28]

Importantly, it is not only the availability of blood for transfusion that is important for patient care, but also access to the appropriate blood group type. Alloimmunisation to red cell antigens occurs commonly in patients with sickle cell diseaser and transfusion-dependent patients, and, at times, can be a real challenge for blood supply.[26] The provision of better matched red blood cell units which might mitigate this risk is highly dependent on the size and diversity of the donor pool. At present, the range of blood groups seen in blood donors in England does not match those commonly present in ethnic minority groups, for example patients with sickle cell disease, thus limiting the ability of the blood service to provide well matched units to minimise the risk of red cell alloimmunisation in these patients. Whether new technologies based on matching genotyped blood donors and recipients, rather than the traditional labour-intensive serological approaches, have a role in addressing and minimising risks of alloimmunisation remains unknown and is the focus of ongoing research (Haem-Match).[29] Another concern is the challenge in providing ABO compatible platelet transfusions.[30] There are opportunities to improve patient outcomes by expanding both the diversity of the donor pool and the methods by which we match blood transfusions.

POOR LINKAGE OF BLOOD SERVICE AND HOSPITAL IT SYSTEMS LIMITS EFFORTS TO REDUCE VARIATION

A major limitation in addressing overall blood supply problems is the inability to visualise in real time the full transfusion chain from blood donors to patients (vein-to-vein mapping). As a result, changes in blood use are not immediately apparent to blood services, thus limiting their ability to respond to the changes in demand. One option in England has been a pilot 'live-link' between selected

hospitals and NHS Blood & Transplant (NHSBT), the blood service in England, to provide near-real-time hospital blood stock and wastage information (vendor-managed inventory). It also faciltates automatic 'top-ups' of individual hospitals' blood stocks to predetermined levels. At present, it has limited current capability, being provided to only 20 out of over 150 hospitals supplied by NHSBT, and it does not allow information to flow from hospitals to NHSBT about the use of blood such as the number and type of patients receiving transfusions.

THE STRENGTHS AND LIMITATIONS OF INTERVENTIONS TO ADDRESS POOR TRANSFUSION PRACTICE

There are a range of interventions to improve transfusion practice and promote adherence to national standards and recommendations. These include education, clinical guidelines, audit and feedback, and CDSS. Soril et al. reviewed the different quality improvement interventions in transfusion and found that the scale of any benefits achieved was often small.[31] None of the included studies was graded as high quality; most were single site, often in tertiary specialist settings, and it was difficult to disentangle the effectiveness of different components within multimodal interventions.

The development of guidelines based on the best current evidence for good practice is a common starting point for addressing variation in practice. However, it has long been recognised that the publication of guidelines alone does not lead to change.[32] Key barriers to evidence-based transfusion practice include clinicians' limited capacity to keep up to date with an evolving evidence base, resistant beliefs about transfusion benefits and the absence of strong drivers for change.[33] Therefore, the dissemination of guidelines often needs to be supported by active implementation strategies. A recent overview using systematic review methodology identified 30 strategies targeting healthcare organisations, healthcare providers and patients to promote guideline implementation, including educational materials and meetings, and audit and feedback.[34] Implementation planning approaches are highly variable.[35–37]

Traditional medical education meetings and workshops probably have only modest effects on clinical practice and, to a lesser extent, patient outcomes.[38] Greater effects may be associated with a number of features, such as shorter meetings, better attendance, provision of additional take-home material, and targeting educational goals perceived as important. Research on educational approaches as a tool to change practice increasingly emphasises the importance of focussed topics and interactive methods, coupled with tools for self-learning and some form of competency assessment. Use of different teaching modalities to deliver education can be helpful[39,40] and this applies equally to transfusion medicine as to other aspects of healthcare.[41,42] The COVID-19 pandemic saw an increased emphasis on distance or virtual learning, often termed e-learning.[43] However, a recent survey of e-learning practices in transfusion highlighted continued uncertainty about its effectiveness.[44] The main message appears to be one of caution that a single educational approach will be effective in delivering the desired change in practice and that it should form part of a wider implementation strategy, as described in a Cochrane review of audit and feedback.[45] Other forms of educational initiative in transfusion such as Transfusion Camp offer a complementary means of education.[46]

AUDIT AND FEEDBACK

Audit and feedback can provide healthcare professionals with summaries of their clinical performance over a specified period of time with the intention of motivating improvement. It generally has modest effects on clinical practice; a meta-analysis of 140 trials of audit and feedback found a median 4.3% absolute effect.[45] Effects varied considerably among trials, with a quarter finding large absolute effects on 16% or greater and a quarter finding no or even harmful effects. Larger effects were associated with lower baseline performance, feedback being delivered by a supervisor or colleague, provision of repeated feedback, providing feedback both verbally and in writing, and including clear targets and an action plan. The modest effects of feedback may translate into worthwhile population healthcare benefits when it is scaled up, such as through national clinical audit programmes. Furthermore, feedback based upon existing, routinely collected data offers efficiencies over relatively time-consuming patient case note reviews. However, there is still a gap between what audit and feedback can achieve and what is actually delivered. Analyses of national audit programmes in the UK found that they often did not fully utilise existing evidence on effective feedback methods, for example incorporating action plans.[47,48]

Audit and feedback has a long history in transfusion medicine. However, limited progress with repeated national audits in the UK motivated the AFFINITIE programme (Audit and Feedback INterventions to Increase evidence-based Transfusion practice).[49] The researchers first undertook a series of interviews and surveys to better understand the challenges of feedback delivery and effectiveness at hospital sites.[50] The AFFINITIE research team then developed and evaluated two empirically and theoretically informed feedback interventions, 'enhanced content' to improve feedback clarity and usability and 'enhanced support' for hospital staff to act on feedback, on transfusion appropriateness. The effectiveness evaluation embedded two linked 2×2 cluster-randomised trials in national audits of transfusion for surgery (135 hospitals) and haematological disorders (134 hospitals) respectively. In this way, the trials evaluated the separate and combined effects of enhanced content and enhanced support against standard feedback. The enhanced feedback interventions were found to be no more effective than standard feedback.[51]

The likely reasons for the lack of effect included a lack of credibility of the audit standards, concerns about the data validity collected by the largely manual-based processes and evidence of variable (and often poor) enactment of the intended feedback at hospital sites. These lessons are directly relevant to the current design and delivery of ongoing or planned transfusion audit and feedback programmes. There remains considerable scope to enhance the effectiveness of audit and feedback programmes,[52] especially by drawing on evidence and expert-informed suggestions for optimising feedback.[53] The AFFINITIE programme also demonstrated a methodology for embedding trials within existing large-scale quality improvement programmes, thereby improving research efficiency and generalisability. It should be noted that the AFFINITIE researchers did not compare audit and feedback against no form of audit and feedback. Given audit and feedback likely has some effect, the key question remains how to enhance the effects, by testing different forms of audit and feedback.[54]

COMPUTERISED DECISION SUPPORT SYSTEMS

There is growing interest in the development of CDSS within electronic health records (EHRs) to improve transfusion practice, although to date such systems are infrequently used and limited to specialist centres with high-quality EHRs. CDSS aim to improve safety by reminding clinicians to deliver recommended care and reducing errors in decision-making. They can include relatively sophisticated systems linked to patient-specific information allowing rapid implementation and scaling within EHR systems. CDSS have the potential to provide real-time feedback to requesters on appropriate blood ordering, as well as to clinicians on the use of blood.

The transfusion team in Oxford have described their experiences of CDSS, which has been reported to contribute alongside other blood management strategies to a reduction in total blood product costs of around 25% which may equate to a saving of around £1 million/annum without any negative impact on patient outcomes.[55] Importantly while much of the focus has been on red blood cell transfusions, these tools may be as effective for transfusions of other blood components such as plasma and platelets.[56] In another system, a recent best practice alert has been tested in a small, randomised trial and was reported to reduce platelet requirements.[57]

CDSS are ubiquitous in primary and secondary care EHR systems. However, a systematic review of 108 studies (including 94 randomised trials) of CDSS found only a modest 5.8% improvement in the proportion of patients receiving evidence-based care and only a marginal 0.3% improvement in clinical endpoints.[58] One striking finding was the significant variability in effect sizes; while some studies found large effects, others found none. System features and clinical context incompletely explained this variability, leading to the conclusion that the current literature 'provides little guidance for identifying the circumstances under which clinical decision support system interventions produce worthwhile improvements in care'. Furthermore, there are well-recognised problems of alert fatigue, distraction, and poor fits with clinician and patient needs during consultations.[59,60] For example, clinicians are prone to ignore or discount multiple hazards highlighted in prescribing safety alerts, especially as alerts typically appear after they have made decisions to prescribe.

A focussed review on CDSS in transfusion described 20 separate studies, but nearly all studies were 'before and after' designs rather than randomised controlled trials or other more methodologically robust clinical trial designs.[61] The review concluded that while implementation of a CDSS might improve red blood cell usage, there were many uncertainties regarding the optimal features of these systems,[62] as well as their impact on cost savings, effects on patient outcomes and the sustainability of any effects. The authors also made recommendations for standardised reporting of outcomes, not least the nature of the algorithm used. The integration of such systems into a diverse NHS landscape of electronic systems will undoubtedly be complex, but adherence to recommended standards will be of particular importance to ensure their widespread adoption and studies to determine their optimal configuration will be needed.

THE VALUE OF HOSPITAL DATASETS AND DATA REPOSITORIES TO EXPLORE UNWARRANTED VARIATION AND UNDERSTAND PRACTICE

This article started with a discussion on variation in transfusion practice. Accurate and timely data on the patterns of blood usage are key to understand and prioritise what needs to be done to improve practice. However, these data are often not readily available. Greater use of data within EHRs has huge potential for identifying variation in transfusion practice and for developing measures to promote appropriate use of blood, reduce blood wastage, improve blood stock management and reduce healthcare costs.[63] Proof of principle work has established the feasibility of electronic collection of transfusion datasets from multiple hospitals in England, with value for more efficient and timely benchmarking of practices.[64] Larger scale data collaborations for research are also underway (NIHR Health Informatics Collaborative, Table 2), but require significant bioinformatics support to standardise the transfusion data across multiple sites with their differing LIMS and EHRS. The initiative in England to create subnational secure data environments[65] should allow large-scale linkage of data between hospitals, primary care and NHSBT. This will provide a wealth of possibilities to transform patient care. For example, it may be possible for the first time to perform comprehensive studies of anaemia

TABLE 2 Examples of data repositories of potential relevance to patient blood management in England.

Dataset	Size	Transfusion research questions
Perioperative Quality Improvement Programme (PQIP), UCLH/UCL Website: https://pqip.org.uk	29 000 patients for PBM research	The effects of being anaemic ahead of surgery and how alternative treatments affect patient outcomes. Analysing complication rates, length of stay and patient-reported outcomes over the next 12 months
British Heart Foundation Data Science Centre (CVD-COVID-UK / COVID-IMPACT database) Website: https://www.hdruk.ac.uk/projects/cvd-covid-uk-project/	1.7 million individuals	The use and effects of iron supplementation on infection and impact of anaemia treatment on cardiovascular outcomes in patients aged over 65
A single site hospital dataset (A digital platform for identifying bleeding patients, REBLEED), Oxford University Hospitals NHS Foundation Trust and BRC Website: https://www.ndcn.ox.ac.uk/research/critical-care-research-group-kadoorie-centre/research-themes/	1 million hospital admissions Successfully linked patient data to Trust transfusion data	Development and validation of algorithms to identify patients with acquired bleeding
The Clinical Practice Research Datalink (CPRD), Primary Care, Oxford University of Oxford Website: https://cprd.com/	13 million registered and alive patients, including adults, pregnant women and children	The epidemiology and management of anaemia in primary care including many patients who go on to have surgery in hospital practice
NIHR Health Informatics Collaborative themes (HIC) for liver disease, colorectal cancer, perioperative anaemia patient blood management (PBM), critical care Website: https://www.hic.nihr.ac.uk/	10 000 patients for perioperative PBM, over 4000 patients liver disease and colorectal cancer	The effects of anaemia presurgery. Real-world data on transfusion use in liver disease and critical care
Health Informatics Collaborative themes (HIC) for transfusion-dependent anaemia and the HAEM-MATCH research programme Website: https://www.haemmatch.co.uk.	Initial analysis of 443 haemoglobinopathy patients in the collection with a complete 5-year transfusion history	Developed code to standardise transfusion-related hospital records and applied it to data from more than 300 000 UCLH patients. To develop AI-based strategies for matching of blood for transfusion in sickle cell disorders
The Blood Stocks Management Scheme (BSMS), NHSBT. Website: https://www.bloodstocks.co.uk	1.79 million NHSBT issued blood component units 79 000 Hospital wasted blood component units recorded. 15 900 RBC units in hospital stock per day. 241 hospitals in England receiving a monthly report—2892 BSMS reports	Improving blood component inventory management in hospitals through measuring and improving engagement and the downstream impact of the BSMS reporting and feedback using both qualitative and quantitative assessments

in surgery and pregnancy in primary and secondary care. Additionally, while current datasets available for research in transfusion medicine are retrospective, they could be combined with more powerful computational servers and cloud software to open up the potential for future iterations to be prospective, or even real-time.

The availability of large-scale datasets creates new opportunities for transfusion research (Table 2). One feature of the research environment in COVID-19 has been the creation of data repositories enabling many features of the social, behavioural, public health, management and economic impacts of the global pandemic to be explored, but which may have broader applicability to areas including transfusion medicine. A NIHR British Heart Foundation Cardiovascular Partnership links population healthcare datasets across the UK to study the relationships between COVID-19 and cardiovascular diseases. Another relevant dataset with over 50 000 patients is the Perioperative Quality Improvement Programme (PQIP), which supports the feedback of national variation in delivery of perioperative PBM interventions. It is being analysed to explore the effects of anaemia before surgery and how treatments such as iron affect patient outcomes.[66]

Preoperative anaemia should be identified and treated at the earliest opportunity when surgery may be indicated, and ideally not in a preoperative assessment clinic in the days prior to surgery. Linkage between hospital and primary care data (e.g. Clinical Practice Research Datalink [CPRD] primary care database) could open up additional treatment opportunities which could positively impact patients' well-being and long-term quality of life. Linkages between a national haemoglobinopathy registry, hospital data and NHSBT could facilitate better and timely access to matched blood for patients with complex antibodies. Although it should be noted that many studies have audited the clinical information of patients who receive blood transfusions, the datasets used in these large-scale approaches should allow us to also consider patients who may have benefitted from

blood components even when they were not administered or indicated. They may also provide a framework for building vein-to-vein linkages from the donor to the recipient.

Further examples of the potential strengths of big data and large-scale datasets include not only national descriptions of patterns of blood use but also at a more granular level exploration of prediction and blood usage.[67–69] Over a million patients are now included in the German Patient Blood Management Network Registry, allowing a more comprehensive analysis of the relationships between anaemia, comorbidities and red blood cell transfusion.[70] The more recent iteration of the Recipient Epidemiology and Donor Evaluation Study (REDS) programme is creating data repositories to include younger age groups.[71] Using data at scale in large datasets should mean the study population is more representative of the entire population.[72] Although evidence exists that inequality (e.g. ethnicity and deprivation) affects population health, this aspect is perhaps under-researched in transfusion medicine, yet data are emerging that practices need to be scrutinised.[73,74]

The rapidly expanding fields of artificial intelligence (AI) and machine learning (ML) have the potential to revolutionise healthcare.[75–77] ML may support the development of algorithms to predict transfusion requirements which could help reduce risk, improve patient outcomes and predict blood stock requirements. Directly embedding learning systems within EHRs has huge potential but their implementation remains a significant challenge.[78,79] There are increasing number of publications reporting advanced techniques to predict transfusion needs in patients.[80–84] Recent studies have shown the potential for data on transfusion usage to forecast the demand for both red blood cell[85–87] and platelet transfusion requirement.[88–91] How widely and rapidly these findings can be rolled out in hospital information systems remains to be seen.

NEW DEVELOPMENTS IN ENGLAND: THE BTRU IN DATA-DRIVEN TRANSFUSION PRACTICE

In England, NIHR provided funding for 5 years for a BTRU programme focussing on 'A data-enabled programme of research to improve transfusion practices'. The overarching aim of the infrastructure grant is to accelerate the development of data-driven methods to optimise blood use and integrate them within routine practice to improve patient outcomes. The core structures of the BTRU are shown in Figure 1, with examples of activities shown in Table 2. This collaborative programme brings together haematologists, methodologists, surgeons, anaesthetists, data scientists and implementation experts to create a cross-cutting multidisciplinary team including both early career and established researchers, with embedded patient and public members. The work of the implementation group includes optimising feedback reports, in comparison with international

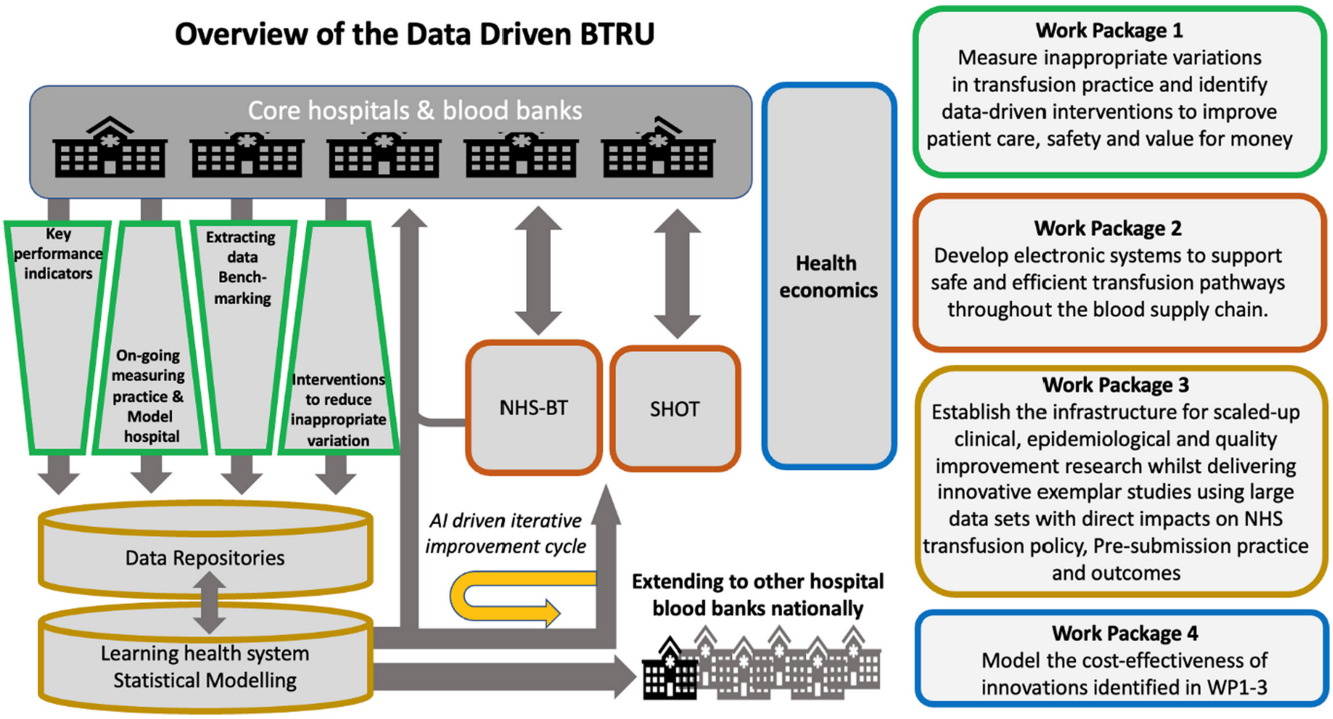

FIGURE 1 An overview of the BTRU. Cross-cutting research work-packages will address the following themes: (1) using hospital data to understand and address variations in blood use in hospitals; (2) using electronic systems to improve the sharing of information between hospitals and blood services for improving the blood supply chain; (3) using data from hospitals and GP practices to develop electronic tools to improve the outcomes for patients who might need transfusion; (4) investigating the costings of different pathways and processes for transfusion, given the need to understand how any electronic systems deliver value for money.

recommendations,[53] for example, in a collaboration between the BTRU and the Blood Stocks Management Scheme (BSMS). The graphical abstract provides an overview of such strategies to address variation, in this case for stock inventory and rates of wastage between hospitals in England.

At the heart of the BTRU programme is planning for novel data linkages and large-scale data repositories including blood transfusion. Later ambitions will be explored by promoting and enabling an integrated process of monitoring and managing blood needs and use, including hospital-level databases, and data linkages between NHSBT as blood supplier to hospitals, to and from hospitals and also to primary care, but it is recognised that these developments will take time and additional resource to deliver. Understanding the cost-effectiveness and efficiency gains from electronic systems for better managing safe transfusions in hospitals and blood supply is an important need given the recent SHOT annual report which continues to highlight significant risks to patients and that errors in the transfusion processes still account for the majority of the reports.[10]

There is increasing evidence to support the impact of meaningful Patient Public Involvement and Engagement (PPIE).[92] In the BTRU, a group of patient and public members play a key role bringing the views and needs of patients from a diverse range of backgrounds to our work, representing many communities commonly under-represented in healthcare research. They are involved in the research process from the design of research questions, data collection and analysis to the dissemination and implementation of our findings. PPIE views have driven a novel strand of transfusion research examining how differences in people's geographical location, ethnicity and socio-economic standing may affect the care they receive. From the perspective of donors, there is a recurring expectation that donated blood will be used to full effect and not be wasted.[93] Patients are clear that unnecessary (inappropriate) transfusions should be avoided, and initiatives pursued to address variation in practice. Other relevant PPIE initiatives include reviewing research priorities identified through the activities of two James Lind Priority Setting Partnerships,[94,95] and the 'Choosing Wisely' for blood transfusion campaign.[96] Technologies and human factor considerations to deliver improvements in the safety of blood administration include avoiding 'never events', such as ABO-incompatible red blood cell transfusions, remain top priorities for patients. Patients and public members are generally supportive of the use of routine clinical data but within clear boundaries and for specific purposes, and within a framework of national guidance (e.g. Goldacre report).[97]

HELPING TO SHAPE THE BROADER INTERNATIONAL EFFORT

The work of the BTRU should be viewed in the context of activities in many countries that are starting to explore the development of a fully linked electronic 'vein-to-vein' systems from the blood donor to the patient recipient. An exemplar system in Europe is the Swedish-Danish Scandinavian Donation and Transfusions (SCANDAT) database[98] and in North America, work through the REDS programmes. Such systems can be used to explore a range of donor and donation factors on patient outcomes.[99]

A longer term vision of the BTRU in England is to establish a so-called nationwide 'learning health system' to use rigorous, data-driven methods to continuously improve transfusion practice. Similar initiatives have been described in other international settings.[100] There is increasing awareness of learning health systems,[101] whereby new knowledge about how to improve healthcare delivery is generated through a series of rapid-cycle randomised trials embedded within electronic systems using routinely collected data in assessing 'real-world' effects.[102–105] These approaches are increasingly discussed in the literature and already used in public policy and in business to deliver cumulative improvements, for example companies 'randomising' potential customers to different presentations of online products to understand what drives purchases. Embedding randomisations efficiently into hospital transfusion systems will be challenging, and more clarity is needed on the optimal approaches for achieving this aim.[57,62] These new strategies provide a real opportunity to improve transfusion practice, which is viewed by patient and public members of our PPIE panel as an imperative for researcher teams, given their custodianship of public health data and blood as a donated altruistic resource. Collaborations with colleagues across the globe promote the building of a strong shared learning approach, so that challenges to the use of data are collectively addressed, to ensure improvements benefit both patients and blood donors in all settings, including low-resource country settings.

CONCLUSION

There is a need to address the disparity between an expanding evidence base informing best transfusion practice and its uptake into routine clinical practice. For example, there are more than 48 randomised trials comparing different thresholds for red blood cell transfusion. In contrast, there have been very few randomised trials of approaches to implement their findings.[106,107] Initiatives such as the BTRU in Data Driven Transfusion Practice aim to capitalise both on the increasing capacity for the collection of routine patient data and on the advent of interactive electronic systems to provide real-time machine-driven learning and thus effective feedback to individual clinicians and clinical teams to ensure optimal transfusion practice. By ensuring we take advantage of the data already being collected on a daily basis within the NHS, it is envisaged that preventative as well as therapeutic interventions can be optimised and improved across the wide range of specialities where transfusions are used. By utilising the emerging technological advances, we hope to develop an iterative flexible learning system which will have a long-lasting positive impact on patient outcomes

including their quality of life by improving transfusion practice for all the patients that need blood.

AUTHOR CONTRIBUTIONS

H. G. Evans, M. F. Murphy, R. Foy and S. J. Stanworth wrote the first draft of the manuscript. All authors contributed to the final version.

ACKNOWLEDGEMENTS

This publication is supported by the National Institute for Health and Care Research (NIHR) Blood and Transplant Research Unit in Data Driven Transfusion Practice (NIHR203334). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. We acknowledge helpful discussions with Jon Benn and Rebecca Walwyn (BTRU), Clare Bankhead (CPRD), and with Lise Estcourt, Shubha Allard, Shruthi Narayan, Farrukha Shah, Sophie Shaples, Louise Sherliker, Rebecca Tinker (NHSBT). We would like to thank Kim Lacey for administrative support.

ORCID

H. G. Evans https://orcid.org/0000-0003-2396-1659
M. F. Murphy https://orcid.org/0000-0002-2375-7503
R. Foy https://orcid.org/0000-0003-0605-7713
P. Dhiman https://orcid.org/0000-0002-0989-0623
L. Green https://orcid.org/0000-0003-4063-9768
A. Kotze https://orcid.org/0000-0002-9310-2895
A. J. Palmer https://orcid.org/0000-0003-4616-7482
S. E. Robinson https://orcid.org/0000-0001-5279-5536
A. Shah https://orcid.org/0000-0002-1869-2231
F. Tomini https://orcid.org/0000-0003-2220-5210
S. Trompeter https://orcid.org/0000-0002-7099-8449
S. Warnakulasuriya https://orcid.org/0000-0001-8372-9857
W. K. Wong https://orcid.org/0000-0002-5742-0108
S. J. Stanworth https://orcid.org/0000-0002-7414-4950

REFERENCES

1. Gray WK, Day J, Briggs TWR, Harrison S. Identifying unwarranted variation in clinical practice between healthcare providers in England: analysis of administrative data over time for the Getting It Right First Time programme. J Eval Clin Pract. 2021;27(4):743–50.
2. Murphy MF, Waters JH, Wood EM, Yazer MH. Transfusing blood safely and appropriately. BMJ. 2013;347:f4303. https://doi.org/10.1136/bmj.f4303. Erratum in: *BMJ*. 2013;347:f4799.
3. Glasziou P, Straus S, Brownlee S, Trevena L, Dans L, Guyatt G, et al. Evidence for underuse of effective medical services around the world. Lancet. 2017;390(10090):169–77.
4. Brownlee S, Chalkidou K, Doust J, Elshaug AG, Glasziou P, Heath I, et al. Evidence for overuse of medical services around the world. Lancet. 2017;390(10090):156–68. Erratum in: *Lancet*. 2022;5;399(10328):908.
5. Atsma F, Elwyn G, Westert G. Understanding unwarranted variation in clinical practice: a focus on network effects, reflective medicine and learning health systems. International J Qual Health Care. 2020;32(4):271–4.
6. O'Malley SM, Sanders JO, Nelson SE, Rubery PT, O'Malley NT, Aquina CT. Significant variation in blood transfusion practice persists following adolescent idiopathic scoliosis surgery. Spine (Phila Pa 1976). 2021;46(22):1588–97.
7. Qian F, Osler TM, Eaton MP, Dick AW, Hohmann SF, Lustik SJ, et al. Variation of blood transfusion in patients undergoing major noncardiac surgery. Ann Surg. 2013;257(2):266–78.
8. Stanworth SJ, Francis JJ, Murphy MF, Tinmouth AT. Chapter 47. Variation in transfusion practice and how to influence clinicians' use of blood in hospitals. In: Murphy MF, Pamphilon DH, Heddle NM, editors. Practical transfusion medicine. Hoboken: John Wiley; 2013.
9. Grüßer L, Keszei A, Coburn M, Rossaint R, Ziemann S, Kowark A, et al. Intraoperative transfusion practices and perioperative outcome in the European elderly: a secondary analysis of the observational ETPOS study. PloS One. 2022;17(1):e0262110.
10. Narayan S, Poles D, et al. The 2022 Annual SHOT Report. 2023 https://doi.org/10.57911/WZ85-3885
11. National Comparative Audit of Blood Transfusion [cited 2023 Nov 10]. https://hospital.blood.co.uk/audits/national-comparative-audit/
12. Stokes EA, Wordsworth S, Staves J, Mundy N, Skelly J, Radford K, et al. Accurate costs of blood transfusion: a microcosting of administering blood products in the United Kingdom National Health Service. Transfusion. 2018;58(4):846–53.
13. Kralievits KE, Raykar NP, Greenberg SLM, Meara JG. The global blood supply: a literature review. Lancet. 2015;27(385 Suppl 2):S28.
14. Mueller MM, Van Remoortel H, Meybohm P, Aranko K, Aubron C, Burger R, et al. Patient blood management: recommendations from the 2018 Frankfurt consensus conference. JAMA. 2019;321(10):983–97.
15. Capdevila X, Lasocki S, Duchalais A, Rigal JC, Mertl P, Ghewy P, et al. Perioperative iron deficiency in patients scheduled for major elective surgeries: a French prospective multicenter cross-sectional study. Anesth Analg. 2023;137(2):322–31.
16. Meybohm P, Schmitt E, Choorapoikayil S, Hof L, Old O, Müller MM, et al. German patient blood management network: effectiveness and safety analysis in 1.2 million patients. Br J Anaesth. 2023;131(3):472–81.
17. Devereaux PJ, Marcucci M, Painter TW, Conen D, Lomivorotov V, Sessler DI, et al. Tranexamic acid in patients undergoing noncardiac surgery. N Engl J Med. 2022;386(21):1986–97.
18. Taeuber I, Weibel S, Herrmann E, Neef V, Schlesinger T, Kranke P, et al. Association of intravenous tranexamic acid with thromboembolic events and mortality: a systematic review, meta-analysis, and meta-regression. JAMA Surg. 2021;156(6):e210884.
19. Roman MA, Abbasciano RG, Pathak S, Oo S, Yusoff S, Wozniak M, et al. Patient blood management interventions do not lead to important clinical benefits or cost-effectiveness for major surgery: a network meta-analysis. Br J Anaesth. 2021;126(1):149–56.
20. NICE Guideline [NG24]. Published 18 November 2015 [cited 2023 July 31]. https://www.nice.org.uk/guidance/ng24
21. NICE Quality Standard [QS138]. Published 15 December 2016 [cited 2023 July 31]. https://www.nice.org.uk/guidance/qs138
22. Grocott MPW, Murphy M, Roberts I, Sayers R, Cheng-Hock T, The UK Royal Colleges Tranexamic Acid in Surgery Implementation Group. Tranexamic acid for safer surgery: the time is now. Br J Surg. 2022;109(12):1182–3.
23. Belete M, Wolff K, Warnakulasuriya S, Stanworth on behalf of Research and Audit Federation of Trainees. (003) Variable practice for peri-operative patient blood management: results of a national survey. Anaesthesia. 2023;78(53):8–66. https://doi.org/10.1111/anae.16112
24. Nuttall Musson E, Donovan K, Murphy MF. Lost in transfusion: patient awareness of receiving blood transfusion on the intensive care unit. Transfusion. 2020;60(12):3064–6.
25. Churchill D, Ali H, Moussa M, Donohue C, Pavord S, Robinson SE, et al. Maternal iron deficiency anaemia in pregnancy: lessons from a national audit. Br J Haematol. 2022;199(2):277–84.

26. Trompeter S, Bolton-Maggs P, Ryan K, Shah F, Estcourt L, Cho G, et al. National comparative audit of blood transfusion: 2014 audit of transfusion services and practice in children and adults with sickle cell disease. Transfus Med. 2020;30(3):186–95.
27. Veseli B, Sandner S, Studte S, Clement M. The impact of COVID-19 on blood donations. PloS One. 2022;17(3):e0265171.
28. Stanworth SJ, New HV, Apelseth TO, Brunskill S, Cardigan R, Doree C, et al. Effects of the COVID-19 pandemic on supply and use of blood for transfusion. Lancet Haematol. 2020;7(10):e756–64.
29. Heam Match [cited 2023 Nov 13]. https://www.haemmatch.co.uk
30. Stanworth SJ, Shah A. How I use platelet transfusions. Blood. 2022;140(18):1925–36.
31. Soril LJJ, Noseworthy TW, Dowsett LE, Memedovich K, Holitzki HM, Lorenzetti DL, et al. Behaviour modification interventions to optimise red blood cell transfusion practices: a systematic review and meta-analysis. BMJ Open. 2018;8(5):e019912.
32. Grimshaw JM, Eccles MP, Lavis JN, Hill SJ, Squires JE. Knowledge translation of research findings. Implement Sci. 2012;31(7):50.
33. Delaforce A, Duff J, Munday J, Hardy J. Overcoming barriers to evidence-based patient blood management: a restricted review. Implement Sci. 2020;15(1):6.
34. Pereira VC, Silva SN, Carvalho VKS, Zanghelini F, Barreto JOM. Strategies for the implementation of clinical practice guidelines in public health: an overview of systematic reviews. Health Res Policy Syst. 2022;20(1):13.
35. Steffen KM, Spinella PC, Holdsworth LM, Ford MA, Lee GM, Asch SM, et al. Factors influencing implementation of blood transfusion recommendations in pediatric critical care units. Front Pediatr. 2021;9:800461.
36. Mohammed AD, Ntambwe P, Crawford AM. Barriers to effective transfusion practices in limited-resource settings: from infrastructure to cultural beliefs. World J Surg. 2020;44(7):2094–9.
37. Peters S, Sukumar K, Blanchard S, Ramasamy A, Malinowski J, Ginex P, et al. Trends in guideline implementation: an updated scoping review. Implement Sci. 2022;17(1):50.
38. Forsetlund L, O'Brien MA, Forsén L, Mwai L, Reinar LM, Okwen MP, et al. Continuing education meetings and workshops: effects on professional practice and healthcare outcomes. Cochrane Database Syst Rev. 2021;9:CD003030. https://doi.org/10.1002/14651858.CD003030.pub3
39. Satterlee WG, Eggers RG, Grimes DA. Effective medical education: insights from the Cochrane library. Obstet Gynecol Surv. 2008;63(5):329–33.
40. Burgess A, van Diggele C, Roberts C, Mellis C. Key tips for teaching in the clinical setting. BMC Med Educ. 2020;20(Suppl 2):463.
41. Molina-Arrebola MA, Fernández-Guerrero E, Aguirre-Ortega FJ, Avivar-Oyonarte C. Digital resources for transfusion education. J Educ Health Promot. 2020;9:173.
42. Karafin MS, Bryant BJ. Transfusion medicine education: an integral foundation of effective blood management. Transfusion. 2014;54(5):1208–11.
43. Delungahawatta T, Dunne SS, Hyde S, Halpenny L, McGrath D, O'Regan A, et al. Advances in e-learning in undergraduate clinical medicine: a systematic review. BMC Med Educ. 2022;22(1):711.
44. Al-Riyami AZ, Peterson D, Vanden Broeck J, Das S, Saxon B, Lin Y, et al. E-learning/online education in transfusion medicine: a cross-sectional international survey. Transfus Med. 2022;32(6):499–504.
45. Ivers N, Jamtvedt G, Flottorp S, Young JM, Odgaard-Jensen J, French SD, et al. Audit and feedback: effects on professional practice and healthcare outcomes. Cochrane Database Syst Rev. 2012;(6):CD000259.
46. Yeung KCY, Kapitany C, Chargé S, Callum J, Cserti-Gazdewich C, D'Empaire PP, et al. Transfusion camp: a retrospective study of self-reported impact on postgraduate trainee transfusion practice. Transfusion. 2023;63(4):839–48.
47. Khan T, Alderson S, Francis JJ, Lorencatto F, Grant-Casey J, Stanworth SJ, et al. Repeated analyses of national clinical audit reports demonstrate improvements in feedback methods. Implement Sci Commun. 2020;1(1):106.
48. Willis TA, Wood S, Brehaut J, Colquhoun H, Brown B, Lorencatto F, et al. Opportunities to improve the impact of two national clinical audit programmes: a theory-guided analysis. Implement Sci Commun. 2022;3(1):32.
49. Foy R, Lorencatto F, Walwyn R, Farrin A, Francis J, Gould N, et al. Enhanced feedback interventions to promote evidence-based blood transfusion guidance and reduce unnecessary use of blood components: the AFFINITIE research programme including two cluster factorial RCTs. Southampton (UK): NIHR Journals Library; 2022.
50. Gould NJ, Lorencatto F, Stanworth SJ, Michie S, Prior ME, Glidewell L, et al. Application of theory to enhance audit and feedback interventions to increase the uptake of evidence-based transfusion practice: an intervention development protocol. Implement Sci. 2014;29(9):92.
51. Stanworth SJ, Walwyn R, Grant-Casey J, Hartley S, Moreau L, Lorencatto F, et al. Effectiveness of enhanced performance feedback on appropriate use of blood transfusions: a comparison of 2 cluster randomized trials. JAMA Netw Open. 2022;5(2):e220364.
52. Foy R, Skrypak M, Alderson S, Ivers NM, McInerney B, Stoddart J, et al. Revitalising audit and feedback to improve patient care. BMJ. 2020;368:m213.
53. Brehaut JC, Colquhoun HL, Eva KW, Carroll K, Sales A, Michie S, et al. Practice feedback interventions: 15 suggestions for optimizing effectiveness. Ann Intern Med. 2016;164(6):435–41.
54. Ivers NM, Grimshaw JM, Jamtvedt G, Flottorp S, O'Brien MA, French SD. Growing literature, stagnant science? Systematic review, meta-regression and cumulative analysis of audit and feedback interventions in health care. J Gen Intern Med. 2014;29(11):1534–41.
55. Staples S, Salisbury RA, King AJ, Polzella P, Bakhishli G, Staves J, et al. How do we use electronic clinical decision support and feedback to promote good transfusion practice. Transfusion. 2020;60(8):1658–65.
56. Shah N, Baker SA, Spain D, Shieh L, Shepard J, Hadhazy E, et al. Real-time clinical decision support decreases inappropriate plasma transfusion. Am J Clin Pathol. 2017;148(2):154–60.
57. Murphy C, Mou E, Pang E, Shieh L, Hom J, Shah N. A randomized study of a best practice alert for platelet transfusions. Vox Sang. 2022;117(1):87–93.
58. Kwan JL, Lo L, Ferguson J, Goldberg H, Diaz-Martinez JP, Tomlinson G, et al. Computerised clinical decision support systems and absolute improvements in care: meta-analysis of controlled clinical trials. BMJ. 2020;370:m3216.
59. Rousseau N, McColl E, Newton J, Grimshaw J, Eccles M. Practice based, longitudinal, qualitative interview study of computerised evidence based guidelines in primary care. BMJ. 2003;326(7384):314.
60. Jani YH, Franklin BD. Interruptive alerts: only one part of the solution for clinical decision support. BMJ Qual Saf. 2021;30(12):933–6.
61. Hibbs SP, Nielsen ND, Brunskill S, Doree C, Yazer MH, Kaufman RM, et al. The impact of electronic decision support on transfusion practice: a systematic review. Transfus Med Rev. 2015;29(1):14–23.
62. Metcalf RA, Goodfellow J, Cail K, Blaylock R, Kawamoto K, Enniss T, et al. Electronic clinical decision support: evidence that default settings influence end-user behavior. Transfusion. 2021;61(3):669–70.
63. Patel RM, Hendrickson JE, Nellis ME, Birch R, Goel R, Karam O, et al. Variation in neonatal transfusion practice. J Pediatr. 2021;235:92–99.e4.
64. D'Souza R, Singh Desi A, Pendry K, Charlton A, Staples S, Watkins NA, et al. Comparing transfusion practice at multiple hospitals using electronically collected and analysed data. Transfus Med. 2023; [in press]. https://doi.org/10.1111/tme.13008

65. The future of healthcare our vision for digital data and technology in health care. Published 17 October 2018 [cited 2023 July 31]. https://www.gov.uk/government/publications/the-future-of-healthcare-our-vision-for-digital-data-and-technology-in-health-and-care/the-future-of-healthcare-our-vision-for-digital-data-and-technology-in-health-and-care
66. Perioperative Quality Improvement Programme [cited 2023 Nov 13]. https://pqip.org.uk
67. Pendry K. The use of big data in transfusion medicine. Transfus Med. 2015;25(3):129–37.
68. Auvinen MK, Zhao J, Lassén E, Lubenow N, Seger Mollén A, Watz E, et al. Patterns of blood use in Sweden from 2008 to 2017: a nationwide cohort study. Transfusion. 2020;60(11):2529–36.
69. Huang Z, Huang C, Xie J, Ma J, Cao G, Huang Q, et al. Analysis of a large data set to identify predictors of blood transfusion in primary total hip and knee arthroplasty. Transfusion. 2018;58(8):1855–62.
70. Blum LV, Schmitt E, Choorapoikayil S, Baumhove O, Bayer A, Friederich P, et al. Association of anaemia, co-morbidities and red blood cell transfusion according to age groups: multicentre sub-analysis of the German Patient Blood Management Network Registry. BJS Open. 2022;6(6):zrac128.
71. Josephson CD, Glynn S, Mathew S, Birch R, Bakkour S, Baumann Kreuziger L, et al. The Recipient Epidemiology and Donor Evaluation Study-IV-Pediatric (REDS-IV-P): a research program striving to improve blood donor safety and optimize transfusion outcomes across the lifespan. Transfusion. 2022;62(5):982–99.
72. Veinot TC, Ancker JS, Bakken S. Health informatics and health equity: improving our reach and impact. J Am Med Inform Assoc. 2019;26(8–9):689–95.
73. Prochaska M, Salcedo J, Berry G, Meltzer D. Racial differences in red blood cell transfusion in hospitalized patients with anemia. Transfusion. 2022;62(8):1519–26.
74. Nutbeam T, Roberts I, Weekes L, Shakur-Still H, Brenner A, Ageron FX. Use of tranexamic acid in major trauma: a sex-disaggregated analysis of the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH-2 and CRASH-3) trials and UK trauma registry (Trauma and Audit Research Network) data. Br J Anaesth. 2022;129(2):191–9.
75. Beam AL, Kohane IS. Big data and machine learning in health care. JAMA. 2018;319(13):1317–8.
76. Nwanosike EM, Conway BR, Merchant HA, Hasan SS. Potential applications and performance of machine learning techniques and algorithms in clinical practice: a systematic review. Int J Med Inform. 2022;159:104679.
77. Ghassemi M, Wu M, Hughes MC, Szolovits P, Doshi-Velez F. Predicting intervention onset in the ICU with switching state space models. AMIA Jt Summits Transl Sci Proc. 2017;2017:82–91.
78. Ben-Israel D, Jacobs WB, Casha S, Lang S, Ryu WHA, de Lotbiniere-Bassett M, et al. The impact of machine learning on patient care: a systematic review. Artif Intell Med. 2020;103:101785.
79. McDermott MBA, Wang S, Marinsek N, Ranganath R, Foschini L, Ghassemi M. Reproducibility in machine learning for health research: Still a ways to go. Sci Transl Med. 2021;13(586):eabb1655.
80. Zhang Y, Fu X, Xie X, Yan D, Wang Y, Huang W, et al. A novel model forecasting perioperative red blood cell transfusion. Sci Rep. 2022;12(1):16127.
81. Levi R, Carli F, Arévalo AR, Altinel Y, Stein DJ, Naldini MM, et al. Artificial intelligence-based prediction of transfusion in the intensive care unit in patients with gastrointestinal bleeding. BMJ Health Care Inform. 2021;28(1):e100245.
82. Walczak S, Velanovich V. Prediction of perioperative transfusions using an artificial neural network. PloS One. 2020;15(2):e0229450.
83. Mitterecker A, Hofmann A, Trentino KM, Lloyd A, Leahy MF, Schwarzbauer K. Machine learning-based prediction of transfusion. Transfusion. 2020;60(9):1977–86.
84. Wu HY, Li ZG, Sun XK, Bai WM, Wang AD, Ma YC, et al. Predicting willingness to donate blood based on machine learning: two blood donor recruitments during COVID-19 outbreaks. Sci Rep. 2022;12(1):19165.
85. Quinn J, Campbell C, Gomez A, Kumar-Misir A, Watson S, Liwski D, et al. The successful implementation of an automated institution-wide assessment of hemoglobin and ABO typing to dynamically estimate red blood cell inventory requirements. Transfusion. 2019;59(7):2203–6.
86. Guo K, Song S, Qiu L, Wang X, Ma S. Prediction of red blood cell demand for pediatric patients using a time-series model: a single-center study in China. Front Med (Lausanne). 2022;9:706284.
87. Li N, Chiang F, Down DG, Heddle NM. A decision integration strategy for short-term demand forecasting and ordering for red blood cell components. Oper Res Health Care. 2021;29:100290. https://doi.org/10.1016/j.orhc.2021.100290
88. Guan L, Tian X, Gombar S, Zemek AJ, Krishnan G, Scott R, et al. Big data modeling to predict platelet usage and minimize wastage in a tertiary care system. Proc Natl Acad Sci U S A. 2017;114(43):11368–73.
89. Motamedi M, Dawson J, Li N, Down D, Heddle N. Demand forecasting for platelet usage: from univariate time series to multivariate models. https://arxiv.org/pdf/2101.02305.pdf
90. Mirjalili M, Abouee-Mehrizi H, Barty R, Heddle NM, Sarhangian V. A data-driven approach to determine daily platelet order quantities at hospitals. Transfusion. 2022;62(10):2048–56.
91. Schilling M, Rickmann L, Hutschenreuter G, Spreckelsen C. Reduction of platelet outdating and shortage by forecasting demand with statistical learning and deep neural networks: modeling study. JMIR Med Inform. 2022;10(2):e29978.
92. Aiyegbusi OL, McMullan C, Hughes SE, Turner GM, Subramanian A, Hotham R, et al. Considerations for patient and public involvement and engagement in health research. Nat Med. 2023;29(8):1922–9.
93. Joshi HJ, Patel KB, Dholu M. An analysis of wastage of blood components in blood bank at tertiary care hospital. Int J Clin Diagn Pathol. 2021;4(1):138–42. https://doi.org/10.33545/pathol.2021.v4.i1c.336
94. Hibbs SP, Brunskill SJ, Donald GC, Saunders HD, Murphy MF. Setting priorities for research in blood donation and transfusion: outcome of the James Lind Alliance priority-setting partnership. Transfusion. 2019;59(2):574–81.
95. Shapiro S, Stephensen D, Camp C, Carroll L, Collins P, Elston D, et al. The top 10 research priorities in bleeding disorders: a James Lind Alliance Priority Setting Partnership. Br J Haematol. 2019;186(4):e98–e100.
96. Callum JL, Waters JH, Shaz BH, Sloan SR, Murphy MF. The AABB recommendations for the Choosing Wisely campaign of the American Board of Internal Medicine. Transfusion. 2014;54(9):2344–52.
97. Goldacre B, Morley J. Better, broader, safer: using health data for research and analysis. A review commissioned by the Secretary of State for Health and Social Care. 2022. Department of Health and Social Care.
98. Edgren G, Hjalgrim H. Epidemiology of donors and recipients: lessons from the SCANDAT database. Transfus Med. 2019;29(Suppl 1):6–12.
99. Roubinian NH, Reese SE, Qiao H, Plimier C, Fang F, Page GP, et al. Donor genetic and nongenetic factors affecting red blood cell transfusion effectiveness. JCI Insight. 2022;7(1):e152598.
100. Foley T, Vale L. A framework for understanding, designing, developing and evaluating learning health systems. Learn Health Syst. 2022;7(1):e10315.
101. Sheikh A, Anderson M, Albala S, Casadei B, Franklin BD, Richards M, et al. Health information technology and digital innovation for national learning health and care systems. Lancet Digit Health. 2021;3(6):e383–96.
102. Horwitz LI, Kuznetsova M, Jones SA. Creating a learning health system through rapid-cycle, randomized testing. N Engl J Med. 2019;381(12):1175–9.

103. McCord KA, Ewald H, Agarwal A, Glinz D, Aghlmandi S, Ioannidis JPA, et al. Treatment effects in randomised trials using routinely collected data for outcome assessment versus traditional trials: meta-research study. BMJ. 2021;372:n450.
104. Morris AH, Stagg B, Lanspa M, Orme J, Clemmer TP, Weaver LK, et al. Enabling a learning healthcare system with automated computer protocols that produce replicable and personalized clinician actions. J Am Med Inform Assoc. 2021;28(6):1330–44.
105. Halpern D, Mason D. Radical incrementalism. Evaluation. 2015; 21(2):143–9.
106. Carson JL, Stanworth SJ, Dennis JA, Trivella M, Roubinian N, Fergusson DA, et al. Transfusion thresholds for guiding red blood cell transfusion. Cochrane Database Syst Rev. 2021;12(12):CD002042. https://doi.org/10.1002/14651858.CD002042.pub5
107. Ivers N, Grimshaw J. Reducing research waste with implementation laboratories. Lancet. 2016;388(10044):547–8.

How to cite this article: Evans HG, Murphy MF, Foy R., Dhiman P., Green L., Kotze A., et al. Harnessing the potential of data-driven strategies to optimise transfusion practice. Br J Haematol. 2023;00:1–12. https://doi.org/10.1111/bjh.19158