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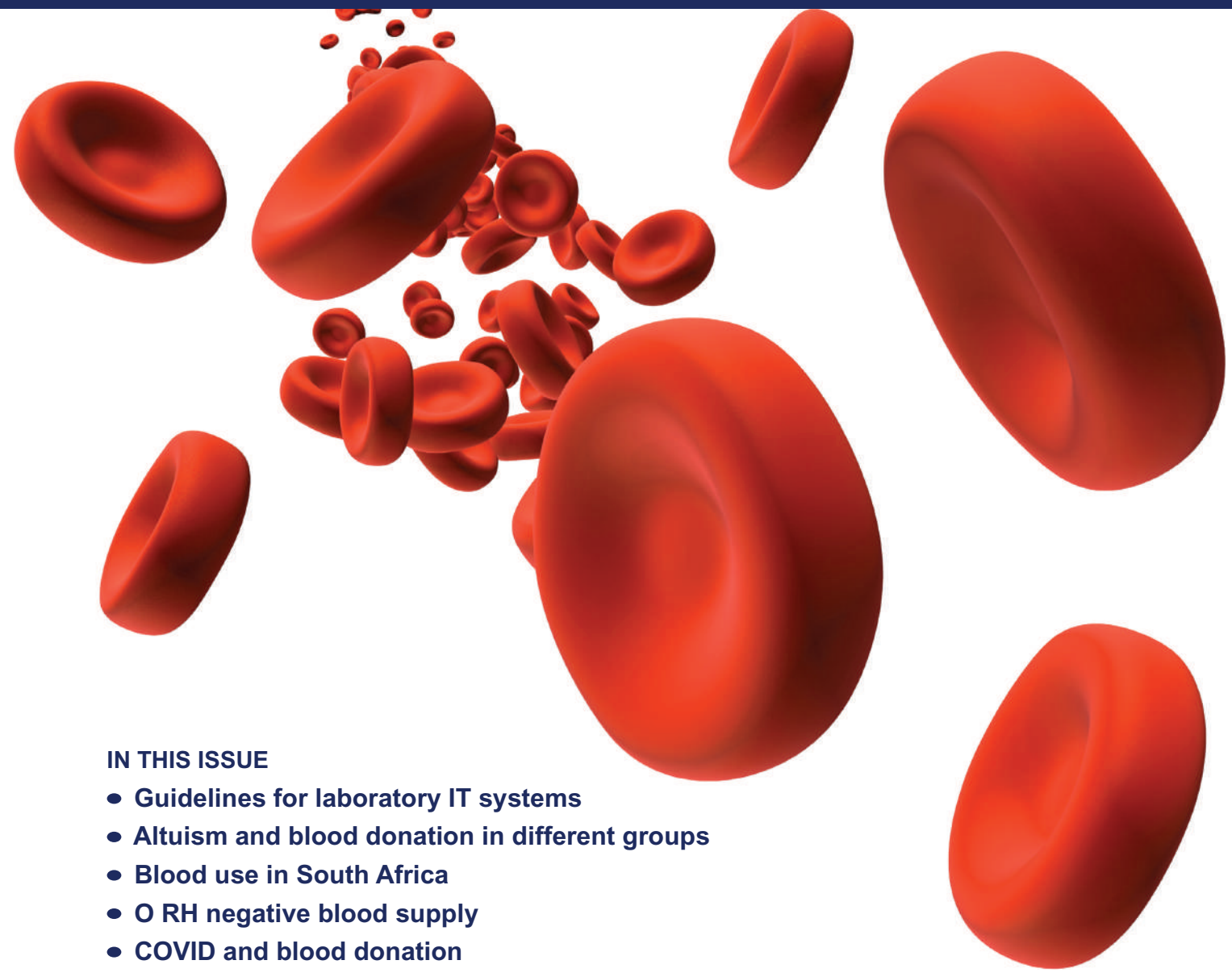

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Transfusion Medicine

An international journal published for the British Blood Transfusion Society

Aims

Transfusion Medicine will publish articles on transfusion medicine in its widest context, including blood transfusion practice (blood procurement, pharmaceutical, clinical, scientific, computing and documentary aspects), immunohaematology, immunogenetics, histocompatibility, medico-legal applications, and related molecular biology and biotechnology.
In addition to original articles, which may include brief communications and case reports, the journal will contain a regular educational section (based on invited reviews and state-of-the-art reports), technical section (including quality assurance and current practice guidelines), leading articles, letters to the editor, occasional historical articles and signed book reviews. Some lectures from Society meetings that are likely to be of general interest to readers of the Journal may be published at the discretion of the Editor and subject to the availability of space in the Journal.

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GUIDELINES

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Guidelines for the specification, implementation and management of IT systems in hospital transfusion laboratories: A British Society for Haematology Guideline

Julie Staves[1] | Paul Ashford[2] | Tom Bullock[3] | Tony Coates[4] | Linda Lodge[5] | Nishil Patel[6] | Megan Rowley[5] | Nigel Sargant[7] | Chloë E. George[8]

[1]Transfusion Laboratory, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

[2]IT consultant, Roper Management Consultants Ltd, Kent, UK

[3]Red Cell Immunohaematology, NHS Blood and Transplant, Bristol, England

[4]Transfusion Laboratory, Betsi Cadwaladr University Health Board, Wales, UK

[5]Clinical Services, Scottish National Blood Transfusion Service, Edinburgh, Scotland

[6]Haematology, Royal Free London NHS Foundation Trust, Barnet, UK

[7]Haematology, East Sussex Healthcare NHS Trust, East Sussex, UK

[8]Clinical Services, Welsh Blood Service, Velindre NHS Trust, Cardiff, UK

Correspondence
Chloë E. George, BSH Administrator, British Society for Haematology, 100 White Lion Street, London, N1 9PF, UK.
Email: bshguidelines@b-s-h.org.uk

1 | METHODOLOGY

This guideline was compiled according to the BSH process at https://b-s-h.org.uk/guidelines/proposing-and-writing-a-new-bsh-guideline/. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at http://www.gradeworkinggroup.org.

1.1 | Literature review details

Pubmed, Cochrane, and Ovid were searched from Jan 2010 to May 2023 using the terms laboratory information management system; electronic blood transfusion system, ECTMS, electronic clinical transfusion management system, EBMS, electronic blood management system, blood tracking, transfusion decision support, transfusion advisory support, transfusion bidirectional interface, electronic issue, patient identification wristband, electronic pre-transfusion checks, electronic patient identification, blood administration systems, electronic remote blood issue, remote issue, electronic data interchange, order comms, electronic prescribing, vendor managed inventory and included all relevant Medical Subject Headings (MeSH) terms and subheadings. The search was limited to humans and the English language.

1.2 | Review of the manuscript

The review of the manuscript was performed by the British Society for Haematology (BSH) Guidelines Committee, the Blood Transfusion Taskforce, the BSH Guidelines Committee and the members of the Transfusion sounding board of BSH. It was also on the members section of the BSH website for comment.

2 | INTRODUCTION

2.1 | Background

Since the last version of the British Committee for Standards in Haematology (BCSH) guidelines for the 'Specification, implementation and management of information technology (IT) systems in hospital transfusion laboratories was published.[1] There has been continued development in IT applications for use in transfusion medicine. IT has made a major contribution to blood safety throughout the transfusion

chain, and there is increasing use of IT solutions to allow laboratories to meet some of the challenges of the Blood Safety and Quality Regulations (F24) SI 50/2005 (as amended) legislation,[2] such as traceability. These guidelines update those published in 2014, to reflect new developments. Further requirements such as the provision of extensively genotype-matched red cell units, have also been addressed.

2.2 | Scope

These guidelines are intended to support hospital blood transfusion laboratories when procuring and validating Laboratory Information Management Systems (LIMS) and provide guidance on the operational use of such systems. The LIMS is the hub of laboratory IT in these settings and whilst many IT systems are in use in transfusion medicine, from vein to vein, these guidelines address applications which interface directly with the LIMS. Supporting blood tracking applications are not covered in detail, but the interoperability with the LIMS is referenced where appropriate. Whilst these guidelines do not specifically address cells and tissues, organisations may wish to consider the requirements and potential need to manage cells and tissues through the transfusion IT system. Wherever possible, other BSH transfusion guidelines are cross-referenced to avoid duplication of information and the potential for inconsistency between guidelines.

It is envisaged this document will be used by transfusion laboratories, hospital IT departments, procurement teams and, where applicable, suppliers of IT systems which support hospital transfusion medicine. The different sections of the guideline are displayed in Figure 1.

Some of the requirements in these guidelines reflect special blood transfusion needs which may have an impact on systems external to the LIMS. Necessary controls to be implemented in these external systems are addressed, including preventing updates to patient demographic data held on the LIMS.

2.3 | Method

The guideline group was selected to be representative of UK-based scientific, technical and medical experts with practical experience in this field. These guidelines are formulated from expert opinion and based on relevant recommendations from professional groups for example the Serious Hazards of Transfusion (SHOT) haemovigilance scheme.[3] Where evidence exists to support new and potentially contentious recommendations, this is referenced in the text.

2.4 | Structure

The guidelines are presented in five sections (Figure 1):

I. Operational use of IT systems
II. Electronic blood administration (tracking) systems
III. Recording administration/final fate information
IV. Information management
V. System management

In addition, planning and implementing system change is covered in Appendix I on the BSH website.

3 | COMPLIANCE WITH THESE GUIDELINES

It is recommended that IT systems are audited against these guidelines on a regular basis in line with the current Medicines and Healthcare Products Regulatory Agency (MHRA) guidance and are included in the audit schedule of Quality Systems, to ensure ongoing compliance. If appropriate, an action plan to address any areas of non-compliance should be instigated.

An example of a gap analysis tool has been provided to assist transfusion laboratories in the preparation of their audit documentation and is available on the BSH website.

3.1 | Major changes from the previous guidelines

- Incorporation of information regarding IT systems being classed as an in vitro diagnostic (IVD) medical device taking into account government guidance for software as a medical device (SaMD).[4,5]
- Clarification of infrastructure requirements including the expectation of environments included within a LIMS system.
- Additional information regarding data integrity of patient records and changes to data protection legislation.
- Recommendations on the use of clinical decision support which is included under SaMD regulations.[4]
- The inclusion of data provision to support laboratories with red cell genotyping results.
- Additional information on business continuity planning.
- Additional recommendations on the provision of data for audit/benchmarking.

3.2 | Use of the term gender

The writing group would like to clarify the use of terms relating to gender as applied to clinical transfusion practice.

The provision of blood components to patients must take into consideration the genetic gender of the patient, that is the sex, male or female, at birth. This is because some critical decisions regarding the selection of the blood component are dependent on whether the patient has childbearing potential, with the purpose of protecting any future children from preventable Haemolytic Disease of the Fetus and Newborn (HDFN).

As such, when the term gender is used in this guideline, we are referring to the genetic gender of the patient, that is the sex at birth.

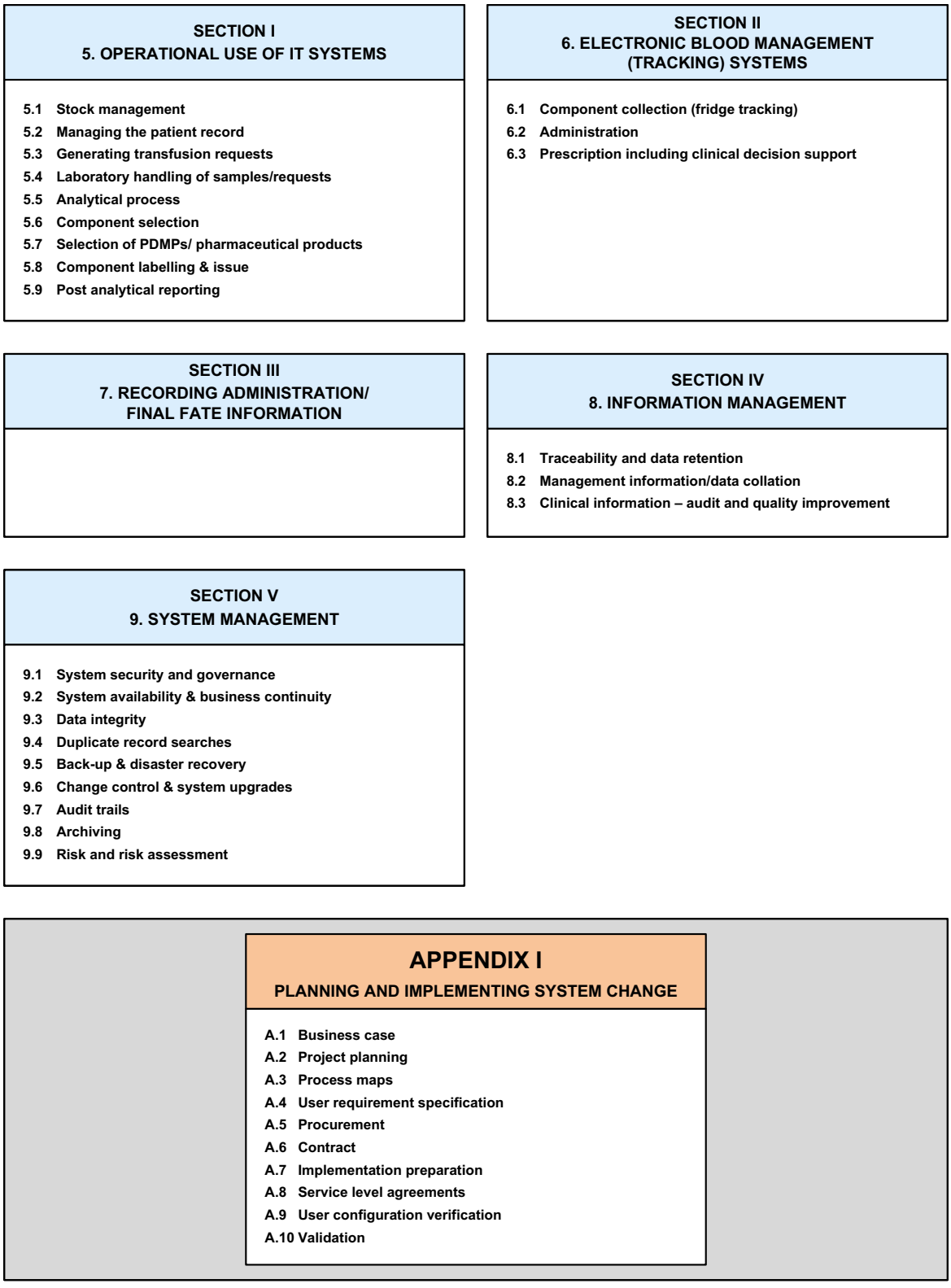

FIGURE 1 Guideline sections.

Transfusion laboratories should ensure that they are aware of, and align with, their local guidelines regarding the recording of gender at the point of patient registration. But equally, those responsible for patient registration guidance should be made aware of patient safety issues as they relate to blood transfusion samples.

It is important to note that it is not legally permissible to record that a patient is transgender on an IT system without their explicit permission as it is a protected characteristic under the Equality Act (2010).[6] Software providers can be approached to provide system upgrades to enable rules-based selection of

components and application of anti-D prophylaxis to be applied on a case-by-case basis.

It may be necessary to update the guideline when national guidance on the use of the term gender becomes available.

Summary of recommendations

There are a large number of recommendations against which compliance should be assessed. This summary shows the high-level concepts underpinning the recommendations.

- Any change to an IT system must be managed through a formal change control process, risk assessment and appropriate validation effort (2B).
- Adequate control and resources are required for any IT project (2B).
- Electronic transfer of data with the use of control and coded data entry will reduce risks to patient safety (2B).
- Patient identification is critical across all IT systems and merging of patient data must ensure traceability is retained (2B).

4 | PLANNING AND IMPLEMENTING SYSTEM CHANGE

This section covers the initial steps for implementing a new IT system in the transfusion department. It includes information and essential guidance on the following topics:

- Business case
- Project planning
- Process mapping
- User requirements specification (including operational functionality; validation requirements; interface specifications; interoperability; hardware requirements; operational environments; data management; data migration; archiving; and maintenance).
- Procurement
- Contract
- Implementation
- Training
- Service level agreements
- Verification and validation

New IT system procurements must comply with the recommendations of this section. As this section of the guidance is only used during new procurements it has been published separately as Appendix 1 on the BSH website (https://b-s-h.org.uk/guidelines?category=Transfusion&fromdate=&todate=).

5 | OPERATIONAL USE OF IT SYSTEMS

This section describes the essential elements of functionality for a LIMS in conjunction with identifying areas where the LIMS can support and facilitate safe practice in the hospital transfusion laboratory. This section may not be exhaustive, and each organisation should define their requirements and good practice to meet their operational needs.

Wherever possible all information should be entered in a structured manner (i.e. coded) to ensure data is easily retrievable and available for audit.

5.1 | Stock management

It is a requirement of the BSQR[2] and the EU Directive 2001/83/EC (EU, 2001)[7] that records are retained allowing traceability of all components and products from source to recipient or final fate and vice versa.

The system should hold a local reference table of blood components and batch products in which label barcodes are associated with descriptions and internal codes. There must be the facility to update this table to allow for new components and products to be added by appropriately authorised personnel. Systems must be able to receive blood components labelled from any of the UK Blood Establishments and other products as defined by the users. If organisations require the ability to manage blood, tissues and cells imported from outside the UK there should be a procedure for entering information into the LIMS to ensure the donor/patient traceability chain is maintained.[8]

If an electronic blood management (tracking) system is in place, consideration must be given to including all component storage locations as part of the overall transfusion management IT system.

5.1.1 | Stock ordering

It must be possible to configure the LIMS to take specific actions, based on user-defined stock levels, for each blood component and plasma derivative. Actions may include: providing warnings when a stock falls below minimum levels; generating advisory reorders; or initiating automatic reordering.

Online blood ordering is available in some areas of the UK but currently is maintained as a stand-alone system. The use of electronically managed inventory and automated stock replenishment systems should be facilitated where available.

5.1.2 | Stock entry—blood components

A secure method of input is required to ensure the correct information regarding each component is held within the LIMS.

The LIMS must allow for storage of the following minimum information for each unit:

- Donation number
- ABO and D group (where supplied)
- Component code, including division numbers, as provided by the supplier.
- Expiry date
- Expiry time (where appropriate)
- Date and time of receipt into the laboratory and /or time booked into the LIMS

- Source of component (from a Blood Establishment or transferred from another hospital)

The LIMS should also allow for the following component characteristics to be retained against the component:

- Antigen typing
- Cytomegalovirus (CMV) antibody negative
- Gamma/X-ray Irradiation
- Haemoglobin S (Hb S) status
- High titre (HT) anti-A and/or anti-B flags
- Volume
- Comment field

It may be desirable to record if the above information was received electronically or entered manually.

The LIMS will need to support the current UK combinations of ISBT 128 and Codabar labelling systems[8] and be future-proofed for the potential full implementation of ISBT 128 and the introduction of two-dimensional Data Matrix codes by the UK Blood Services.

Receipt handling with electronic delivery note

Electronic delivery notes (EDN) meeting the standardised specification written by the Joint Professional Advisory Committee (JPAC) Standing Advisory Committee for Information Technology (SACIT)[8] are available from Blood Establishments. A LIMS which can upload information on received stock using this method either directly from the Blood Establishment or via blood tracking systems provides a rapid and secure means of data capture.

When the delivery is received at the hospital each component received should be reconciled to the information captured from the EDN. This can be achieved by scanning the relevant pack barcodes, for example donation number and component type. Other information may be transferred electronically, including additional information such as red cell phenotype or genotype, which may not be evident on the label. The LIMS should be able to store this additional information in a manner that can be searched to support the selection of appropriate antigen-negative units.

In line with the adoption of Health Level Seven (HL7) International Fast Healthcare Interoperability Resource (FHIR) by NHS Digital, work is currently in progress to further develop electronic messaging using the FHIR Standard.[9] Release 5 of this Standard includes resources for biologically derived products suitable for carrying information on blood components, and allowing this information to be consistently referenced in electronic dispense and clinical use records.[9] In line with this work, further development of the ISBT 128 Standard supports a wide range of additional information, including full red cell phenotypes, to be carried in the resource.[10]

Receipt handling without EDN

If the EDN message is not supported, then the entry of stock via individually scanning the relevant barcodes, for example donation number, group, component type and expiry date barcodes is required. All codes should be entered for each unit and pre-filled fields for this information must not be used, although defaults for supplier and stock storage location are permissible. Manual entry, via keyboard entry, of unit number, component type and blood group should be prevented for routine use and only available for backup purposes (Please note manual entry must prevent Electronic Issue [EI] of red cell units).

It is recommended that additional information should also be recorded in terms of antigen status and special requirements and a robust process (e.g. barcode or double-blind entry) should be in place to ensure this information is entered correctly. A risk assessment should be carried out on the amount of data to be entered.

5.1.3 | Stock entry: plasma-derived medicinal products/pharmaceutical products

The system must store the following details of the product:

- Date and time of receipt
- Manufacturer
- Name of product
- Expiry date
- Quantity of units received
- Batch number
- Batch comments, including volume and amount of product/bottle (e.g. IU/mL or bottle), where appropriate

Additional items could include:

- Supplier, if different to the manufacturer
- Type of product, for example intravenous immunoglobulin (IVIg)
- ABO group (if applicable)

In general plasma-derived medicinal products (PDMPs)/pharmaceutical products are only identified by the manufacturer down to the level of batch number. The LIMS should be capable of managing the traceability of each batch of a PDMP at an individual item level. Individual transfusion laboratories can allocate local serial numbers to individual items within the batch to support this level of traceability.

There is an international move towards standard barcoding of PDMPs/pharmaceutical products. Information on this is available from GS1,[11] the supply chain standards organisation.

5.1.4 | Stock tracking

The system must allow the location of stock to be recorded and must support the transfer of stock between locations to fridges both on the same site and remote sites.

Laboratories must have procedures to manage the return to the stock of reserved units by national guidelines and local rules. The LIMS must be able to support compliance with these procedures by electronic de-reservation and the production of a list of units which are beyond their reservation period.

Care should be taken to ensure that the electronic de-reservation on the LIMS is aligned with operational procedures for the physical removal of units from their storage facility.

The system must support the recall of units including the ability to quarantine units and maintain records of the reason and any incidents related to the component/product.

5.1.5 | Management of unused units

Not all components issued to patients will be transfused. The system must allow units to be retrieved from being issued/allocated to a patient and returned to the stock of unallocated units. Units which are no longer suitable for use (e.g. past their expiry date or out of temperature control) must be blocked from being reissued or returned to stock. There must be a facility to record the fate of discarded and transferred units.

5.2 | Managing the patient record

Correct patient demographics are a key feature of any IT system involved in the transfusion process. This applies to the Electronic Patient Record (EPR), Patient Administration System (PAS), LIMS, Electronic Blood Management (tracking) Systems (EBMS) and any electronic communication system (e.g. Order Comms) used to make requests of the transfusion laboratory. Unless the data is correct and consistent between these systems there is the potential for serious patient harm.

Laboratories should produce and maintain a document which describes the interfaces, functionality, and flow of information between all systems.

Data integrity is fundamental to safe transfusion practice and must be maintained during sample acceptance, registration, requesting of tests, components (and any subsequent manipulations) and edits on the LIMS system. Processes should be validated to ensure that complete and correct patient and component/product data are entered into the LIMS. Wherever possible, information should be entered in a structured manner (e.g. coded) to ensure data can be easily retrieved and searchable.

It is an essential feature of transfusion records that sample information is associated with the patient demographic information relevant at the time of processing. For this reason, when the patient demographic details are amended/updated, the previous patient details should be retained against relevant samples. It must be possible to see the previous patient details relating to the date/time when looking at the records.

It is of particular importance that external systems are not able to update patient demographic data held on the LIMS, and that patient record merging/linking on external systems is verified by the transfusion laboratory where the patient has a transfusion history.

5.2.1 | Unique patient identifiers

The LIMS system must support the use of the NHS number (or equivalent) in addition to other numbering systems as required by the user, for example, A&E or temporary numbers.

The use of the NHS number in England and Wales (or equivalent—Health and Care Number in Northern Ireland and Community Health Index Number in Scotland) is preferable. This is particularly relevant in the modern NHS Healthcare systems with the movement of patients and the merging of organisations. Temporary numbers for unknown or unidentified patients in line with Patient Safety Alert NHS/PSA/RE/2018/008[12] must be supported.

5.2.2 | Patient Information

The system must be capable of holding the following essential information:

- Basic patient demographic information including first and last name, date of birth, gender
- All relevant transfusion-related patient data
- All previous transfusion/grouping records relating to a patient
- Historic blood group information
- Special requirements
- Patient antibodies and antigens (should be coded to the international coding structure for antibodies/antigens[13])
- Previous names and addresses if applicable
- Patient diagnosis/clinical details/reason (justification) for transfusion

The entering of patient demographics directly from an order comms system is desirable as this will reduce data entry errors. Any discrepancies between systems should be flagged to the user and demographics only be updated as they become available in accordance with local risk management policy.

There will be occasions when records from one individual will need to be associated with another individual's record and the LIMS system must support this, for example mother with infant and partner association in pregnancy-associated testing.

5.2.3 | Merging/linking

Duplicate patient records within a healthcare database have the potential to create a serious risk to patient safety by increasing the risk of incorrect or inappropriate actions from a lack of recognition of previous results. There must be a method available to merge/link duplicate records in a way which ensures the integrity of the transfusion record.

The system must ensure that traceability records are not lost or changed when merges are undertaken in the LIMS, especially if the LIMS is the primary method of maintaining the traceability record for 30 years.[2] It is imperative to have documented policies and procedures to control the merging/linking process.

Merging within the LIMS

Systems must provide a facility for handling duplicate patient records. Duplicate records will be managed either by merging or linking depending on the system being used. 'Merging' is where two or more

records are converted into a single merged record usually under one of the original patient identifiers. 'Record linking' is where the independent records are retained but a link is generated such that accessing any one of the records automatically provides access to information from all the linked records. In general, it is usually simpler to undo a linked record than to undo a merged record.

In the remainder of this section the term 'merging' also applies to 'linking'.

Locally defined rules for merging records must be in place and must address the following:

- Only nominated staff with appropriate password privileges can use the merge function
- Clear, precise documentation on when and how a merge can be undertaken (a Merging and Linking Policy and associated standard operating procedures [SOPs]), including the safety criteria and checks applied to ensure that the merge is correct. This should address the retention of all historic grouping and screening information, special requirements (e.g. irradiation) and any specific antibody investigation information plus the identity of the person undertaking the merge
- Training procedures (and records) relating to the SOP
- Maintain documentation to (i) ensure that traceability requirements as listed in the BSQR[2] are met, and (ii) provide an audit trail of the individual records merged to form the single record

The system must identify and alert the user if the records to be merged have:

- Different ABO and/or D blood groups
- Different antibody and/or antigen profiles
- Different special transfusion requirements

Differences must be resolved or accepted by an appropriately qualified person before the merge can proceed. Password control must be in place in order to override routine control criteria.

Consideration should be given to whether paper or suitably archived electronic records may need to be maintained to ensure that traceability and other information critical to patient safety are protected.

The audit trail must include:

- The full patient details of both records prior to the merge
- The date/time of the merge
- The relevant details of the individual who performed the merge

Merging/linking outside the LIMS

There must be safeguards to prevent changes made to other systems or disciplines from automatically updating the transfusion database. It is not acceptable for any external system to be able to merge LIMS records directly without applying the following specific rules:

- There must be a clear, precise organisational policy on when a merge can be undertaken, and the staff involved must have a clear understanding of the effect of merging on patient healthcare records
- Where transfusion records are present the policy must ensure appropriate notice and authorisation to show the integrity of the transfusion record is not compromised
- Documentation must be sent to the laboratory on what and who has been 'merged'
- Traceability records must be maintained

This could be achieved in shared pathology LIMS systems by having an independent blood transfusion database.

Where there is a link between the PAS/EPR and the LIMS, the LIMS should recognise when an external merge has occurred and alert transfusion staff accordingly for appropriate updates of the LIMS records.

Blood components issued against a patient sample must be labelled with the patient details as per the associated sample. There must be safeguards in place to ensure this, as per the recommendations of the BSQR.[2]

Undo linking/merging

It should be recognised that undoing a merge is a high-risk process which has the potential to compromise mandated traceability. If no subsequent information has been assigned to the record, a system for undoing a linkage or merge must be available which has a full audit trail.

5.2.4 | Accessing data from non-interoperable systems

Where possible LIMS and other IT systems used in hospital transfusion practice should be interoperable through an electronic interface. Where there is no electronic link for data transfer, but it is necessary to access transfusion records on another system, i.e. from a previous LIMS archive or from a cross-site LIMS, it should be recognised that this is a manual look-up which cannot be used to facilitate electronic issue but is important for patient care, particularly specific requirements. There should be a clear laboratory policy stating when such a look-up is necessary, which systems should be interrogated and how to determine the patient demographics are correctly matched (see sections 'Merging within the LIMS' and 'Merging/linking outside the LIMS'). It should also be recorded on the current system that such a look-up has taken place.

5.3 | Generating transfusion requests

Transfusion requests for tests and components can be generated electronically or by manual systems. Guidance for manual request management is provided in the BSH Guideline on the Administration of Blood Components[14] and is not addressed further in this document.

This section addresses the electronic request for transfusion work to be undertaken on a uniquely identified patient and may include the collection and labelling of appropriate samples from the patient. This

is a critical control point in the system and both automated and procedural controls must be in place to prevent errors.

Electronic request systems come in a variety of forms, from a simple messaging system between the ward and the laboratory through to a comprehensive Order Comms system with full interfacing to the LIMS. In all cases, the processes and controls must be clearly specified and interfaces between the electronic request system, LIMS and manual actions well defined.

Electronic request management implementation is often a Trust/Hospital-wide project with many disciplines involved, often with competing requirements. Management controls must be in place to ensure that the Transfusion Laboratory Manager is informed of all pending changes to systems interfacing with the laboratory. The Transfusion Laboratory Manager must ensure that changes are managed and appropriately version-controlled and validated to ensure that the transfusion pathway continues to meet regulatory and quality requirements.

5.3.1 | Electronic requesting and reporting systems (Order Comms)

When electronic request systems (Order Comms)[15,16] are used careful consideration must be given to how the transfusion process is managed. Order Comms may improve the management of information but positive patient identification requirements at the bedside must not be compromised.

The use of Order Comms[16] may facilitate behavioural changes in blood product ordering with a reduction in inappropriate orders. Further improvements in ordering can be observed if clinical decision support (CDS) assisted transfusion order entry is combined with educational programmes. CDS is an electronic solution designed to aid clinical staff when undertaking ordering. It is intended to ensure that the orders being made are appropriate for the clinical circumstances and the patient usually by comparing the haemoglobin concentration with accepted transfusion guidelines.[17] CDS can potentially improve patient safety and be used to indicate to clinical staff when special requirements are required such as irradiation.[17] Following the introduction of CDS, reports of an improvement in orders being made that follow agreed policies have been observed with continued improvement demonstrated up to 4 years from implementation.[15]

There are a number of different features which should be considered when implementing an Order Comms system depending on the intended use of the system. All features should be risk-assessed and validated to ensure the correct functionality is present. A summary of good practice is:

- Bidirectional communication with the LIMS
- Access control ensuring that critical process steps within the laboratory are only available to authorised staff who are transfusion trained
- Support for the ordering of components including capture of information required by the transfusion laboratory
- Support for the entry of clinical special requirements (e.g. irradiated or CMV negative) and flag these to the laboratory
- Appropriate rules to determine whether a blood sample is required based on information supplied from the LIMS[14]
- Alert in situations where a sample is NOT required or is already in the laboratory but when action by the laboratory is needed (e.g. issue of components)
- Monitoring of the electronic interfaces between the IT systems required to support the electronic request management process (Order Comms/PAS/LIMS) with user alerts in the event of interface failure
- Automatic detection of any discrepancy of demographic data between the systems with appropriate user alerts
- A warning to the requestor if a request is rejected and the reason why
- A mechanism to monitor work progress and to alert users if predefined sample receipt or process time are not met

Some of the operational and safety benefits of Order Comms include:

- Ensuring only those with up-to-date training are involved with the transfusion process
- Prevention of transcription errors by electronic data transfer into the LIMS
- Ensuring a structured requesting process, for example use of prompts and mandatory fields, which should lead to more complete coded clinical information reaching the laboratory and improved quality of management reports
- Immediate and more convenient access to laboratory results and blood component availability with improved flow and faster turnaround times
- The ability to highlight 'on-screen' those patients with antibodies, special requirements, etc.
- Reduction in the need for patients' samples to be repeated
- Prompts to users to follow the best practice or agreed institutional guidelines for blood or blood product ordering
- Faster requesting of products
- Reduction in the number of unnecessary orders placed by clinical areas
- Provides all users with accessible documentation of prescription and administration of blood products (e.g. speed of administration etc.)
- Allows any alerts on blood shortages or patient safety alerts to be seen by all users accessing the system

If Order Comms is used manual requests should be kept to a minimum but will have to be used:

- During the rollout of a new system
- During periods of system unavailability, that is planned or unplanned downtime

Mechanisms for manual requesting will therefore need to be in place. It is important to develop robust processes for manual data entry to mitigate risk at each stage of the process.[14] Care must be taken to ensure any patient special requirements are captured. Appropriate controls will need to be in place to manage the subsequent update of the relevant IT systems and accommodate any changes in agreed local guidelines or policies.

5.3.2 | Sample collection (Order Comms)

Acceptance criteria for patient samples are covered in the BSH Guideline for the Administration of Blood Components[14] but, since publication, there is new evidence supporting the use of electronic systems for sample collection, and labelling. Order Comms can be used to support sample collection,[18] however labels which are not printed at the patient's bedside cannot be used. As such the printing of these types of labels must be suppressed.[19]

The use of electronic identification, for example patient barcoded wristbands can reduce the risk of patient identification errors however, there remain manual steps in the process and the IT system must not be used to replace existing positive patient ID verification steps.[17,18]

Each sample must be uniquely identified preferably including a unique barcoded sample identification number that can be used throughout the laboratory process thus eliminating the need for any re-labelling (so-called 'run-through labelling'). If sample labels are printed by the electronic request management system, the following must apply:

- Verification of the match between the patient and the computer record and printing of the sample label must be performed at the bedside at the time of phlebotomy with time limits and locks on the systems to prevent labels being produced away from the bedside or prior to patient sample being taken
- Date and time of collection of the sample must be recorded on the label
- Where request forms are retained, it is essential that patient details on the collected sample match the information on the request form and are sent to the laboratory together

Some applications have been developed that use radio-frequency identification (RFID) technology.[20,21] These may help as a supplementary tracking application and for matching the patient ID, transfusion order and the unit to be transfused. ISBT has provided guidance on RFID technology.[22]

5.4 | Laboratory handling of samples/requests

Receipt of requests into the laboratory may be through either an electronic or a manual system. Receipt of samples and the matching of the request to the appropriate sample is a critical point in the system and the correct association of sample and request is essential.[23] Processes and controls must be clearly specified and interfaces between Order Comms, LIMS and manual actions well defined.[24]

Care must be taken to ensure that the laboratory staff are appropriately alerted to all requests especially where there are no accompanying samples. Ideally, there should be automated request and activity monitoring that will alert management if the activity is not performed in a timely manner.

5.4.1 | Manual receipt and entry onto LIMS

Manual receipt covers situations where the requesting process is entirely manual or where there may be some electronic requesting support at the bedside that is not directly linked to the LIMS.

When patient demographics are entered into the LIMS from the request form, the LIMS should be able to identify if the patient is already known and provide options to match a record in the system. If no match is found a new patient record must be created. If during this process it is identified by the LIMS that a potential duplicate record is being created (i.e. same/similar details but different unique patient identifier entered) the user should be alerted.

Once all patient identification checks are complete the request together with the accompanying samples must be allocated a unique barcoded laboratory number.

When the patient record has been identified or created the unique laboratory number should be scanned and the request details, the collection date and time and any relevant additional information (e.g. special requirements) entered. Any necessary record association (e.g. mother, infant) should be made at this point.

5.4.2 | Electronic receipt and entry onto the LIMS (Order Comms)

This covers situations where there is an electronic transfer of information from Order Comms to LIMS. The request must always be identified with a unique request/episode number.

Where samples are required, it is strongly recommended that these be labelled with a unique barcode identification number electronically generated at the bedside. The preferred option is for this barcode number to be suitable for use in the laboratory, thus removing the need for renumbering, so called run through labelling.

If samples need to be re-numbered in the laboratory, then appropriate procedures based on local risk assessment must be followed.

The matching of the request to the appropriate LIMS patient record is a critical point in the system. The degree to which this can be automated will depend on the individual system design. Special rules will need to be in place to cover situations where it has not been possible to fully identify the patient.

The date and time the sample is collected must be entered into the LIMS.

Special patient requirements may be identified in the electronic request or by the LIMS on the basis of patient demographics, clinical diagnosis or previous history. Any necessary record association (e.g. mother, infant) should be made at this point.

Manual systems must be in place to support transfusion activity when Order Comms is unavailable due to planned or unplanned downtime. When the systems are available again appropriate mechanisms must be in place to update them.

The use of standardised systems for the digital exchange of requests and reports is recommended, as this will enable reports to be shared across multiple systems so reducing the type of errors seen from manual transcription.

5.5 | Analytical processes

Wherever possible, automated links between laboratory equipment and the LIMS should be in place. Where manual entry is necessary robust controls must be in place (e.g. double-blind entry) to prevent manual transcription errors.

Ensuring continuity of sample and patient identification is vital throughout the transfusion process. It must be possible to identify testing undertaken against a specific request at a specified time, as the immunological status of the patient can change.

5.5.1 | Test allocation

The LIMS should have a role in the determination of tests required for a specific request in accordance with predefined test profiles. These tests should be allocated either directly to test equipment through electronic communication or to laboratory staff through worksheets/pick lists for manual action.

Testing should follow the guidance provided in the BSH guidelines for pre-transfusion compatibility procedures in blood transfusion laboratories.[23]

The LIMS should be able to add additional tests to existing samples already held within the laboratory and respond to test results that trigger further laboratory investigations by allocating follow-up tests (reflex testing, e.g. positive antibody screen requires antibody identification). Examples of such reflex testing are shown in Appendix 2 on the BSH website.

There should be a mechanism to prioritise and flag emergency samples for easy identification.

5.5.2 | Worksheets

The system should be able to produce worksheets, configured to user requirements, for recording laboratory results and/or checking specimen identity. It should be possible to view and update worksheets on-screen or print copies for manual completion including downtime use.

The system must also maintain the ability to directly enter sample results without the use of a worksheet.

5.5.3 | Laboratory testing

Result entry is a critical process and robust control of the process is essential. Wherever possible, laboratory testing should be performed by automated systems with electronic data transfer to the LIMS. Where such systems are in use both the system and the interface used for sending results must be validated. As part of the result information for each test, the LIMS should hold the following administrative information:

- Whether results have been entered by automatic links or manually
- Whether the result has been edited
- Date (and time) of testing
- Audit trail of activities

Where interpreted results are sent from the analyser to the LIMS, results which have been edited on the analyser must be flagged. This is essential for the algorithm for electronic issues (EI).[25] All quantitative results from an analyser should be stored individually on the LIMS against the relevant test element. The LIMS should then be able to process these results to derive an interpretation, for example blood group ABO and Rh type or antibody screen status. If the analyser cannot flag interpreted results that have been edited, then it is preferable that un-interpreted individual test results are sent for interpretation by the LIMS. Any necessary editing would be performed on the LIMS and stored appropriately.

Where manual interpretation and/or manual result entry are required, procedures must be in place to reduce the risk of a manual error remaining undetected (e.g. use of double-blind interpretation and entry).

Where results are entered manually into the IT system, the historic results should not be displayed on-screen and, where possible, results should be entered into the system as double-blind entry or, if this is not possible, verified by a second operator as soon as possible.

ABO/D testing

Robust ABO and D typing, and storage of results are essential for safe transfusion practice. Any discrepancies between current ABO/D results and historic results due to a genuine change in the group following ABO/D incompatible haemopoietic stem cell transplant or due to patient or sample misidentification errors must be flagged by the system and investigated prior to the issue of blood components. The LIMS should be able to derive the blood group from individual test results providing a further check on the blood grouping process.

If a laboratory stores a composite result on the LIMS, for example O D Positive as an interpretation rather than the individual test results, there should be a risk assessment in place to assess the robustness of the system and the potential impact of the loss of an extra level of LIMS controlled protection.

Antibody screening

Antibody screening results should be stored as individual results against each cell by each technique.

Positive antibody screening results must alert the user and should automatically trigger a request for antibody identification.

Antibody identification

Antibody identification results can be stored either as individual results against each cell by each technique or as a composite result, including the antibody specificity.

Antibody identification interpretation should be entered as separate specificities, using drop-down (coded) lists or equivalent. There should be controls in place to minimise the risk of manual error. It should be possible to store electronic versions of associated antigrams against the sample records.

The system should have the ability to categorise antibody specificities[23] according to their clinical significance and use this information to support the generation of reports using standard comments (e.g. delay in provision of red cells). The system should allow adjustment of these comments in specific cases.

Red cell genotyping and phenotyping

Red cell phenotyping results can be stored either as individual results against each antigen by each technique or as a composite result. Genotyping results can also be stored either individually against each allele result or as a composite set of results. These results should be transferred electronically from an analyser to separate phenotyping and/or genotyping result locations on the LIMS. The LIMS may have the facility to crosscheck phenotype/genotype (if present) and automatically flag any discrepancies for further investigation and resolution if required.

IT companies/LIMS suppliers should consider providing functionality to incorporate extended red cell (RBC) matching algorithms for Rh/K and extended blood group genotype/phenotype matching depending on the patient cohort's need or clinical condition. The degree of matching required should be indicated by diagnosis, presence of alloantibodies and transfusion dependency, and should not be applied to all patients. Consideration should be given to the functionality of LIMS software to enable the use of algorithms to identify and suggest units in the inventory which are to be matched to the patient either by phenotype or genotype and prioritise their use based on bloodstock management principles.

Crossmatch

When performed on an analyser crossmatch results for each unit tested should be transferred electronically from the analyser and both the individual results by technique and interpretation should be stored. If an interpretation is transmitted, it should ideally be verified by the LIMS.

If results have been manually entered there should be a risk assessment in place to assess the robustness of the system and the potential impact of the loss of an extra level of IT-controlled protection. A second check process may be considered to mitigate this risk.

Whatever the method of entry the following information must be stored:

- Patient identifier
- Donation number
- Test conclusion or results of the individual test by technique and reaction grade
- Date, time and identity of personnel/analyser for all actions

Pregnancy-related testing

Testing should be undertaken as outlined in the BSH guideline for blood grouping and antibody testing in pregnancy.[26]

The IT system should store the following additional information to that identified above:

- Number of weeks gestation and estimated date of delivery (EDD)
- Where EDD only has been supplied, the LIMS should automatically calculate and display the weeks of gestation

And, where relevant:

- Partner phenotype
- Titre/quantitation results where clinically significant antibodies are present
- Date anti-D immunoglobulin (anti-D Ig) prophylaxis administered and dose
- Genotype testing using cell-free fetal DNA (cffDNA)

On the basis of patient information, and the results entered, the LIMS should be able to:

- Provide recall testing information against a user-defined algorithm with reference to the BSH guideline for blood grouping and antibody testing in pregnancy[26]
- Indicate requirements for Routine Antenatal Anti-D Prophylaxis (RAADP)[27]
- Previous transfusion reactions and transfusion adverse events

5.5.4 | Quality assurance of analytical processes

Analytical processes should be subject to quality assurance including both internal quality control (IQC) and external quality assessment (EQA). The BSH guidelines for pre-transfusion compatibility procedures in blood transfusion laboratories[23] should be referred to for the content and frequency of IQC.

Internal quality control

The method of recording and storing Internal Quality Control (IQC) data might depend on whether the data is generated on automation linked to the LIMS, or in manual systems. However this is handled, it must be possible to associate all tests with valid IQC.

For automated testing, where IQC data are generated but not used by the instrument to control result interpretation and transfer, IQC data should be sent to the LIMS and the LIMS should verify IQC data before accepting the test results.

For automated testing, where the automated system validates IQC data prior to the transfer of test results, IQC data should still be retained but can be on the automated system provided there is an approved backup and restore process.

External quality assessment

The LIMS should facilitate the processing of EQA samples and be able to interpret and store the results of EQA samples in the same way as clinical samples.

It should be possible to flag EQA samples so that they are easily identifiable and can be excluded from laboratory workload statistics if required.

5.5.5 | Technical authorisation

The LIMS should be able to support automated authorisation ('auto-validation') when results are transferred from a fully automated analyser; there has been no editing of results; and where there are no discrepancies identified from previous results.

All automated results that do not fulfil the above criteria should be manually reviewed and approved by authorised staff. Staff performing the review must have access to all information associated with the results.

5.6 | Component selection

The LIMS must ensure that the components selected meet all necessary requirements to ensure their suitability (e.g. antigen negative units, neonatal requirements etc.).

In clinical emergencies some requirements may need to be overridden in accordance with pre-agreed protocols and any concessions must be documented by means of a complete audit trail including justification and details of any overrides.

It is important to take into account the special requirements flagged for the individual patient. Incorrect component selection is a common adverse event identified in the Annual Serious Hazards of Transfusion (SHOT) reports (SHOT 1996–2022).[3] Patient special requirements may be known from previous transfusion history/testing[28]; specified on the sample request; identified through current testing; or determined by the application of predefined demographic/clinical rules. This includes patients with haemoglobinopathy/sickle cell disease and patients who have had ABO/D incompatible haemopoietic stem cell transplants.

Selected components should be reserved for a defined period in accordance with the BSH guidelines for pre-transfusion compatibility procedures in blood transfusion laboratories.[23]

5.6.1 | Additional requirements for the selection of red cells

The selection of red cells will proceed along one of the following paths:

- Serological crossmatch (manual or automated)
- Electronic issue (EI) without serological crossmatch
- Emergency issue of red cells

In all cases, the LIMS must ensure that the controls and rules expressed in the BSH guidelines for pre-transfusion compatibility procedures in blood transfusion laboratories[23] are followed. The guidance below addresses the management of some of these requirements by the LIMS.

The following requirements apply:

- The LIMS must not allow the selection of ABO-incompatible red cell units
- The LIMS must prevent the use of results from an invalid sample

The system must control sample validity in line with local policies and current guidelines.[23]

The LIMS should ensure patients requiring matched red cells receive the correct red cells which are issued by the most suitable means.

Controls in the LIMS must prevent the following unless an appropriate override has been authorised:

- Selection of D-positive red cells to a D-negative female patient of childbearing potential
- Selection of incompatible or previously incompatible units for a patient with known antibodies
- The issue of antigen-positive units to patients with clinically significant antibodies

The system must be able to search the stock available to aid the provision of red cells for patients requiring phenotype/genotype-matched red cells.

IT companies/LIMS suppliers should consider providing functionality to incorporate extended red cell matching algorithms for Rh, K and extended blood group genotype/phenotype matching depending on the patient cohort's need and clinical condition. The degree of matching required should be indicated by diagnosis, presence of alloantibodies and transfusion dependency, and should not be applied to all patients.

Serological crossmatch (manual or automated)

Units for serological crossmatch should be reserved on the LIMS using the barcoded entry of selected donations. Some systems can be configured to manage the selection process. This may help stock rotation however this requires staff to locate the selected units from within the available stock.

Electronic issue without serological crossmatch

The LIMS must perform checks to ensure that all the requirements for EI have been met including all criteria identified in the BSH guidelines for pre-transfusion compatibility procedures in blood transfusion laboratories.[23] The MHRA has published guidance on EI and this should be referred to Ref. [25]. It is desirable that in the event of an EI exclusion the LIMS displays to the user why EI is not permitted.

Extensive validation of the EI procedures, protocols and systems must be performed prior to implementing EI and repeated following system maintenance and upgrades.

EI must not be used:

- In the event of planned or unplanned LIMS downtime
- Where the patient group or antibody screening results have not been transferred electronically from automation to the LIMS
- With units that have not been entered into blood bank stock electronically
- Where automated results have been manually edited

Emergency issue of components

There will be occasions where it is necessary to release blood for transfusion without performing/completing pre-transfusion testing or crossmatching. In these circumstances, the LIMS should allow emergency issues as identified in the BSH guidelines for pre-transfusion compatibility procedures in blood transfusion laboratories.[23] This must include the use of O D positive red cells and group A high titre negative fresh frozen plasma (FFP) and platelets where appropriate.

In all cases, entry of retrospective testing for example post periods of planned or unplanned downtime, must be possible with a full audit trail of entries and amendments available.

If patient information is not available at the time of issue, later reconciliation must be possible once the full patient record has been established.

5.7 | Selection of PDMPs/pharmaceutical products

The LIMS should enable the selection of PDMPs/pharmaceutical products based on clinical algorithms. These could utilise flags or logic rules to prompt accurate and/or timely selection of the right product (e.g. management of anti-D Ig prophylaxis, issue of anti-D immunoglobulin).

5.8 | Component Labelling and Issue

The labelling of blood components is a critical step, and components must be identified with a securely attached compatibility tag before issue.

Units should be authorised, and the labels printed and attached, one patient at a time, at a single workstation location. Multiple workstations using a single printer are a potential source of error and should be avoided.

When attached to components, labels should not cover or obscure donation or manufacturer information on the unit base labels.

There must be a process to verify, ideally within the system, that the correct label has been attached to the correct unit.

5.8.1 | Compatibility tag

The compatibility tag should be printed out once the units have been authorised as compatible or suitable for issue. The information required to be printed onto each label is identified in BSH guidelines for pre-transfusion compatibility procedures in blood transfusion laboratories[23] and this should be reviewed in conjunction with these guidelines.

It should be possible to print a comment on the compatibility tag, for example to highlight where the blood group of the unit and the patient are compatible but not identical.

Where a blood tracking system is to be used in conjunction with the IT system there may be a requirement for additional barcodes.

5.8.2 | Label attachment verification

There must be a specific process step to ensure the correct label has been attached to the correct component. Ideally, this verification should be done by automated means using electronically readable information.

This verification step must include:

- Check to ensure the donation number on the component is identical to the donation number on the compatibility tag
- Check to ensure the product type on the compatibility tag is correct

Where automated support for verification of the donation number is employed, this will require printing a barcoded donation number on the compatibility tag, which can be differentiated from the ISBT donation on the component pack. The automated system must be designed to ensure that the donation numbers from both the component and the compatibility tag have been compared (i.e. duplicate entry of one barcode would be detected as an error).

5.8.3 | Remote electronic issue

In some hospital configurations, it may be beneficial[29] to store blood components close to the point of use and this may be at a location that is distant from the hospital transfusion laboratory. In such cases, components will be accessed by staff other than laboratory staff. This is referred to as remote electronic issue[29] and should always be supported by electronic systems under the control of the LIMS to ensure correct component release.

Components in remote issue refrigerators (or platelet incubators/agitators) must be managed by the transfusion laboratory and

procedures in place to ensure that only suitable components are available. Information on the current location of all blood and components, including thawed FFP, should be available in the laboratory. Records must be kept of all movements of all components.

Remote electronic issues of red cells must only be used for patients who have been determined as eligible for EI, which must be controlled by the LIMS. Each organisation should define whether patients with special requirements (e.g. irradiated) will be handled through remote electronic issues.

Remote electronic issues must be rigorously controlled using standard operating procedures, trained and competent staff and validation of the system in use. The following controls must apply to all remote electronic issue systems:

- The user must be positively identified by the system and verified to ensure they are authorised for the procedure
- Procedures must be in place to ensure all stock is suitable for issue and appropriate stock rotation is in place to ensure units are removed prior to expiry
- The identification of the patient and the request for components must follow the same rules as identified in Section 5.3 and the BSH guidelines on administration of components[14]
- Request information must be transferred to the LIMS either through electronic requesting or direct input to the remote electronic issue system. The latter will require secure systems for entry, preferably utilising barcoded information
- The LIMS must verify the patient request and authorise the issue of group-compatible components
- The LIMS must take into account any special requirements that apply to the patient and ensure that these are met
- Selected units must be scanned into the remote issue system and a label produced
- There must be a system for label verification to ensure that the label attached to the component matches exactly in terms of donation number
- The system must generate local and remote alarms if a user scans the wrong unit and gives a prompt to return the unit and take out the correct one

Records stored must include:

- Identity of individuals undertaking any step in the process
- Identification of the patient
- Donation numbers of the units placed into stock or issued
- Component /product type(s)
- Date and time of placement and issue

There should be an alarmed electronic override feature as this is essential for use in emergencies, that is release of emergency group O blood. All events should be logged and investigated retrospectively.

All blood that has been recalled or removed from the remote electronic issue system for longer than the specified time (depending on the storage conditions) must be quarantined so that it cannot be issued to a patient.

Remote electronic issue systems must not be used if the interface to the LIMS or any element of the system fails. Contingency plans and procedures for planned and unplanned downtime must be in place.

5.9 | Post-analytical reporting

Although electronic reporting is now best practice, the system must support both printed reports and electronic reports available online. It should be possible to format reports so that they are clearly presented and contain terminology that is clear and unambiguous.

Reports must be designed to give all information required for full identification of the patient and essential user information as laid down by ISO15189 standards.[28]

The report must draw the clinical user's attention to the date of final authorisation and advise the clinical user to take this into consideration when interpreting the information, for example report may state that the patient is suitable for electronic issue but this may no longer apply depending on the sample date.

There should be options to have reports by:

- Type of test
- Consultant/requestor
- Location
- Blood component/product

Others as defined by the local specification which may include

- Reason for the transfusion
- Justification for the transfusion
- Appropriateness of the transfusion
- Single unit transfusions
- Consent

Reports can either be:

- Final—released following authorisation
- Interim—released prior to authorisation but clearly marked as 'unauthorised' or 'incomplete'

Electronic reports showing details of components issued should be dynamic and reflect the status of the units so as not to cause confusion as to whether units are available or not. That is to say, when a unit is transfused the report should change to state the unit is transfused, and if returned it should state the blood is no longer available for use.

Increasingly reporting needs will include the transfer of information to other IT systems. Such transfer should comply with applicable healthcare communication standards. Dispatch of the reports must be to a recognised system and must meet the security and information governance recommendations.

Consideration should be given to the use of national reference reporting systems (such as NHSBT Sp-ICE system and WBS ABS system) including the use of electronic data exchange to permit reporting of results at a Trust/Hospital level without the need for manual transcription which is a source of potential error.

5.9.1 | Corrections to reports

Corrections to issued reports must be treated as a quality incident with appropriate investigation, corrective and preventive actions including:

- Withdraw all copies of the report
- Inform the relevant users that the report has been changed
- Follow-through of actions that other electronic systems have taken on the basis of the original report, for example Order Comms
- Monitor, track and trend the number of incidents where this occurs

The LIMS and associated software should support this activity by:

- Providing lists of users who have viewed online reports
- Issue of an updated report that clearly indicates its revised status
- If reporting is via associated software this must also be indicated

Where interim reporting is supported, consideration should be given to the procedures to be followed when information is changed prior to authorisation.

Recommendations

- Electronic transfer of data is recommended to ensure patient safety (2B).
- Electronic issue and remote electronic issue should only be used if all criteria identified in the relevant sections in these guidelines are met (2B).
- The IT system should use configurable logic rules to support good transfusion practice (based on current guidance). These should also control the issue of components where patients have special requirements (2B).
- Processes must be in place to ensure that patient identification data are consistent and accurate across all interlinked systems. Special consideration should be given to the interface between the transfusion system and external systems to ensure changes in the external systems cannot automatically update the transfusion system (2B).
- There must be a method available to merge/link and unmerge/unlink duplicate records in a way which ensures the integrity of the transfusion record and maintains traceability (2B).
- Wherever possible, information should be entered in a structured manner (i.e. coded) to ensure data is easily retrieved and auditable. This should include the clinical indication for transfusion (2B).

6 | ELECTRONIC BLOOD MANAGEMENT (TRACKING) SYSTEMS

Traditional LIMS provide control of activities that take place in the laboratory. Increasingly there is recognition of the need to extend the scope of electronic control through to patient administration. Specialist systems have been developed that interface to the LIMS and control these additional steps.

Electronic systems can be used at the following stages of the transfusion process:

- Component collection
- Remote electronic issue (see Section 5.8.3)
- Component administration
- Component prescription/authorisation
- Clinical decision support for transfusion

Electronic control of all steps in the transfusion process using an electronic blood management system means that the risk of errors is reduced, and data are instantly available with real-time warnings/alerts generated (e.g. if blood is available for collection has expired).

It is important to define how each system is managed to maintain the necessary control. There should be electronic communication between the LIMS and all electronic blood management systems. All traceability information should be collated into a single system for lookback and retention. It is recommended that the LIMS should be the ultimate recipient of traceability information for maintaining this for the legal requirement of 30 years.[2]

The following criteria apply to all these systems:

- Access to the system must be by a unique user ID
- Staff must be given training before access to the system is allowed
- Systems should utilise machine readable information and electronic transfer of critical information wherever possible
- Alerts should be seen/heard at the site where action is required, but the transfusion laboratory should also receive these alerts to ensure that appropriate action is taken
- Every transaction on the system must be logged with a user ID, date, and time and a full audit trail must be maintained
- The boundaries of responsibility between the LIMS and the electronic blood tracking system must be defined and managed
- Robust manual procedures must be documented for use during planned or unplanned system downtime
- Adequate and robust backup of data must be in place

6.1 | Component collection (fridge tracking)

A component tracking system is specifically designed to manage and control the movement of components within the cold chain, it is recognised this may be included with the LIMS or by implemented as a stand-alone electronic blood management system (EBMS).

The degree of control imposed by these systems will vary from simple data capture to electronic locking of blood refrigerators/platelet incubators which control release, down to the unit and patient level.

The following requirements apply to fridge tracking systems:

- Configuration of the system should be such that there is real-time communication between the LIMS and the issue locations
- It must be possible to configure the system to allow access to group O emergency units where required
- The LIMS should electronically notify the fridge tracking system when components are issued to specific patients
- The LIMS should be able to update the fridge tracking system if units are no longer suitable for use and the system should respond accordingly
- Where multiple storage locations are used, each must have a unique identification code
- Systems should require entry of the unique patient identification, in an electronically readable format. Ideally, this should be generated from the patient's wristband
- The system should control access to the blood refrigerator/platelet incubator with some form of electronic lock. System design should ensure procedurally controlled access and system alerts in the event of network downtime, power failure, clinical emergency etc
- The fridge should only unlock if components are available for the specified patient.
- The system must electronically read and recognise unique component IDs including donation number, component code (including split number)
- Alerts/warnings should be generated if units are no longer suitable for transfusion
- The transaction history of each component must be stored. This should include, where applicable, the physical transfer of components from stock to issue locations; details of unit movements including transfer between unreserved and reserved stock; transfer to and from satellite refrigerators; issues to wards and departments; and transfers to other hospitals
- Contingency plans must be in place to ensure safe collection should the electronic system fail

6.2 | Administration

A bedside tracking system is also part of an EBMS and is designed to:

- Prevent administration errors by controlling the pre-transfusion checks required between the patient and the component to be administered
- Capture administration information in real-time at the bedside

The use of a bedside blood tracking system does not replace the role of the well-trained and competency-assessed clinical staff who administer blood components.

SHOT has shown that an administration error has the potential to cause significant patient morbidity. The use of bedside tracking systems with electronic capture of information from the patient wristband, component label and compatibility tag significantly reduces the risk of manual transcription errors and omissions.[29] For this reason, bedside tracking systems should be considered for all transfusions.[18]

The bedside tracking system must perform pre-transfusion checks at the patient's side including the following:

- Electronic capture of the unique patient identification from the wristband or equivalent
- Electronic capture of the donation number, component code, blood group and expiry date from the unit
- A verification process using information from the LIMS (either transmitted by direct communication with the bedside tracking system or by the use of electronically readable information on the compatibility label) which securely links patient and donation information
- Alert to errors in real time to prevent incorrect blood component transfusions

There must be regular monitoring and audit of data downloaded from these bedside devices whether in wireless-enabled areas or via docking devices.

6.3 | Prescription including clinical decision support

Electronic prescribing (more correctly called 'authorisation') of blood components is becoming more prevalent. Planning for implementation must include a robust design of the order template which may require input from a multi-disciplinary team.

Each prescription must ensure usual prescription standards and therefore must contain the patient's minimum identifiers and specify the component required, including volume and rate of transfusion. In addition, consideration must be given to recording indication for transfusion, and the consent of the patient.[14,30] The assistance of electronic prescribing to encourage the ordering of single-unit top-up transfusions with patient assessment between units and the inclusion of a transfusion-associated circulatory overload (TACO) assessment should also be considered. There should be consideration for special areas such as Emergency Departments or Theatres where massive transfusions may occur to ensure any prescription system is not cumbersome to patient care.[31]

Computer-based CDS systems have been demonstrated to bring national transfusion triggers into clinical practice, reduce component usage and reduce pressure on transfusion laboratory resources. CDS should be implemented with electronic prescribing, where possible.

Bedside tracking systems may also be able to capture and support the administration information including:

- Date and time of transfusion
- Healthcare staff identity
- Transfusion start and end time

- Patient observations

This information may be transferred back to the LIMS together with the patient identification and donation information and support the legal traceability requirements.[2]

If there are emergency overrides these must be risk-assessed and have appropriate procedural controls in place.

Recommendation

- Electronic blood management (tracking) systems have proven patient safety benefits. The ongoing requirements of user support and equipment maintenance should be considered when the systems are being procured and implemented (1D).

7 | RECORDING ADMINISTRATION/FINAL FATE INFORMATION

Mechanisms must be in place to ensure the final fate of each component is captured. Hospital final fates may include but are not limited to transfusion to the identified patient; discard; transfer to another hospital; and recall by the blood service.[14]

Final fate information can be provided to the LIMS in a number of ways including:

- Manual or barcoded entry in the laboratory from the return of paper documents
- Manual or barcoded entry onto the LIMS from the clinical area
- Electronic transfer from a tracking system

Where manual entry is used it should be performed as soon as possible after the transfusion to ensure the integrity of specimen validity algorithms. It is essential to assure the accuracy of the data entry. This may be facilitated using a barcoded donation number on the compatibility tag. If a barcoded entry of the donation number is not supported, then double-blind manual entry is required, and check digits/characters associated with the donation number must be verified.

Blood components that are not transfused because they are either not required or are not suitable for transfusion must be returned to the blood transfusion laboratory. Following the assessment of the cold chain, a decision will be made to return blood/components to stock or discard. It is important that the blood tracking system clearly warns of any cold chain breaches and that any overrides or changes are auditable. If the unit is to be discarded the final fate must be recorded in the LIMS.

8 | INFORMATION MANAGEMENT

Effective information management must ensure that: information is available when and where it is needed; confidentiality, including General Data Protection Regulation (GDPR) requirements,[32] is ensured to prevent access by unauthorised individuals or systems; the integrity of the accuracy and consistency of information is maintained; and information can be stored and retrieved throughout mandated storage intervals.

It is essential to ensure traceability throughout the transfusion pathway from donor to recipient (or other fate), and traceability within hospital systems is an essential element of this system. The legal requirements for traceability are laid out in the BSQR.[2]

8.1 | Traceability and data retention

All records necessary to provide rapid and effective tracking from receipt of the donation into the laboratory until the final fate of that donation must be available for 30 years as required by legislation.[2] This will include the final fate traceability captured at the time of use or other disposal. Special care must be taken to ensure the traceability of components is maintained when transferring components between organisations.

The data set to be retained by hospital blood banks should be a complete audit trail relating to the unit and include:

- Donation number
- Component type
- Blood Establishment/supplier
- Date and time received
- Identity of the patient who received the blood component or final fate if not transfused
- Date and time the unit of the fate of the unit

Traceability of components is a legal requirement for the organisation and requires cooperation between transfusion laboratories and the organisation. This must be documented and identified:

- Where traceability information is held
- How information elements are linked between systems
- The mechanism and frequency of traceability audits

This strategy must be updated as part of any IT system upgrade or replacement to ensure historic records are not compromised.

Further information on traceability is available from the ISBT Guidelines for Traceability of Medical Products of Human Origin.[22]

8.2 | Management information/data collection

The LIMS must be able to support the reporting requirements of the organisation which should have been identified as part of the URS. This may include pre-defined reports, locally configurable reports or the ability to produce ad hoc reports. If data items can be associated with standard codes this approach to data entry and storage is recommended (e.g. Systematised Nomenclature of Medicine Clinical Terms [SNOMED CT]).

The LIMS must be able to extract data for statistical analysis such as billing, audit and monitoring of key performance indicators (KPIs).

Examples of KPIs would be:

- Turnaround times for various laboratory processes
- Information to support MHRA Serious Adverse Blood Reactions and Events (SABRE) reporting
- Information to support MHRA hospital blood bank compliance reporting

There will always be requirements to run ad hoc enquiries. Staff involved in the production of ad hoc and locally configurable reports should be trained and have appropriate knowledge of how the system works and what needs to be extracted (this should be undertaken in accordance with local policy).

Data stored on the LIMS should be accessible for further analysis by the system and by third-party applications. Any use of data must comply with GDPR[32] guidance. Access to the database by third parties must always be adequately controlled to ensure data security requirements are not compromised. Third-party usage may be by local users (e.g. through spreadsheets or statistical software) or to approved third-party organisations such as:

- Blood Stocks Management Scheme (England, Wales and Northern Ireland)
- Account for Blood (Scotland)
- Bone Marrow/Stem Cell Registries
- Blood service stock management requirements
- Benchmarking data

8.3 | Clinical information—audit and quality improvement

The LIMS contains information on blood and blood component usage that can be used by clinicians, managers and hospital transfusion committees when reviewing clinical transfusion practice and service developments that may increase or decrease blood usage.

Blood and blood component usage and wastage can be attributed to the LIMS to patients, clinical locations, clinicians and specialities and extracts of this information can be used to produce regular 'clinical accounts' for blood. The same data can be analysed on an ad hoc basis for clinical audit and quality improvement initiatives.

It is desirable to have a standard clinical transfusion data set and to code clinical information such as the indication for transfusion and the reason for transfusion so that all fields are searchable. This greatly improves the ability to undertake clinical audits and quality improvement (QI) and to produce regular data for key clinical performance indicators as well as the previously mentioned clinical accounts.

The demographic and clinical information given at the time of the request for testing or request for blood and blood component issues can either be entered manually or input via Order Comms systems. Where it is possible to configure the Order Comms systems to use the same indication and reason codes for transfusion these can be transmitted to the LIMS with the request.

The LIMS and Order Comms systems can be used to support national and local transfusion policies. This might include getting data from a haematology LIMS such as haemoglobin levels when ordering a red cell transfusion to see if locally agreed transfusion triggers and targets are complied with. It could also be used to record when valid consent for transfusion has been obtained or to record a pre-transfusion platelet count against the issue of a platelet unit. It is desirable that the LIMS system should support the ability to transfer information about blood and blood components transfused to the patient EPR and discharge summary.

Although this clinical functionality may not be widely used, it is important when implementing a LIMS for blood transfusion, to consider the opportunities and specify the fields that will be able to accept these sorts of clinical data.

9 | SYSTEM MANAGEMENT

The transfusion laboratory will need to ensure effective information security (confidentiality, integrity and availability) in line with regulations, best practices and effective control of system changes and upgrades.

9.1 | System security and governance

Information held on laboratory systems must be appropriately managed to ensure that confidentiality, integrity and availability are maintained in compliance with legislation, regulations, codes of practise and NHS guidance. Each individual UK nation utilises its own Information Governance Toolkit.[33]

Governance applies to all databases including legacy systems and data archives. Consideration must be given to the retained EU GDPR 679/2016 commonly known in UK law as UK GDPR. Further information on UK GDPR can be found within the UK Data Protection Act, 2018.[32] It is noted that UK legislation on the traceability of blood components may mean a request to remove patient information may not be possible to undertake until the end of the period of retention of traceability has passed (currently 30 years).[2]

Access levels must be controlled to ensure that staff can only have access to functionality that is appropriate for their job roles and to which they have been appropriately trained and assessed as competent. Procedures must ensure a prompt removal of access once an individual's authorisation terminates. For systems generating, amending or storing GXP data, shared login or generic user access should not be used (MHRA 'GXP' Data Integrity Guidance and Definitions).[34]

Pathology services should comply with cyber and data security good practice to reduce the risk of IT failure. Examples of current guidance and best practice are available via NHS Digital and the National Cyber Security Centre.[35]

9.2 | System availability and business continuity

Systems will normally need to be available 24 h a day, 7 days a week, but this may vary according to local situations. Appropriate fall-back and support arrangements need to be in place that can ensure continued service delivery in the absence of the IT system, whether this is planned or unplanned downtime. Availability requirements must be reflected in the system and network design and maintenance/support arrangements.

When determining acceptable IT system downtime, the following must be considered:

- Throughput
- Staff resources
- Manual data recovery
- Interaction/impact on other IT systems

Even in the most robust systems there will be inevitable downtime. Risk assessments must be performed to identify those risks associated with system failure and be used to inform system design, implementation and backup and recovery procedures.

The system architecture should be designed to have no single point of failure, for example where possible there should always be an alternative server or connection that can be brought into play manually or automatically. For multi-site organisations, the wide area network (WAN) configuration must support the necessary degree of resilience and recovery.

It is expected that the business continuity management system will be compliant with the ISO standard on business continuity systems ISO22301.[36] Business continuity plans must be tested to demonstrate their effectiveness and identify their limitations. This must include the recovery phase where the IT system is brought up to date with all the transactions. Both backup and recovery processes should be validated and periodically tested.

9.3 | Data integrity

According to the MHRA 'GXP' Data Integrity Guidance and Definitions,[34] 'data integrity is the degree to which data are complete, consistent, accurate, trustworthy, reliable and that these characteristics of the data are maintained throughout the data lifecycle'.

Transfusion-related data are stored in the LIMS and other associated systems. It is essential that its integrity is maintained in a consistent state across all systems, for example it would be unacceptable for the status of a donation to be 'in stock' in the LIMS but 'issued' on the electronic blood management (tracking) system.

If the system in use has the software to conduct data integrity reviews, they should be run in accordance with the manufacturer's instructions to identify if any areas of inconsistency that have developed. This can be included in the laboratory audit schedule. Additionally, in response to incidents where a data discrepancy has arisen, a data integrity review can be included as part of the corrective and preventative action.

There should be a procedure in place that describes the process for review and approval of data. The review should document if any data integrity issues were identified and the corrective and preventive actions to be implemented.

9.4 | Duplicate record searches

A system should be in place for searching the LIMS for potential duplicate patient records. SHOT annual reports have highlighted the clinical problems which can arise when more than one patient record is in existence. Amalgamation of organisations, and hence LIMS records, has increased this problem. Where patient records are being merged/linked across networks it is important the local hospital transfusion laboratory is involved.

The following functionality should be supported:

- Searches should run automatically at predetermined time periods with the ability to activate manually if required
- User-definable search criteria
- Use of a limited dataset search to allow for misspellings of patient names or amended date of birth entries
- Soundex or similar intelligent-style searches

Local procedures should be in place to define the corrective and preventive actions to be taken if a duplicate is found. Merging of any duplicate records should be handled as outlined in Section 5.2.3.

9.5 | Back-up and disaster recovery

Back-up (a copy of current editable data, metadata and system configuration) should comprise a regular copying of the database to secure media which are stored separately and away from the main database and a journal system which allows recovery of data from the period of last back-up to the time of failure.

The storage location for backup media must be based on an appropriate risk assessment of the likely disaster scenarios.

The backup and recovery processes must be documented, validated and periodically tested to demonstrate their ongoing effectiveness. Each backup should be verified to ensure that it has functioned correctly, for example by confirming that the data size transfer matches that of the original record.[34] Recovery procedures must cover all steps from the moment of system failure through to the resumption of routine operations. This must include verification that:

- The data has been fully retrieved
- The system has been returned to the same state as the time of failure
- Operational processes resume from the point of failure

9.6 | Change control and system upgrade

Systems are being continually updated by vendors and new versions of the software are being released. System upgrades should be evaluated both in terms of their immediate impact and the long-term consequence of not installing when available. Care must be taken to ensure that the software is updated in line with the vendor support strategy to prevent loss of vendor maintenance. It is important to understand what elements are included in support contracts and those that may be excluded or subject to additional fees.

The change control process must apply to all individuals involved in the management and use of the LIMS and associated transfusion systems. This may include other pathology disciplines and hospital IT departments where transfusion is part of a larger pathology discipline. Any change to the system, however minor it may seem at the outset, will need to be critically evaluated, a change control raised, and appropriate risk assessments performed to identify the level of validation required.

Vendor access to systems must be controlled to prevent unvalidated system changes.

9.7 | Audit trails

It is essential that audit trails are available on the system to provide accountability and to assist in investigation. The system must:

- Maintain an audit trail of critical actions associated both with patient records and transfusion activity including changes to or deletion of data while retaining previous and original data
- Record the date and time of all significant process actions (create, amend, delete) along with the identification of the individual performing the action
- Provide access to records for review and retrospective search, as necessary

Each organisation should risk assessing and document which actions and processes need to be maintained in the audit trail and should validate and carry out periodic audits to ensure system conformance. The MHRA GxP Data Integrity Guidance and Definitions[34] provide further details on the requirements for audit trails.

9.8 | Archiving

Archiving of all data and documentation must conform to BSQR[2] and the guidelines from the Royal College of Pathologists and Institute of Biomedical Science on the retention and storage of pathological records and archives.[30]

9.9 | Risk and risk assessment

All manual systems are associated with risk and it should also be recognised that the implementation and use of an IT system will also have associated risks but that these may differ from the manual process.

It is critical that no IT system is implemented without a good understanding of the risks involved and an associated risk assessment. The risk assessment must indicate if the system is in line with guidelines. Failure to comply with guidelines and the use of alternative processes could increase the risk. The final decision on the implementation should be guided by the risk assessment and must be documented.

Recommendations

- All transfusion laboratories must have an effective business continuity plan which allows safe continuation of service provision in the event of an IT system failure (2A).
- All IT systems including EBMS must have an appropriate backup strategy that safeguards system data and supports system recovery to minimise the time the business continuity plan needs to be in operation (2A).
- Any updates or amendments to the system must be controlled through the QMS using a formal change control and validation process (2B).
- Access and security of the system must be controlled in line with the Trust/Hospital and National IT policies and recommendations (2B).

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CONFLICT OF INTEREST STATEMENT

The BSH paid the expenses incurred during the writing of this guidance.

All authors have made a declaration of interest to the BSH and Task Force Chairs which may be viewed on request.

REVIEW PROCESS

Members of the writing group will inform the writing group Chair if any new evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be reviewed regularly by the relevant Task Force and the literature search will be re-run every 3 years to search systematically for any new evidence that may have been missed. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made an addendum will be published on the BSH guidelines website (www.b-s-h.org.uk).

DISCLAIMER

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AUDIT TOOL

See website for template.

ORCID

Paul Ashford https://orcid.org/0000-0002-9256-8239
Tom Bullock https://orcid.org/0000-0001-5486-0389
Megan Rowley https://orcid.org/0000-0002-9322-8527
Chloë E. George https://orcid.org/0000-0003-3857-378X

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APPENDIX A: PLANNING AND IMPLEMENTING SYSTEM CHANGE

This section covers the initial steps for implementing a new system into the transfusion department. Many of these steps will also apply to major upgrades and to separate procurement of subsidiary systems such as analytical systems and associated middleware and electronic blood administration (tracking) systems.

A.1. | Business case

The business case captures the reasons for initiating the purchase of a new or updated system and identifies resources, either capital, revenue or staff, that will be required to deliver the specific business need. Information in a formal business case should include the background of the project, the expected business benefits, the options considered (with reasons for rejecting or carrying forward each option), the expected costs of the project, and the identified risks. IT systems may qualify as an in vitro diagnostic (IVD) medical device as set out in Directive 98/79/EC and as such these regulations must be taken into account [1].

The business case will need to be developed in line with local policies, but the output should clearly identify:

- The scope of the project – what is included and what is excluded with clear boundaries;
- Management responsibilities, identifying the project owner and project team members;
- Resources required for the project (staff, equipment, accommodation and financial).

The business case must also consider the impact on linking to other systems, both within the organisation (e.g. Patient Administration Systems [PAS], Electronic Patient Records [EPR]) and outside [e.g. links with Primary Care & Blood Establishments]), and Electronic requesting systems and define how this will be managed and the degree of interaction permitted between the systems.

A.2. | Project planning

Once the business case has been approved the project planning approach needs to be defined. A multi-disciplinary team, including subject matter experts, IT personnel and a project manager should be established and a project plan and project quality plan created. This will help to ensure the necessary controls are in place and managed under the regulatory framework. The transfusion requirements for an IT system may be very different from broader Pathology requirements. Potential systems must be fully evaluated to ensure compliance with the transfusion requirements.

Where a new system will bring together information from multiple existing PAS or Laboratory Information Management Systems (LIMS), particular care needs to be taken to ensure that differences in the way information has been structured and entered in these systems is taken into account (e.g. code tables, locally agreed terms and abbreviations etc.). Assumptions about the compatibility of information cannot be made and each system should be fully assessed in its own right at the outset.

Project Management must include:

- Change Management: A new LIMS or an upgrade to the current LIMS must be managed under the formal change control system in operation within the organisation.
- Risk/impact assessment: In any project a risk assessment must be performed to identify all the factors that impact on the project itself or continuing service provision and define ways to mitigate the identified risks. Risk assessment must be ongoing throughout the project and should be used to focus the validation effort on the higher-risk areas.
- Responsibilities and authorities: The project management documentation should include: project scope and boundaries; project management and delivery approach; roles and responsibilities; project governance; resource management; and quality assurance.

A.3. | Process maps

It is important to gain a common understanding of the entire process, the specific roles and contributions of personnel, process inputs and

outputs and the interactions of the LIMS system with external IT systems/devices. This can be achieved using a process mapping technique. All processes within the scope of the project should be mapped, together with relevant boundary processes.

Implementation of a new system may impact and change existing processes. Where this occurs, both existing and new process flows should be mapped to help understand the impact of the changes.[33]

This type of mapping will help to formulate the details of the User Requirement Specification (URS). It is also a valuable tool in system configuration to ensure that all necessary process interactions are supported.

A.4. | User requirement specification

System requirement specifications are created at a number of levels of detail and points in a system lifecycle. The initial specification often called the Operational Requirement Document (ORD) is created during the system procurement process. It is used to inform potential suppliers of what process or processes the system is expected to support and the functionality it is expected to provide. Depending on the complexity of the process the requirements in the ORD may be broken down into more detailed requirement specifications often referred to as the URS. Following initial implementation, as time progresses business requirements often change and this will require amendments to system configuration and in some cases additional functional development. For each change required a further specific URS should be created specifying the amendments now required. An example of the basic information required in the ORD and URS is shown in Appendix IV.

A.4.1. | The operational requirement document

The ORD is a structured document which identifies all of the essential and desirable requirements of the system and will be issued to potential suppliers with the invitation to tender. Each requirement should be clearly marked as essential or desirable, recognising that failure to satisfy all essential requirements will eliminate a bid. This is the document which informs suppliers what a system is required to do. This document should be at a relatively high level with the requirement statements saying in broad terms what functionality is required, for example 'the system must allow for the registration of the mandatory patient demographics; mandatory identifiers are…'. At this stage, it is an open statement and suppliers will be asked to demonstrate that as a minimum the mandatory identifiers can be registered. During the procurement process suppliers who can meet this requirement will pass on this point however some suppliers may be able to demonstrate that they can accommodate not only the mandatory identifiers but a whole host of other useful patient data and therefore on this point may become the preferred option. The ORD should be used to draw out information about the system's capabilities, ensuring that all mandatory requirements will be met. It is a contractual document which a supplier can be held to deliver however the onus will be on the organisation to prove non-compliance with a requirement.

For complex sets of requirements or where requirements must be delivered in a more precise manner it may be necessary to give a more detailed insight into a requirement. In this case, a detailed User Requirement Document (URS) may also be created however the same fundamental principles apply for both documents and the terms ORD and URS are often used interchangeably. URS is the more common term and will be used for the rest of this document.

A.4.2. | The user requirement specification

In developing the URS, consideration should be given to current and future developments in the field of transfusion medicine information management. The document should be developed by a multi-specialist team and should include specialist subject matter experts from the laboratory, clinical teams including consultant involvement and Trust and Laboratory IT.

As modern LIMS offer extensive configurability it is important to specify in the URS what is required but to avoid specifying how it is to be achieved unless this is essential to the operational need.

A.4.3. | Operational functionality

The URS is a structured document. Every functional requirement of the system needs to be detailed within the URS. Requirements should be written in clear numbered paragraphs, with each paragraph identifying a single requirement. Each requirement should be written so that it clearly specifies what is required giving any specific capabilities and the criteria against which compliance will be measured. This format ensures clarity and provides a means to reference validation evidence back to requirements. Vague and ambiguous statements must be avoided.

The writing group have provided a sample URS/ORD as part of the guideline to provide assistance in writing such documents. This contains a small number of examples and is not intended to be a complete example.

A.4.4. | Validation requirements

The URS should outline the validation/qualification strategy and clearly define the roles and responsibilities of both the supplier and purchaser. For this reason, it is important to specify requirements such that they can be readily tested and evidence provided of both compliance and non-compliance with the requirement statement. In a procurement situation validation will be at two levels. Level one is to validate that the supplier is offering a system that has the potential to fulfil the operational requirements. Level two is to validate that on implementation the system actually does sufficiently meet the requirements in a way that is operationally fit for purpose.

A.4.5. | Interface specification

Many instruments and analytical devices provide a means of communicating electronically with LIMS however there is a lack of standardisation in this area and communication formats vary from device to device. An example of a commonly occurring interface is that between a grouping analyser and the LIMS. Interface software provides a mechanism to convert the communication from the instrument to a format the receiving system can understand.

Some specialist interface software, known as middleware, may be used to allow multiple analysers and multiple sites to communicate with the LIMS using a common format. Middleware may also undertake some interpretation of raw data to provide a test conclusion to the LIMS. A decision needs to be made and recorded as to whether or not the interpretation of results is undertaken by the LIMS or by the middleware. Any system undertaking interpretation of results is classified as an IVD medical device and as such must meet the specifications set out in Directive 98/79/EC.[1]

All required interfaces (current and anticipated) should be identified in the URS. Details should include the data which is to be transferred; batch or real-time transfer, error detection and alarms. Equipment suppliers can usually provide communication specifications for the interfaces to connect their equipment to LIMS which will also indicate what data and/or flags can be transmitted.

When specifying interface requirements consideration should also be given to ensuring support of existing and developing information transfer standards to increase flexibility and reduce the overhead of future change.

A.4.6. | Electronic data interchange (interoperability)

System-to-system communication is an essential requirement of healthcare computing. The LIMS will need to be able to communicate with other systems including the PAS, Electronic Request Systems (Order Comms) and Electronic Blood Management/Tracking systems. There is a growing expectation for seamless information sharing between systems and this needs to be supported by effective interoperability.

Electronic Data Interchange (EDI) is the term used to describe the structured messages and protocols used for such communications in a way that the receiving system can correctly interpret the value, meaning and context of the information sent from the transmitting system. Required EDI functionality should be identified, and EDI standards that are used within the national and local healthcare IT environment should be specified.

Interfaces between computer systems, in particular between the PAS and LIMS must be configured and validated to ensure compatibility between the information formats used by each system. Care should be taken to ensure no pre-existing LIMS data is altered automatically by PAS links. Any such alterations would be by positive authorised user action within the laboratory.

EDI may be unidirectional such as the Electronic Delivery Note (EDN)[8] used to send information from blood services to hospitals using a fixed format file, or may be bi-directional such as the information interchange that occurs between an electronic request system (Order Comms) and a LIMS during ordering of blood components. There is an expectation for seamless information sharing between systems and this needs to be supported by effective interoperability. An example of interoperability is shown in Figure A1.

A.4.7. | Peripherals and hardware requirements

Any items of hardware should be appropriate in terms of specification and numbers to ensure the running, security and performance of the software application. To ensure that the necessary requirements are met the following should be considered when purchasing:

- Number of concurrent users.
- Maximum transaction rate to be supported.
- Anticipated growth rate.
- Resilience to a single point of failure.

A.4.8. | Operational environments

An operational environment is a version of the system (software, hardware, peripherals) used for a specified purpose. The 'live' environment is the one in routine use on a day-to-day basis.

All systems should support multiple environments with a minimum of two environments to allow a separation of live and validation/training environments. The optimum set-up would include environments for testing, validation, live, training and disaster recovery (DR) although it's recognised that DR may need to be on a separate server/installation. Each environment must be completely independent and version-controlled. Modern configurable systems may support larger numbers of environments and users should specify the number and type required in the URS.

All environments will need to be able to link to other operational systems (e.g. Order Comms). Consideration must be given to how this can be achieved without impacting on live data and live operational use.

A.4.9. | Data management

The information held on existing systems forms an essential record, some of which falls within the record retention requirements of the Blood Safety and Quality Regulations (BSQR) and the Medicines and Healthcare Products Regulatory Agency (MHRA) 'GXP' Data Integrity Guidance and Definitions.[34] In addition, much of this information is critical to the ongoing operation of the department. It is therefore of critical importance to ensure that the management of this information through the system transfer and into the future is well-defined and

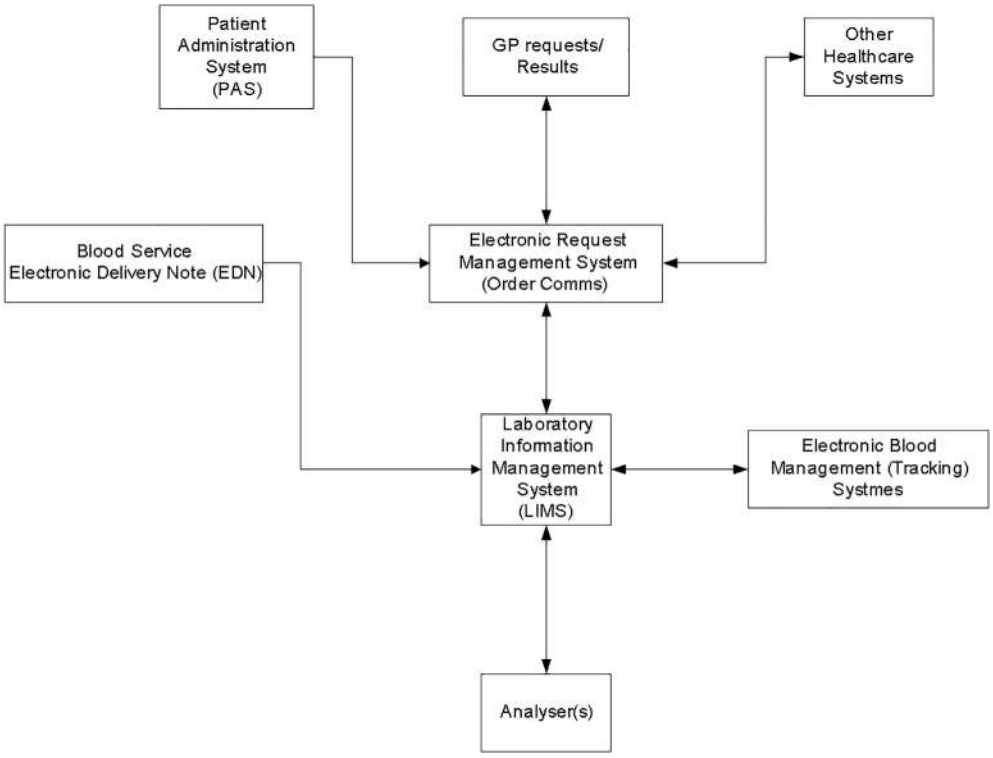

FIGURE A1 An example of interoperability. EDN: electronic delivery note; GP, general practitioner; PAS, patient administration systems; LIMS, Laboratory Information Management Systems.

captured within the URS. This is an area where typically the ORD states if migration of legacy data into the new system is required and if it is a more detailed URS is created to specify the exact data to be migrated. Data that needs to be retained may either be migrated to the new system or may be archived in a manner that makes it accessible for lookback purposes.

The decision on whether this data is migrated or archived will depend on several factors. These will include the historical data needs of the new system; the proposed manner in which the new system interacts and displays historic data; the quality of the legacy data; and the cost-effectiveness of archiving versus live database retention.[2] It is recommended that a formal risk assessment is performed to determine the most appropriate approach.

A.4.10. | Data migration

Data migration is the process of moving stored data from one durable storage location to another. This may include changing the format of data to make it more usable or visible on an alternative computerised system, but not changing the content or meaning. Data transfer/migration procedures should include a rationale and be robustly designed and validated to ensure that data integrity is maintained during the data lifecycle.[4] Careful consideration should be given to understanding the data format and the potential for alteration at each stage of data generation, transfer and subsequent storage and should take into account:

- Legal requirements (e.g. traceability as defined by the BSQR[2] in terms of the final fate of all components).
- Operational requirements (e.g. historic group, antibody information, special requirements).

The most direct form of migration is to transfer records directly into the new database although data reformatting may be required. Where any form of data migration is performed it is important that the quality of data migrated is verified (see Section A.7.1). All patients must be uniquely identified and should have an NHS number (or equivalent).[35]

In more complex situations where information from multiple legacy systems is being transferred into a single new system, variations in the use of key identifiers and the format of data can cause difficulties.

Secure operational procedures must be in place to ensure data integrity and minimise the potential for incorrect linking to occur. Each piece of data may need to be evaluated through a number of phases before migration to the new system. A full audit trail for this process is essential.

Retaining operational data on a legacy system that is not electronically linked to the operational system (i.e. interrogating a separate database which is a manual step), is not acceptable for maintaining patient safety within the transfusion laboratory.

A.4.11. | Archive data storage

Some data may not be required for routine operational purposes but will need to be retained for 'lookback'/audit. Where it is decided not to migrate this data consideration will need to be given to ensuring that it remains readily accessible. It is important that the archived data

can be searched using search criteria including patient identifiers; donation number; and batch/lot number to ensure all 'look back' requests can be met. It is essential to ensure the same data security controls are applied to the archived data as apply to the live system.

There are several possible archiving options including:

- Migrate the data into a data warehouse or equivalent reference database;
- Maintain the legacy system in a non-operational, read-only configuration (see below).

Managing legacy systems may be complex and costly. Consideration must be given to long-term sustainability (the current regulation for data retention, at present, is a minimum of 30 years).[2]

In order to effectively maintain the legacy system, the following requirements will need to be met:

- Adequate backup of the legacy database.
- Ongoing system maintenance contract and licensing.
- Regular start-up and running of the system.
- Maintaining staff access to and skills in the use of the system.
- Regular 'lookback' validation exercises.
- Regular review to ensure ongoing hardware and software support.
- Planning for ongoing migration or archiving when the system can no longer be supported.

Regular Audit of who is accessing the system is required to ensure there are personnel who remain competent at accessing the legacy system. The archiving strategy documentation needs to be retained to support the 'lookback' activity. Whichever approach is adopted the archive system must be fully supported with Standard Operating Procedures (SOPs) and staff training. Included in this documentation will be the requirement to develop new SOPs to ensure 'lookback' activity is controlled.

It may be appropriate to categorise the legacy data into that which will be migrated to the new system and that which will be archived. This may be done on the basis of time (e.g. data from the last 5 years is migrated and prior data archived) or maybe specific to information types depending on the database structure (e.g. it may be more important to transfer patient information, blood group and antibody status than test data and component details). Where an existing database is to be split into data for migration and data for archive careful consideration needs to be given to the boundary cases to ensure there is a clean division.

Consideration should also be given to how data is matched/linked when storing data from more than one site. This is especially important where the format of data held on each site prevents an exact match.

A.4.12. | Maintenance requirements

The maintenance of the system will include aspects which are undertaken by the Trust/Hospital IM&T department as well as those which are in the remit of the supplier. Responsibilities must be agreed upon and covered by relevant contractual agreements.

A.5. | Procurement

Procurement of a LIMS will require a multi-disciplinary approach and will need to follow the healthcare organisation's purchasing procedures. Requirements should be clearly identified as 'essential' or 'desirable,' recognising that a bid that fails to provide all 'essential' requirements would be eliminated from consideration. Any weighting to be applied to the bid evaluation should be pre-determined and documented prior to the release of the tender invitation.

A.5.1. | Bid evaluation

Bid evaluation will follow standard procurement procedures for the specific organisation and will include financial considerations. A technical evaluation using a scoring and weighting system should be employed in order to compare the degree of compliance of submitted bids to the URS. Bids will only be technically acceptable if all essential requirements have been addressed. Some bidders may indicate that essential requirements are not currently supported and can be developed and the evaluation scoring system will need to consider how to address this.

A.5.2. | Gap analysis

Once a supplier has been selected, the process maps, URS and technical evaluation should be used to identify all areas of the selected system where there are identified gaps, for example desirable requirements that are not met.

These gaps may be addressed by:

- Modification of the new system either prior to installation or as an upgrade following installation.
- Modification of existing operational processes to address the gap outside of the new system.
- No action required, limitation accepted.

In all cases a risk assessment should be performed to determine the appropriate action and decisions documented. Where change is required this should be handled through a formal change request process with the supplier.

A.6. | Contract

Once the tendering process is complete and a supplier has been selected there will be a phase of contract negotiations to ensure all parties are clear on their responsibilities and commitments. Negotiations may include:

- Project management responsibilities of supplier and purchaser.
- Communications between parties.
- Identification of any changes required as a result of the gap analysis of the bid.
- How training is to be delivered.
- Documentation and technical support arrangements.
- Implementation planning and support.
- Configuration support.
- Testing and validation support.

Good Automated Manufacturing Practice 5 (GAMP5)[35] category classification provides guidance on what the Supplier should deliver for the lifecycle of the system.

A.7. | Implementation preparation

This section addresses tasks which will need to be completed prior to implementation, some of which may be undertaken concurrently with earlier stages of the procurement process.

A.7.1. | Data cleansing

Data in an established database is rarely 100% consistent and accurate. Anomalies and corruptions of data can occur for a variety of reasons and whilst these may not cause problems in their home system, problems can arise when the data is migrated. Data cleansing is a structured approach to examining and analysing an existing database with a view to identifying and correcting anomalies prior to migration. This is an essential process, particularly when migrating data across organisations or across networks and a strategy and methodology should be defined to ensure that it is effectively managed. Data cleansing should be carried out in a quality-controlled manner with fully documented procedures in place. Critical areas include patients with antibodies (ensure all codes match across data to be migrated) and patients with special requirements.

A.7.2. | Duplicate records

Searches for duplicate records should be regularly carried out on the legacy system and duplicates resolved prior to data migration.

A.7.3. | Implementation strategy

An implementation strategy is required to define how the new system will be brought into routine operation. The implementation of a new LIMS must be managed in a manner that will meet the regulatory requirements. The strategy to be adopted will depend on several factors including:

- The degree and complexity of data migration.
- Whether multiple legacy systems are being combined.
- Staff resources, space and infrastructure availability.
- Available operational environments.
- Consideration must be given to the impact of the implementation on the routine operation of the laboratory. There will necessarily be operational downtime associated with data migration, system configuration and physical connectivity. This will necessitate the transfusion laboratory implementing business continuity plans and engagement with clinical and administrative services to manage interruptions of service and the recovery phase.

Whichever implementation strategy is decided upon appropriate risk management plans must be developed. Possible strategies include that are described as follows.

A.7.4. | Parallel running

In parallel running, both new and old systems are run together with the routine workload being put through both systems. This involves migrating data from the old to the new system, and performing each action in the appropriate areas on both systems. Parallel running allows staff to become fully familiar with full load running of the new system prior to 'go live' and can provide a high level of assurance that the new system is performing as expected post implementation. However, such an approach will be resource-hungry in terms of staff input. A variation to this approach may involve running only a proportion of the workload in parallel.

The parallel running approach may be facilitated or limited by instrument interfaces, blood management systems, and power and IT points availability. It is not always possible to send instrument data to two interfaces or systems simultaneously. Switching an instrument interface between two LIMS systems or environments needs careful control to ensure no changes are made that will require validation. The functionality of the instrument interfaces needs to be understood and carefully managed.

A.7.5. | Phased approach

This will involve staff using both systems whilst transferring specific functions or sites from the existing to the new system over a period of time. The decision will involve identifying when operational areas are to be transferred. This method presents some technical and logistical difficulties such as data transfer and managing the boundaries between functions running on each system. Each step of a phased approach will need its own risk assessment to address these challenges.

A.7.6. | Big bang

This approach will ensure total transfer to the new system on a defined date. The organisation must ensure that procedures have been written and validated, staff have undergone thorough training, in

every area, prior to 'go live' and that trial transfer has been run on test environments. The implementation plan should include a 'fall-back' plan in the event of a major problem preventing completion of the implementation within the determined time frame and should identify the 'point of no return' where outstanding issues must be resolved without fallback.

A.7.7. | Validation strategy

The validation strategy should comply with regulatory requirements and associated guidance, taking into account the principles of GAMP5[35] as set out in the BSH Guidelines for Validation & Qualification including Change Control, for Hospital Transfusion Laboratories and the International Society of Blood Transfusion (ISBT) Guidelines for the Validation of Automated Systems in Blood Establishments.[37]

A.7.8. | Application configuration

LIMS solutions take advantage of techniques in software design that are inherently configurable and adaptable. In order to configure such systems to operate to the requirements of a particular organisation a set of logic rules and configuration settings has to be established and applied.

These logic rules and configuration settings ensure that, under a defined set of circumstances, the system will consistently take the actions specified. This is a powerful tool to ensure reproducibility of actions and it is essential that they are established, managed and monitored closely. Staff who are designated to configure the system, often referred to as 'super-users', should be trained and competent prior to beginning the configuration of the system. The involvement of an individual who is a transfusion expert is imperative. They should have overall responsibility for determining what the rules and settings should be and the appropriate validation steps in agreement with the Hospital Transfusion team, in order to ensure results and actions support good transfusion practice. This individual may be supported by other super-users.

The computer follows the rules specified and is a valuable asset in terms of security. Care must be taken to set up and test rules to ensure they are comprehensive and patient safety is not endangered through an incomplete rule set. The risks/benefits should be assessed before each rule is implemented. Rules may require an 'over-ride' function to deal with legitimate exceptions. If incorporated, this must be available only at defined security levels and if used the system should require and document a reason.

Examples of scenarios that may be controlled through configuration include:

- Associating user and supervisor alert flags with a specific result profile.
- Enabling the issuing of blood & components by authorised staff.
- Prompting users to perform specific follow-up actions or reflex testing (e.g. request additional samples, issue a specific blood product).
- Setting action reminders or flags into the patient record.
- Determining whether a patient is suitable for electronic issue of blood.
- Helping to prevent issues of incompatible units (e.g. patients with antibodies).
- Helping to ensure appropriate blood products are issued to a patient (e.g., depending upon their gender/age details prompting selection of appropriate units such as K-, CMV negative etc.).
- Ensuring appropriate comments are added to reports.

A selection of logic rules, based on BSH guidelines and good practice is supplied in Appendix II.

A.7.9. | Data migration preparation

Achieving an accurate data migration will be an iterative process which may be time-consuming and will require close co-operation between laboratory staff, IT specialists and the suppliers of both the legacy and the new system.

The iterative loop has several distinct steps which include:

- Identify the data to be migrated giving clear, documented rationale for the decisions made.
- Document the structure and meanings of all fields and values to be migrated and build necessary translation tables.[30]
- Extract the required data into a separate file/table/database.
- Transformation: manipulate and format the extracted data for upload to the new system ensuring the transformations accurately map data content and meaning.
- Upload data into new system.
- Create an audit log detailing all steps in the process (who, what, when and why).
- Define the number of records for verification, and the process for selecting a representative sample.
- Perform data verification.
- Identify migration failures and assess impact.
- Revise migration tools as required.

Validation of data migration is a critical process and requires careful planning. The scope of the validation will need to include external systems that interact with the LIMS data. Defining the sampling plans of migrated data can be undertaken using a risk based approach.

A.7.10. | Training strategy and plan

The training requirements for implementing a new LIMS should not be underestimated and it is important that a critical mass of staff is fully trained prior to implementation. The contract with the supplier should identify where the responsibility for training lies and how this will be delivered (e.g. direct training, train the trainer). The training requirements within the organisation should be evaluated to identify:

- Who to train: for example Blood Sciences/IT/Clinical staff.
- What to include: for example Discrete areas/whole system.

Before training can commence SOPs/training manuals should be completed, as a minimum in draft format.

All staff involved in the development, running and maintaining of the LIMS will require training and competence assessment which is relevant to the role and these will determine the level of security access permitted. Assessments should be completed and signed off prior to granting access to the live system.

The training and competency assessment programme should be reviewed on a regular basis and following any software upgrades.

A.8. | Service level agreements

In addition to maintenance contracts held directly with system suppliers, there must be a specific service level agreement (SLA) between the transfusion department and any other IT service provider (internal or external) whose activities could impact the LIMS or associated systems. Such SLAs must clearly define the service provision, controls and authorisations, and performance expectations for any IT support arrangements including system data backups.

A.9. | User configuration verification

Prior to validation the users should perform informal testing to ensure the system has been configured appropriately to support operational requirements. This is an informal testing process that:

- Familiarises staff with the system.
- Allows the development of SOPs which are required for validation.
- Ensures that the system configuration meets the users' needs.
- Reduces the time required for formal validation.
- Any configuration changes identified should be implemented prior to formal validation. The system must be placed under change control on commencement of formal validation to ensure that any future changes are appropriately controlled.

A.10. | Validation

The Validation strategy will have been determined during implementation preparation (see Section A.7). Validation is the formal testing and ensures that the system meets the operational requirements of the URS. Both supplier and user will have responsibilities for validation and these should be in line with the BSH Validation and Qualification guidelines.

The content and scope of validation is well documented in the ISBT Guidelines for the Validation of Automated Systems in Blood Establishments[37] which has application for hospital transfusion laboratories and the Guidelines for Validation and Qualification, including Change Control, for Hospital Transfusion Laboratories.

Recommendation

- A formal process of change control is essential when implementing a new IT system. All of the steps identified in section I are necessary and must be adequately resourced and change controlled (2B).

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ORIGINAL ARTICLE

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The importance of need-altruism and kin-altruism to blood donor behaviour for black and white people

Eamonn Ferguson[1,2] | Erin Dawe-Lane[1] | Oluwafemi Ajayi[3] | Bodunrin Osikomaiya[4] | Richard Mills[1,2] | Abiola Okubanjo[5]

[1]School of Psychology, University of Nottingham, Nottinghamshire, UK

[2]National Institute for Health and Care Research Blood and Transplant Research Unit in Donor Health and Behaviour, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK

[3]Blood Sciences, Dorset County Hospital NHS Foundation Trust, Dorchester, UK

[4]Lagos State Blood Transfusion Service, Gbagada Centre, General Hospital, Lagos, Nigeria

[5]Action on Blood, London, UK

Correspondence
Eamonn Ferguson, School of Psychology, University of Nottingham, University Park Campus, Nottingham, Nottinghamshire, UK.
Email: eamonn.ferguson@nottingham.ac.uk

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Abstract

Background: Need-altruism (a preference to help people in need) and kin-altruism (a preference to help kin over non-kin) underlie two hypotheses for voluntary blood donation: (i) Need-altruism underlies motivations for volunteer blood donation and (ii) Black people express a stronger preference for kin-altruism, which is a potential barrier to donation. This paper tests these hypotheses and explores how need- and kin-altruism are associated with wider altruistic motivations, barriers, and strategies to encourage donation.

Methods: We assessed need- and kin-altruism, other mechanisms-of-altruism (e.g., reluctant-altruism), barriers, strategies to encourage donation, donor status, and willingness-to-donate across four groups based on ethnicity (Black; White), nationality (British; Nigerian), and country-of-residence: (i) Black-British people ($n = 395$), and Black-Nigerian people (ii) in the UK ($n = 97$) or (iii) across the rest of the world ($n = 101$), and (v) White-British people in the UK ($n = 452$). We also sampled a Black-Nigerian Expert group ($n = 60$).

Results: Need-altruism was higher in donors and associated with willingness-to-donate in non-donors. Levels of kin-altruism did not differ between Black and White people, but need-altruism was lower in Black-British people. Kin-altruism was associated with a preference for incentives, and need-altruism with a preference for recognition (e.g., a thank you) as well as an increased willingness-to-donate for Black non-donors. Need-altruism underlies a blood-donor-cooperative-phenotype.

Conclusion: Need-altruism is central to blood donation, in particular recruitment. Lower need-altruism may be a specific barrier for Black-British people. Kin-altruism is important for Black non-donors. The blood donor cooperative phenotype deserves further consideration. Implications for blood services are discussed.

KEYWORDS
altruim, barriers, blood donor behaviour, ethnicity, incentives, kin-altruism, motivations, need-altruism, rewards

1 | INTRODUCTION

There is a large literature exploring the mechanisms-of-altruism (MOA) that underly voluntary non-remunerated blood donation (VNRDB).[1–3] Key among these are: (i) reluctant altruism, (ii) impure-altruism, (iii) warm-glow and (iv) reputation building.[1–6] Reluctant altruism refers to a preference to help when others cannot be trusted to help, especially where the number of people helping is low.[1,2,4,6,7] This is critical for first-time donors.[5,6] Warm glow is a preference to help based solely on the positive feelings experienced from helping.[8] Impure-altruism is a preference to help, not only to experience warm-glow but also to make a difference by helping others.[8] Warm-glow and impure altruism are important for donor retention.[1–3,5] Finally, by helping, people can signal a good reputation to others, which is critical to maintaining altruism, as those with good reputations are more likely to be helped by others.[9] As a high-cost behaviour, blood donation offers an ideal reputational signal.[1,6,10] While these mechanisms are critical, two general mechanisms underlying altruism are missing from the analysis of altruism and blood donation: *Kin-altruism* and *need-altruism*.[11] This paper explores people's preferences to help in general based on either kin- or need-altruism, how these predict willingness-to-donate, and their associations with other MOA specific to blood donation.

Kin-altruism is a preference to help family over strangers, and *need-altruism* is a preference to help those in need, irrespective of the relationship to the helper.[11] Both are central mechanisms for sustained altruism and cooperation.[11] However, need-altruism, rather than kin-altruism, *s*hould be the central motivator for VNRDB which encompasses helping *strangers in need*, and not family members. This paper tests the hypothesis (H1) that need-altruism is a central motivator for VNRBD. Furthermore, it has been reported that Black people demonstrate a stronger preference for *kin-altruism* than White people, with the assumption that this preference for *kin-altruism* acts as a potential barrier to VNRBD.[12–19] We test the hypothesis that the expression of kin-altruism is higher in Black people compared to White people (H2). We do this by exploring preferences for kin- and need-altruism across people from different ethnicities and how kin- and need-altruism are related to (i) blood donor status (current, lapsed, non-donor) and (ii) willingness-to-donate.

1.1 | Kin-altruism, need-altruism and voluntary blood donation

It has been argued that a stronger preference for kin-altruism among Black people, as well as people from ethnic minorities, is one reason for reduced levels of voluntary blood donation observed in these communities.[12–19] Indeed, Tran et al.[16] in their discussion of Black people in Montreal, state: 'The gift of blood … is normally destined to a stranger. But … the preferred figure of the receiver might not be that of a complete stranger but that of a community member" [p. 522], with community members often referring to close family.[16] Three potential mechanisms could support the stronger preference for kin-altruism in Black people: (i) the cultural symbolism of blood,[15,16] (ii) discrimination,[13] and (iii) Hamilton's rule.[12,16,20,21]

In terms of cultural symbolism, blood is seen as the main conduit for the transmission of family ties and kinship.[12,13,16] Perceived discrimination leads to a focus on family and community, as does reduced trust in healthcare and the government[7] and supports a stronger preference for kin.[16,17,19] Hamilton's rule $r > \frac{c}{b}$ where r = the genetic relatedness between individuals [ranging from 0 for no degree of relatedness, (i.e., stranger) to 1 (i.e., identical twins)], and $\frac{c}{b}$ is the cost–benefit ratio (where c = the cost to the helper and b = the benefit to the recipient), indicates that to choose to help someone, r must exceed the cost–benefit ratio $\frac{c}{b}$.[20,21] One implication is that people are willing to pay a higher cost, relative to benefits, to help a relative (r is higher) than a stranger (r is lower). Blood donation is seen as high cost,[10] and Tran et al.[14] in their analysis of Black people in Montreal, state that "…giving blood was almost described as a sacrifice that would be worth it if a loved one's life was in danger." (p. 520[14]). Indeed, Black people report that donating blood carries costs in terms of lost vitality[12,22–24] or personal identity.[14] This increased cost means r needs to be higher for members of Black communities to donate, manifesting in a preference for kin over strangers.

The hypothesis that people from Black communities have a stronger preference for kin-altruism is based on qualitative evidence,[12–19] that crucially has not considered the role of need-altruism across different communities or wider motivations and barriers to donation. We, therefore, test the hypothesis (H2) that kin-altruism is endorsed more by Black compared to White people.

1.2 | Blood donor cooperative phenotype: Kin-altruism, need-altruism, motivations/barriers and recruitment strategies

High levels of cooperation are essential for the functioning of human societies, from dyadic relationships and small group settings (e.g., helping family, friends, and strangers) to supporting wider collective social goals (e.g., increasing vaccinations[25]). To be effective across such a wide range of behaviours, the different assessments for cooperative preferences based on trust, generosity, and reputation should all be positively associated with each other forming a domain-general cooperative-phenotype.[26] Indeed, this is the case.[26] Here we explore how domain-general preference to help based on *kin-* and *need-altruism*[11] are associated with the key MOA for blood donation, as well as barriers to donation, and preferences for recruitment strategies. With this in mind (i) reluctant altruism, (ii) impure-altruism (iii) warm-glow, and (iv) reputation building[1–5] should all be positively associated with need-altruism, but not kin-altruism.[2]

These altruistic motivations have their counterpart in barriers to donation.[7,22] In terms of barriers, we focus on common barriers to donation based on health (e.g., feeling faint), fear (e.g., fear of needles), trust in medical professionals, and physical effects (loss of vitality) that have been identified as important within Black communities.[13,23,24] As distrust in the medical profession represents

the negative influence of external agencies, over which the person has little control, distrust should lead to a focus on in-group processes such as protecting family.[27–29] As such, kin-altruism should be associated with greater distrust in the medical profession.

In terms of strategies to encourage blood donation, a wide range of have been documented.[22,28] Conceptually, distinctions can be drawn between incentives (i.e., strategies offered before donating to motivate action: e.g., payment), and rewards/recognitions offered after donating to reinforce warm-glow (e.g., thank you texts,[30]). Kin-altruism is concerned with directing resources to maximise benefits to family (and friends) rather than society generally.[31,32] Thus, kin-altruism should be associated with endorsing financial incentives and gifts as effective ways to encourage blood donation, as these could potentially be distributed to family members or converted to money. However, the intrinsic nature of need-altruism (e.g., a primary focus on the well-being of the recipient, regardless of their relationship to the helper), should be associated with viewing 'recognitions and rewards' as a good recruitment strategy and incentives less positively.[33] Thus, we test the hypothesis (H3) that high levels of kin-altruism are positively associated with viewing incentives as a good recruitment strategy and higher levels of need-altruism associated with viewing rewards and recognitions as a good strategy.

1.3 | Cultural diversity and blood collection systems

To better understand associations between ethnicity and donor behaviour, we need to not only consider the person's ethnicity, but also their nationality, and country of residence.[34] Nationality provides a potential marker of the values, beliefs and experiences a person holds with respect to their country of birth or adopted national status. Country of residence indicates the current value system that the person is living in. These parameters are important when considering the role of ethnicity and how blood is collected. For example, the UK, like many countries in the Global North, operates a VNRBD system, however, in many countries in the Global South, family replacement and/or paid donations are the main method of collecting blood.[35] With increased population movement, there will be people who have grown up in a country with a family-replacement/paid system and now live in a country like the UK with a VNRBD system. Assessing ethnicity solely does not allow for this degree of specificity. Thus, we explore ethnicity (Black; White), nationality (British; Nigerian), and country-of-residence (Nigeria, rest-of-the world, UK). We focus on people from Nigeria as a country where family-replacement/paid system is the major method of collection. As well as the voice of lay people, we also explore the perceptions of a Nigerian expert group, made up of Nigerian people living in Nigeria, who had experience and expertise in haematology, healthcare, and volunteer blood donation in Nigeria. Understanding the views and opinions of these Nigerian experts is critical as the opinions of experts are often sought to drive policy (e.g., advisory groups) and can diverge from the opinions of the public.[36] This is important as the WHO has recommended that all countries aim to adopt VRNBD. Thus, information on how experts and laypeople differ allows initial insights into ways to bridge gaps and move policy forward.[37,38]

1.4 | Study aims and rationale

We add to the literature by presenting the first quantitative comparison of preferences for kin- and need-altruism across different ethnicities, blood donor status and willingness-to-donate. We test three main hypotheses: (i) Need-altruism is positively associated with being a blood donor and the willingness-to-donate (H1), (ii) A preference for kin-altruism is greater in Black people compare to White people (H2), and (iii) kin-altruism predicts incentives and need-altruism rewards and recognitions (H3) We also explore the presence of 'blood donor phenotype' by exploring the associations between domain-general kin- and need-altruism and the main MOA for blood donation.

2 | METHODS

2.1 | Samples

The study was conducted between 14th and 28th February 2022 with the general population samples through Prolific (https://www.prolific.co/about/) and the experts sampled through professional societies and volunteer donor organisations in Nigeria. All participants completed an online, unlinked, anonymous survey hosted on Qualtrics (https://www.qualtrics.com/uk/). Samples were defined in terms of their ethnicity (Black; White), nationality (British; Nigerian), and country-of-residence (Supplementary File S1). There were four samples from Black communities. Three are lay Black samples: (i) Black-Nigerian people living in the UK (Black-Nigerian-UK: $n = 97$), (ii) Black-Nigerian people living across the rest of the world (Black-Nigerian-World: $n = 101$), and (iii) Black-British people living in the UK (Black-British-UK: $n = 395$). One is a Black-Nigerian expert group (Nigerian-Expert: $n = 60$). Finally, there is a single lay sample of White-British people living in the UK (White-British-UK: $n = 452$).

The following variables are assessed (Supplementary File S2 for details of all questions).

Demographics: Age (continuous measure [years]), gender (men = 0, women = 1), healthcare worker status (no = 0, yes [current/previous] = 1).

Donor status: People were asked if they had ever donated blood, and if so, how long ago.[7] Non-donors were coded as those who had never donated (=0); lapsed donors were coded as those who had donated 2+ years ago (=1); current donors were coded as those who had donated ≤2 years-ago (=2).

Kin/Need-Based Altruism: Questions were developed based on the theoretical literature to assess kin- (items reflect a direct comparison between a preference to help family or a stranger) and need-altruism (items reflect helping based on need regardless of relation to the person in need).[11] People indicated the extent to which each statement applied to them: 1 = not at all, 7 = completely.

Blood donation focused altruism: These questions were derived from an existing mechanism-of-altruism (MOA) scale to cover, warm-glow, reputation building, and reluctant altruism.[7] People indicated the extent to which they agreed or disagreed with each statement: 1 = strongly disagree, 2 = disagree, 3 = somewhat disagree, 4 = neither agree or disagree, 5 = somewhat agree, 6 = agree, 7 = strongly agree.

Barriers: A wide range of barriers to donation were derived from the existing literature[7,22] and selected based on discussions with colleagues who have knowledge of encouraging blood donation for Black communities in the UK and Nigeria. These focus on common barriers to donation based on health (e.g., "I worry that I might faint"), fear (e.g., "I do not like needles"), trust in medical professionals (e.g., "I do not trust medical professionals or systems"), and physical effects (e.g., "If I donate blood, I will become physically weak").[22] These are responded to using the following scale (1 = strongly disagree, 2 = disagree, 3 = somewhat disagree, 4 = neither agree nor disagree, 5 = somewhat agree, 6 = agree, 7 = strongly agree).

Strategies: A wide range of strategies to encourage blood donation were derived from the existing literature,[39] and we selected strategies based on the distinction between incentives (e.g., "Being paid to donate blood"), and rewards/recognitions (e.g., "Being sent a text/email to say thank you after donating blood")[30] through discussion with colleagues who have knowledge of encouraging blood donation for Black communities in the UK and Nigeria. People indicated the extent to which they perceive each strategy as encouraging: 1 = not at all, 7 = very encouraging.

Willingness-to-donate: A dichotomous index is used as it has been shown to be a reliable predictor of future donation behaviour[40,41]: Yes = 1, No = 0.

2.2 | Ethical approvals

Ethical approvals were received from the University of Nottingham, School of Psychology (F1326) and the National Health Research Ethics Committee of Nigeria (NHREC/01/01/2007–04/02/2022). All participants provided full informed consent to participate in the studies reported.

2.3 | Pre-registration

The study was pre-registered (https://osf.io/72dj9).

2.4 | Data analysis

Continuous measures for all the predictor variables were created by summing the items that make up each scale. Continuous data were analysed in SPSS-28, Stata-18, and M*Plus* 8.4, with all *p*-values two-tailed. To explore the psychometric structure of kin- and need-altruism, we applied principal axis (PAF) factor analysis with varimax rotation. Path models in M*Plus* 8.7 were used to test general support for Hypotheses 1–3 directly. Seemingly-Unrelated-Regression (SUR) models were used to explore Hypotheses 1–3 in more detail. SUR models were used as the continuous outcome measures are correlated with each other, and the SUR models account for this overlap in the residual error across the outcome measures.

Power analysis: Power calculations were conducted to achieve 0.80 power with an α of 0.05 (two-tailed). As there are no existing quantitative data on kin- and need-altruism by ethnicity, we based calculations on variation in trust in individuals by ethnicity reported by Ferguson et al.[7] Trust in individuals was seen as an appropriate index as it underlies altruism and cooperation generally.[42] The effect size for the comparison across the four ethnic groups (Asian, Black, Mixed, White) reported in Ferguson et al.[13] equates to a Cohen's d of 0.4871, indicating that for a comparison across the five groups, 66 people are required per group. Based on Ferguson et al.,[7] the effect size comparing a White and overall Ethnic minority sample was a Cohen's d of 0.363, indicating that 120 people per group are required for these comparisons reported in studies 1 and 2. For EFA sample size of 300 is needed, and the participants-to-items ratio to be ≥10:1.[43,44] These conditions were met.

3 | RESULTS

3.1 | Samples

Sample characteristics (Table 1).

3.2 | The latent structure of kin- and need-altruism

PAF analyses (Table 2 Panel A: Supplementary File S3 for details) showed that kin- and need-altruism formed two distinct factors. The three items representing kin-altruism and the three items representing need-altruism were summed to create two scales.

3.3 | Mechanisms of altruism, barriers, and strategies

The results of the PAF analyses of the blood-specific measures of altruism (mechanisms-of-altruism: MOA), barriers and strategies are summarised in Table 3 (Supplementary File S3 for full analytic details). Corresponding to previously reported distinctions,[5,6] the MOA items formed three factors: (i) impure-altruism, (ii) reputation building, and (iii) reluctant-altruism. There were three barrier factors: (i) negative health effects, (ii) lack of trust in medical professionals and healthcare systems, and (iii) fear of the donation process, corresponding to extant literature.[12–18,22] Mapping onto distinctions drawn between incentives (i.e., strategies offered before donating to motivate action), and rewards or recognitions (offered after donating to reinforce feelings of warm-glow), two strategy factors emerged: (i) 'incentives', and

TABLE 1 Demographic details.

	Black-British-UK		Black-Nigerian-UK		Black-Nigerian-World		Black-Nigerian-Experts		White-British-UK	
	N	Mean (SD)	*N*	Mean (SD)	*N*	Mean (SD)	*N*	Mean (SD)	*N*	Mean (SD)
Age	383	32.76 (9.95)	96	32.86 (7.91)	99	28.57 (8.10)	50	34.86 (9.10)	450	36.73 (10.62)
	N	%	*N*	%	*N*	%	*N*	%		
Gender										
Male	129	32.8%	36	37.5%	40	40.4%	37	61.7%	174	38.8%
Female	264	67.2%	60	62.5%	59	59.6%	23	38.3%	274	61.2%
Blood donor status										
Non-donor	277	71.4%	64	66.0%	51	53.7%	27	49.1%	284	62.8%
Lapsed	69	17.8%	26	26.8%	27	28.4%	4	7.3%	118	26.1%
Current	42	10.8%	7	7.2%	17	17.9%	24	43.6%	50	11.1%
Healthcare worker										
Yes	110	28.4%	55	58.5%	42	43.8%	36	62.1%	80	17.8%
No	277	71.6%	39	41.5%	54	56.3%	22	37.9%	370	82.2%

TABLE 2 Exploratory factor analysis of kin- and need-altruism.

Item	Need	Kin	Factor	Donor cooperative phenotype	Barriers	Kin-altruism incentives
If a stranger was in need, I would help them	**0.546**	−0.046	Impure altruism	**0.729**	**−0.385**	−0.060
I would help the person who needs help the most whether that be my family, a friend, or a stranger	**0.715**	−0.115	Rewards, recognitions & benefits	**0.606**	−0.135	0.106
I would try and help family, friends, and strangers equally	**0.774**	−0.241	Reputation building	**0.554**	0.047	0.108
If I had to choose, I would help my family and friends rather than people I do not know	−0.155	**0.743**	Need-altruism	**0.450**	−0.172	**−0.485**
I would rather help a family member I do not like than a stranger	−0.133	**0.567**	Reluctant-altruism	**0.398**	−0.003	−0.058
If it was between helping my family or a friend, I would help my family	−0.056	**0.617**	Fear of negative health effects	−0.018	**0.870**	0.076
			Lack of trust in medical professionals and systems	−0.170	**0.549**	0.096
			Process	−0.012	**0.527**	0.068
			Kin-altruism	−0.005	0.046	**0.519**
			Incentives	0.261	0.101	**0.385**
Eigenvalue	2.410	1.411		2.660	1.751	1.232
% Total variance	40.162	23.513		26.599	15.512	12.323
Cronbach's alpha	0.725	0.679		0.669	0.681	.302[a]
Mean (SD)	15.20 (3.70)	14.87 (3.65)		95.86 (15.53)	28.05 (10.17)	
n	1077			1018		

Note: Extraction was with Principal Axis Factoring (PAF) with Varimax Rotation. Number of factors to extract is determined by both Scree tests and Parallel Analyses. Items/scales with a loading greater the 0.30 were classed as being a meaningful marker of a factor (in bold).[43]

[a]Mean inter-item correlation as the factor only has two items.

TABLE 3 Factor analyses of indices of motivators (altruism), barriers and strategies to encourage donors.

	Panel A				
	General altruism kin vs. need		Mechanism of Altruism for blood donation		
	Kin-based	Need-based	Impure altruism	Reputation building	Reluctant altruism
	3 items on a preference to help kin over strangers. (e.g., 'I would rather help a family member I do not like than a stranger')	3 items on helping based on need. (e.g., 'If a stranger was in need, I would help them')	8 items on donating blood to help others and feel 'warm-glow'. (e.g., 'I would be doing something to help others')	2 items on donating blood to boost reputation. (e.g., 'I would want to show people that I am a good, kind person')	2 items on donating blood because others do not. (e.g., 'I cannot trust others to donate blood, so I must')
Mean (SD) range, [mid-point]	15.20 (3.70) 3–21, [12]	14.86 (3.65) 3–21, [12]	45.48 (7.22) 8–56, [32]	8.23 (3.03) 2–14, [8]	6.80 (2.70), 2 to 14, [8]
Interpretation	Higher scores indicate strong Kin-Altruism	Higher scores indicate strong Need-Altruism	Scores over 32 indicate Impure-altruism motivates blood donation	Scores over 8 indicates reputation building motivates blood donation	Scores over 8 indicates reluctant altruism motivates blood donation
Cronbach's α	0.683	0.728	0.893	0.795	0.694
	Panel B				
	Strategies		**Barriers to voluntary blood donation**		
	Rewards, recognitions & benefits	**Incentives**	**Fear of negative health effects**	**Fear of donation process**	**Lack of trust in medical professionals and systems**
	4 items on the impacts of blood donation for donors and others and tokens of appreciation (e.g., 'Being sent a text/email to say thank you after donating blood')	3 items on tangible compensation for donating. e.g., 'Being given a small gift when you donate blood', 'being paid)	4 items on fears of the health impacts of donation. (e.g., 'If I donate blood, I will become physically weak')	3 items on fears of the blood donation process (e.g., 'I worry that I might faint')	3 items on lack of trust in medical professionals and systems. (e.g., 'If I donate blood, my blood will be sold for profit')
Mean (SD) range [mid-point]	20.62 (5.51) 4–28, [16]	13.63 (5.83), 3–21, [12]	10.17 (4.53), 4–28, [16]	9.25 (4.66), 3–21 [12]	8.63 (3.81), 3–21 [12]
Interpretation	Higher scores indicate greater perceived effectiveness	Higher scores indicate greater perceived effectiveness	Scores over 16 indicate that fear of negative health effects	Scores over 12 indicate fears of the donation process	Scores over 12 indicate a lack of trust in medical professionals and systems
Cronbach's α	0.845	0.839	0.768	0.719	0.718

(ii) 'rewards, recognitions & benefits'.[30] The items making up each factor were summed to create continuous scales.

Figure 1 (Panel A) details the correlations between the main study variables for the whole sample. Need- and kin-altruism are negatively associated with each other, while the three MOA factors, the barriers and strategies are positively associated with one-another (Supplementary Files S4 for means and SDs by ethnicity; Supplementary File S5 for associations by donor status).

3.4 | Hypotheses 1 to 3: Path models

The path model in Figure 2 (Panel A) is for the full sample, predicting if people have ever donated blood, and Figure 2 (Panel B) shows the models predicting willingness-to-donate for non-donors (upper coefficients, not in parentheses) and those who have ever donated (current and lapsed: lower coefficients, in parentheses). These models test hypotheses 1–3. In support of H1, Figure 2 (Panel A) shows that need-altruism, not kin-altruism, predicts being a previous donor, and Figure 2 (Panel B) shows that need-altruism, not kin-altruism, predicts willingness-to-donate in non-donorsi. There is no support for H2, as ethnicity does not predict a preference for either need- or kin-altruism. There is some support for H3, as kin-altruism predicts viewing, not only incentives as a good strategy but also, 'rewards and recognitions,' whereas need-altruism predicts viewing 'rewards and recognitions' as a good strategy, but not incentives (Panel A). Figure 2 (Panel B) shows that viewing incentives and 'rewards and recognitions' as a good strategy is

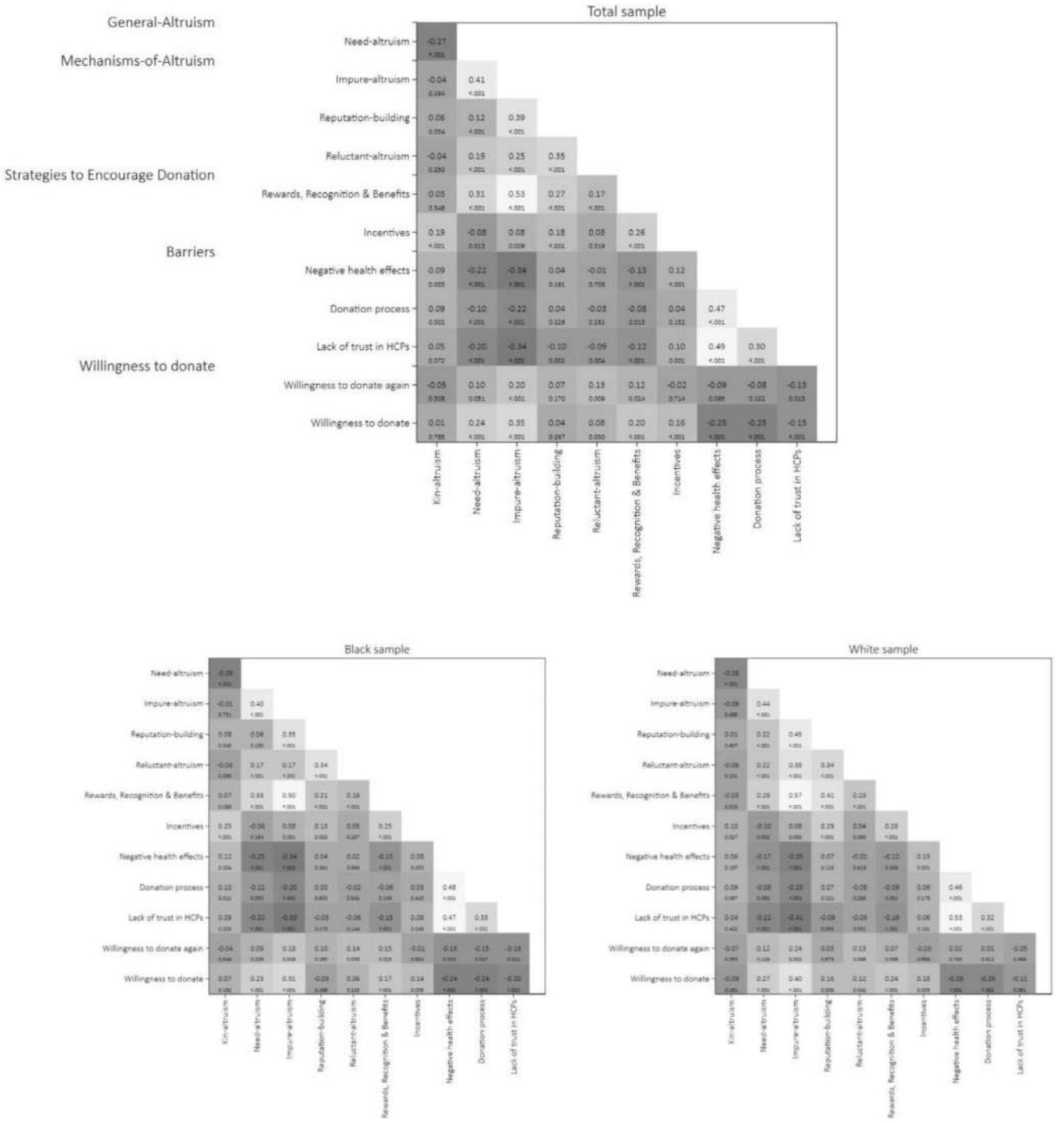

FIGURE 1 Pearson correlation coefficients for main study variables for the total sample and Black and White People separately. Exact p-values are shown. Panel A: Total sample; Panel B: Black (left) and White (right) samples.

positively associated with willingness-to-donate in non-donors only. Whereas seeing 'rewards and recognitions' as a good strategy is positively associated with willingness-to-donate, for those who have ever donated, but incentives are negatively associated with willingness-to-donat (Panel A). With these broad conclusions in place, we will now explore the influence of ethnicity and donor status in more detail.

3.5 | Altruism, barriers, and strategies: effects of ethnicity and donor status

Table 4 provides a summary of the SUR models exploring the role of ethnicity and donor status with respect to altruism, barriers, and strategies (Supplementary File 6 provide the detailed model information, including exact p-values and 95% CIs).

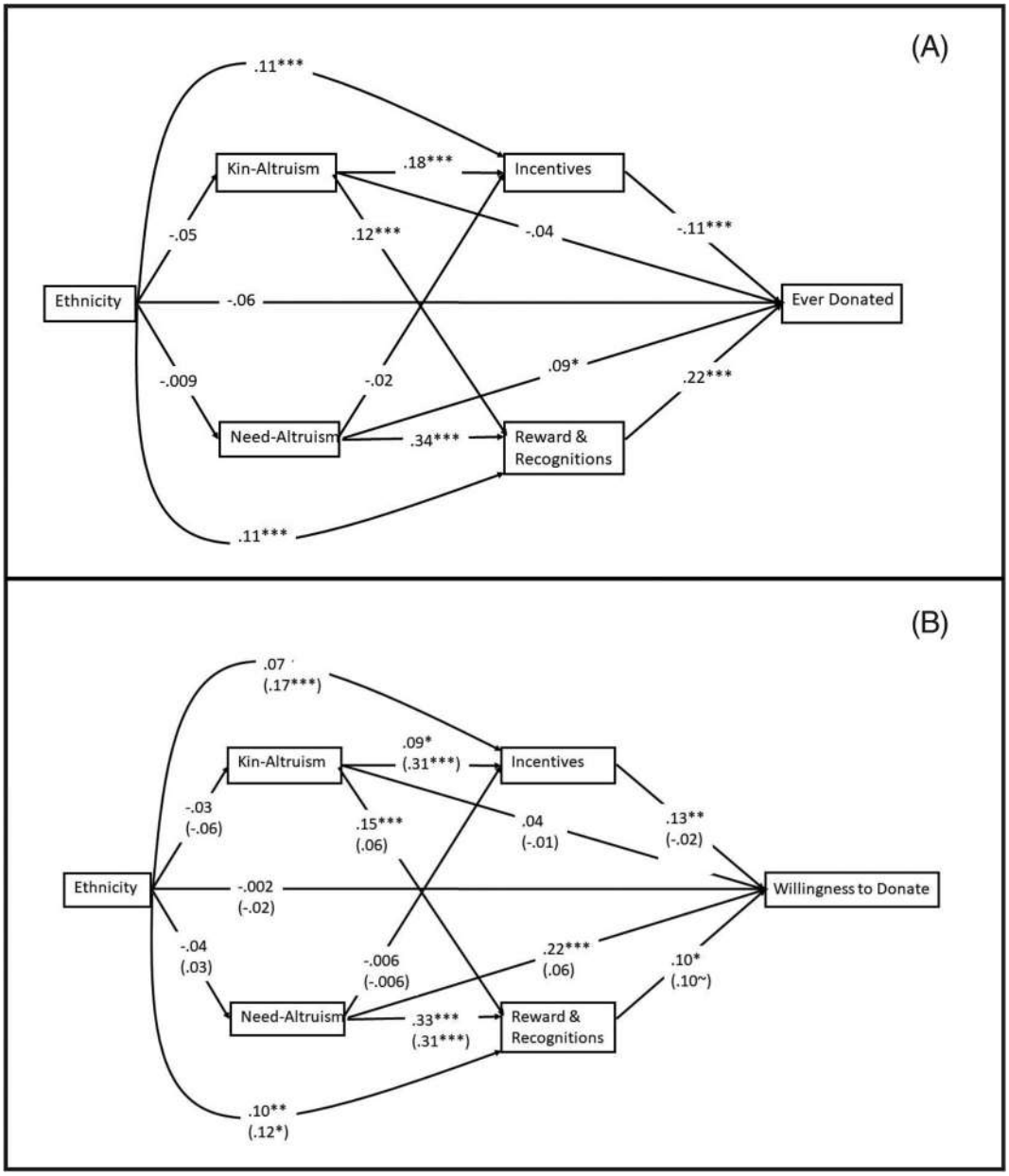

FIGURE 2 Saturated Path Models. Panel A (whole sample, $n = 1053$) predicts having ever donated blood, estimated using diagonally weighted least with mean and variance adjustment to account for the mix of continuous and dichotomous outcomes. Panel B predicts willingness-to-donate for the first time in non-donors ($n = 658$: coefficients on top not in parentheses) and to donate again for previous donors ($n = 365$: coefficient below in parentheses), estimated using maximum likelihood as all outcomes are continuous. Ethnicity (0 = White, 1 = Black), Ever Donated (0 = no, 1 = yes). All coefficients are standardised. $\sim p = 0.06$, * p . > 0.05, ** $p < 0.01$, *** $p < 0.001$.

With respect to kin- and need-altruism, the results in Table 4 show that kin-altruism does not vary across four lay groups (Black and White), however, the Black-Nigerian-Expert group report lower kin-altruism than the White-British-UK sample. Interestingly need-altruism is less likely to be endorsed by Black-British-UK residents compared to the White-British-UK residents. In terms of MOA, we observe that in comparison to the White-British-UK residents (i) the Black-Nigerian-Experts were more likely to endorse 'impure-altruism', and (ii) people from Black communities (except Black-Nigerian-Experts) are less likely to be motivated by 'reputation building' and 'reluctant altruism'.

For strategies to encourage donation (i) all Nigerian people (lay and expert) saw 'rewards, recognitions & benefits' as encouraging strategies, (ii) Black-British-UK and Black-Nigerian-World residents see 'incentives' as an encouraging strategy, while (iii) the 'Black-Nigerian-Experts' felt incentives were less encouraging.

Finally, in terms of barriers, compared to the White-British-UK people, (i) people from all Black communities were more likely to report a 'lack of trust in medical professionals and systems' as a barrier compared, and (ii) Black-UK-residents (Black-British-UK and Nigerian-Black-UK) reported greater 'fear of negative health effects'.

TABLE 4 Summary of SUR models for altruism, strategies and barriers as a function of agen gender, ethnicity, healthcare worker and donor status.

		General altruism kin vs. need		Mechanism of altruism for blood donation		
		Coeff.	Coeff.	Coeff.	Coeff.	Coeff.
		Kin-based	Need-based	Impure altruism	Reputation building	Reluctant altruism
Ethnicity	Black-British-UK	0.0655	**−0.6038***	−0.7328	**−0.5487***	**−0.5412****
	Black-Nigerian-UK	−0.7723	0.5889	0.8454	**−1.3910****	**−1.4033****
	Black Nigerian-World	−0.6486	0.7259	0.2087	**−1.4620****	**−1.3170****
	Black-Nigerian-Expert	**−4.2853****	**1.2341***	**3.7613****	−0.6364	−0.4438
Donor status	Lapsed donor	−0.1963	**0.7969****	**3.2714****	**0.4884***	**0.8674****
	Current donor	−0.4029	**1.3148****	**4.5358****	**1.2725****	**1.0476****
Age	Years	**−0.0293***	0.0180	0.0182	−0.0098	−0.0047
Gender	Female	**−0.9067****	**1.7033****	**2.7135****	0.3122	0.1984
HealthCare worker	Yes	−0.2334	0.2654	**1.1705***	0.3389	0.0921
Constant		**17.2628****	**12.8292**	**41.4967****	**8.5324****	**6.9648****

		Strategies		Barriers to voluntary blood donation		
		Rewards, recognitions & benefits	Incentives	Fear of negative health effects	Fear of donation process	Lack of trust in medical professionals and systems
		Coeff.	Coeff.	Coeff.	Coeff.	Coeff.
Ethnicity	Black-British-UK	0.0431	**0.9224***	**0.8892****	−0.3074	**2.2459****
	Black-Nigerian-UK	**2.1016*****	−0.3211	**1.1136***	−0.2832	**3.4584****
	Black Nigerian-World	**2.2796****	**1.9596*****	0.1772	−0.2236	**2.4390****
	Black-Nigerian-Expert	**2.3976****	**−2.8434*****	−0.3047	−1.0206	**1.7999*****
Donor status	Lapsed donor	**1.0648***	−0.5107	**−2.5387****	**−2.4014****	**−1.2199****
	Current donor	**3.0731*****	−0.3895	**−3.3485****	**−2.9232****	**−2.3128****
Age	Years	−0.0091	**−0.1106****	−0.0027	−0.0251	0.0099
Gender	Female	**1.0012***	**−0.8706*****	−0.4525	**0.5779***	**−0.4509***
HealthCare worker	Yes	0.6145	−0.0627	0.3341	−0.4538	−0.4007
Constant		**19.0175****	**17.8159****	**11.0094****	**11.0511****	**7.7989****

Note: The comparison group for ethnicity is White-British-UK., for gender, it is male, for healthcare worker it is being a non-healthcare worker and for donor status it is being a non-donor. Coeficients are unstrandardised (in bold).
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$.

3.6 | Blood donation cooperative phenotype

Differentiating donors into current and lapsed donors (Table 4), we observed that, compared to non-donors, both are associated with increased need-altruism, impure-altruism, reputation building and reluctant-altruism and perceiving rewards, recognitions, & benefits' as an encouraging strategy. Additionally, both lapsed and current donors also are less likely, than non-donors, to endorse all barriers. The consistency of response pattern across donors (lapsed and current) versus non-donors, is indicative of unique pattern of heightened motivation (general and specific altruism and strategies) and reduced barriers for blood donation, suggesting a cooperative phenotype. Indeed, strong associations between motivation and barriers are observed in the whole sample (Panel A) and Black and White samples separately (Panel B) of Figure 1. To explore the cooperative phenotype further, we applied PAF analysis with varimax rotation to all the measures of motivations and barriers simultaneously (Table 2, Panel B). This resulted in a three-factor solution. The first factor represents a 'Blood-Donor Cooperative Phenotype' with impure-altruism, reputation building, need-altruism, and reluctant-altruism all positively loading and forming a distinct factor along with a preference for 'rewards and recognitions'. All the mechanisms on this factor support blood

donor behaviour. The second factor contains the barriers to donation and the third factor is a kin-altruism/incentives factor. Need-altruism also has an inhibitory role on the kin-altruism/incentives factor. The same pattern is observed for Black and White people separately, and for donors and non-donors separately (Figure 1 and Supplementary File S8, Supplementary Tables S16 and S17 and Supplementary Table S18 for additional SUR models).

4 | DISCUSSION

We tested three key hypotheses: (i) need-altruism is associated with blood donor behaviour, (ii) kin-altruism is higher in Black people, and (iii) a preference for kin-altruism predicts seeing incentives as a good recruitment strategy, whereas need-altruism is linked to seeing rewards and recognitions as an effective strategy. We also explored the nature of a blood-donor-cooperative-phenotype. Several clear findings emerge. First, there is clear support for the first hypothesis, need-altruism, not kin-altruism, is expressed more highly in those who have previously donated and predicts future willingness-to-donate for non-donors. Supporting this finding, we observe that need-altruism is strongly associated with other MOA known to predict donor behaviour (impure-altruism, reluctant-altruism, and reputation building) and rewards and recognition, forming a blood-donor-cooperative-phenotype. Second, no support for hypothesis two is observed as kin-altruism is equally expressed across all lay people. However, Black-British people express lower levels of need-altruism, compared to White people. There is clear support for hypothesis three, with a preference for kin-altruism predicting a preference to view incentives as a good recruitment strategy and a preference for need-altruism predicting seeing rewards and recognitions as a good recruitment strategy. Importantly preference for incentives predicted willingness-to-donate in non-donors.

4.1 | Theoretical implications

Need-Altruism and the Blood Donor Cooperative-Phenotype and Blood Donation as a 'Risk-Pooling' activity: Need-altruism predicts willingness-to-donate in non-donors, is highly endorsed by donors, and loads on a 'blood-donor-cooperative-phenotype' with MOA that support blood donation (impure-altruism, reputation building and reluctant-altruism[1–6]) and non-financial rewards and recognition that support altruism.[30] Work should now start to more formally assess the blood-donor-cooperative-phenotype, based on a mixture of psychometrics (e.g., warm-glow), and behavioural economic games.[26,40,45,46] Economic games allow for formal behavioural assessment of cooperative preferences, to avoid any social desirability effects.[2] Specifically, some domain general games have been shown to be linked to blood donation such as the dictator game as well as its warm-glow variant.[40] Thus, using multi-group factor analysis, it would be possible to explore if the same domain-general cooperative-phenotype differentiates between different types of charitable giving (e.g., time, money, bodily substances) or if there are domain-specific cooperative-phenotypes that can be cross-validated with a psychometric assessment of preferences. The work reported here suggests that this is a definite possibility.

Need-altruism is central to need-based-transfer (NBT) systems supporting human altruism and cooperation to mitigate future risk.[47–50] In an NBT system, people enter into an agreement to help each other. When help is needed, the person (people) with sufficient resources, helps the person (people) who need help, without expectation of reciprocity, as long as this does not place the helper in need.[47–49] This unconditional help mitigates future risk by ensuring that everyone is helped and has access to resources if they are in need. This process of non-financial mutual risk management is termed 'risk-pooling'.[47] As need-based altruism is central to VNRBD, then it too may be characterised as a 'risk-pooling' system. That is, donors with sufficient resources (health), help recipients with fewer resources, with no expectation of reciprocity, but with the sense of future-proofing their own and their family's risk by ensuring that this is a sufficient supply of blood.[51,52] This risk-pooling social insurance policy is brokered by the blood services.

Acculturation and Barriers to Donation. It has been argued that through processes of acculturation, Black people are more willing to donate to a stranger, but the barrier is a belief that their blood will not be used.[53,54] Consistent with this, we observe that Black people endorse all barriers to donation, which include a lack of trust in healthcare professionals and the system, the idea that blood will be sold or a lack of certainty concerning what blood will be used for.

Lower Need-Altruism in Black People. We find no evidence that there is a greater preference for kin-altruism among lay people from Black communities compared to White communities. However, we do observe that need-altruism is lower in Black-British people in the UK. Lower levels of need-altruism have previously been reported in Black communities,[12] and thus, it may be that it is lower need-altruism acting as a barrier to donation in some Black communities rather than kin-altruism. Further work needs to identify what is driving the lower preference for need-altruism. However, it should be noted that while need-altruism is relatively lower it is still very high in absolute terms.

4.2 | Practical implications

Trust, health concerns and rewards: We replicate previous findings that impure-altruism and reluctant-altruism motivate donors.[5,6] We extend this by showing that reluctant-altruism is less motivating for Black people living in the UK. This adds to our growing understanding of the role of trust in motivating donations in Black people.[7] There is evidence that people from ethnic minority communities are more likely to consider donating blood if they trust others, indicating that what is important is that others also donate.[7] This is consistent with observed lower reluctant altruism, as reluctant altruism reflects a motivation to donate because others cannot be trusted to donate.[2,5] Thus, interventions that make the donation behaviour of others visible are likely to be effective.[7,55] We replicate findings that Black people have lower trust in healthcare.[7]

Consistent with other reports, people expressed concern that donating blood had negative health effects.[12,22,56] The negative effects of blood donation are starting to be recognised,[57] and as such, these concerns need to be addressed. We also show a clear difference in endorsement of strategies to encourage donation, with 'recognition' seen as important for Black-Nigerian people and 'incentives' as important for Black-British people, respectively.

Kin- and Need-altruism: The preference for kin-altruism did not differ across the lay communities we observed nor was it associated with blood donor behaviour. Need-altruism did predict blood donor behaviour, and was lower in Black-British people, therefore, an effective way to encourage blood donation would be to highlight the needs of the recipient.[58,59] This could be further strengthened by priming the concept of future cooperation and highlighting how friends and family would benefit from sufficient blood supply.[52]

4.3 | Limitations

While many of our reported findings replicate and extend previous findings, some, such as the positive association between kin-altruism and incentives, require replication in larger and more diverse samples to gauge the extent to which they can be generalised. This study has focused on Black communities, and while it has been noted that a preference for kin-altruism may be a potential barrier to blood donation in people from Asian communities,[16] our findings cannot be generalised to other ethnic minority communities.

AUTHOR CONTRIBUTIONS

Ferguson E, Dawe-Lane E, Ajayi 0, Osikomaiya B, Okubanjo A conceived and designed the study and contributed to the acquisition of these data. Ferguson E, Dawe-Lane E, Mills R analysed these data. Ferguson E, Dawe-Lane E, Ajayi 0, Osikomaiya B, Okubanjo A, Mills R contributed to the interpretation of these data. Ferguson E drafted the initial manuscript and all authors contributed to re-drafting and critically revising the manuscript for intellectual content. All authors provided final approval for the version to be published.

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CONFLICT OF INTEREST STATEMENT

The authors have no competing interests.

ORCID

Eamonn Ferguson https://orcid.org/0000-0002-7678-1451
Erin Dawe-Lane https://orcid.org/0000-0002-8479-6696
Oluwafemi Ajayi https://orcid.org/0000-0001-9204-434X
Bodunrin Osikomaiya https://orcid.org/0000-0002-2481-6958
Richard Mills https://orcid.org/0000-0002-6644-7011
Abiola Okubanjo https://orcid.org/0000-0002-9629-3172

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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GUIDELINES

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The influence of the COVID-19 pandemic on blood donation and supply in China

Si-Cong Yu [1] | **Yun-Tai Yao** [2] | **Evidence in Cardiovascular Anesthesia (EICA) Group**

[1] Department of Anesthesiology, Taizhou Central Hospital (Taizhou University Hospital), Taizhou, China

[2] Department of Anesthesiology, Fuwai Hospital, National Center for Cardiovascular Diseases, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, China

Correspondence
Yun-tai Yao, Department of Anesthesiology, Fuwai Hospital, National Center for Cardiovascular Diseases, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing 100037, China.

Email: yuntaiyao@126.com

Abstract

INTRODUCTION: During the COVID-19 pandemic, there was a sharp decline in blood donation which posed a serious threat to the clinical blood supply worldwide. The aim of this study was to evaluate the influence of the COVID-19 pandemic on blood donation and supply in China on a nationwide level.

METHODS: A comprehensive review of the published literature was performed using eight databases including PubMed, Web of Science, Cochrane Library, Ovid, Embase, CNKI, WANFANG, and VIP by searching relevant words combinations.

RESULTS: Twenty-seven studies were determined to be eligible and included. Among them, 21 studies reported the situation of blood donation during the COVID-19 pandemic in China. The donation of both whole blood and platelet concentrates declined (with a decline of 5%-86% for whole blood and 3%-34% for platelet concentrates), with this especially evident in February 2020. The COVID-19 pandemic changed the pattern of blood donation and the composition of blood donors accordingly. Fifteen articles reported the supply of various blood components during the COVID-19 pandemic. The supply and usage of both packed red blood cell (PRBC) and fresh-frozen plasma (FFP) decreased (with a decrease of 4%-40% for PRBC and 9%-58% for FFP). The proportion of blood transfusions in different departments changed too. Compared to 2019, there was a decrease in surgical blood transfusions, and an increase in that used in treatments performed in emergency and internal medicine departments.

CONCLUSION: The COVID-19 pandemic has led to an overall reduction of blood transfusion activities in most cities in China, in particular blood donations and blood demands.

KEYWORDS:
COVID-19; China; blood donation; blood shortage; blood supply.

1 | INTRODUCTION

In 2020, the emergence of the severe acute respiratory syndrome Coronavirus 2 (SARS CoV-2) resulted in significant disruption to the US healthcare system. During March April 2020 and extending through 2020, mitigation measures intended to control virus transmission resulted in reduced utilization of healthcare services.1-3 The Centers for Medicare & Medicaid Services (CMS) issued recommendations to delay all nonessential medical procedures.4 Subsequently, this recommendation along with the implementation of

other mitigation measures resulted in a reduction in patients seeking routine preventive
and screening measures, emergency services, surgical procedures, and other hospital-based
care.1-3,5,6their lifetime. Therefore, asymptomatic HTLV-1 carriers could be at risk of becoming blood donors in Japan. Regarding the transfusion-transmission of HTLV-1.

2 | VISION

1 | INTRODUCTION

The incidence of hip fractures continues to increase, along with the global expansion of aging population observed secondary to improved healthcare and quality of life.1 Subtrochanteric fractures are defined as fractures encountered between the inferior border of lesser trochanter and 5 cm distal to it.2 They represent a complex subset of injuries surrounding the hip, which are most commonly managed with intramedullary (IM) nailing.3,4 However, their moderate blood supply and being subjected to high concentration of stresses5–8 meant

a serological test for all blood donors was mandated by the Japanese Red Cross Blood Centre (JRC) in 1986. At the same time, the JRC has permanently declined blood donation from HTLV-1-seropositive donors, and subse- quently, in 1999, a notification programme for HTLV-1-seropositive blood donors was started in order to ensure the safety of blood products for transfusion, according to the recommendation from the government committee on notification of HTLV-1 infection. Althougha unified docu-

study and completed the questionnaire. The median age of the male and female respondents was 56.0 years (range 20-64 years) and 53.0 years (18-66 years), respectively (Table 1). Sixty (58.3%) of the 103 respondents accepted the notification of HTLV-1 infec- tion calmly and viewed the contents of the booklet favourably. Thirty-nine (37.9%) experienced anxiety and 5 (4.9%) experienced discomfort after being notified of their HTLV-1 infection status (Figure 1A). Forty donors answered that they had been aware of HTLV-1 before receiving the notification, and 17 (42.5%) of them had learned of HTLV-1 through maternity examinations and prena- tal (pre-mom) classes. Six (15.0%) had received the same notifica- tion at their previous blood donations. Two of the four responders who answered 'Other' revealed how they had learned about
HTLV-1 (at school, n = 1; at their workplace, n = 1). Nine (22.5%)
had received information on HTLV-1 from acquaintances and rela- tives, possibly reflecting the fact that this study was conducted in a highly endemic area (Figure 1B).
We obtained 154 answers from 80 donors about the information they needed. Forty-five (29.2%) requested knowledge about the transmission of the virus among family members and its prevention. Following that, 34 (22.1%) sought information about HTLV- 1-associated diseases, 33 (21.4%) sought information about available medical institutions and 19 (12.3%) and 12 (7.8%) sought information about the virus itself and experiences of other HTLV-1 carriers, respectively (Figure 1C). The most commonly used tools to obtain on-
demand information were an Internet search engine (n = 33, 45.2%),
followed by consulting an HTLV-1-specialised doctor at a medical institution (n = 20, 27.4%; Figure 1D).
In addition, we received 35 telephone inquiries, saying that the word
'HTLV-1' was unfamiliar and difficult to remember and pronounce for ordinary people or even the notification recipients. Therefore, when creating a booklet, we chose 'HAD', as the easy-to-remember and easy-to- pronounce word; this was taken from JSHAD. Namely, 'HAD' is the abbreviation of 'HTLV-1 and associated diseases'.
We collected the latest information for the contents of the new information booklet to address the unmet needs of notification recipi- ents as follows: the virological and epidemiological aspects of HTLV-1 virus, the routes of infection, associated diseases, transmission and prevention of transmission in normal life among the family and in the

workplace, and medical institutions to consult, along with comments from and experiences of other HTLV-1 carriers. A question-and- answer format that used easy-to-understand expressions was adopted, with technical terms eliminated when possible. The illustra- tions, which were drawn by an illustrator, an HTLV-1 carrier who had also learned about the infection after donating blood, were appropri- ately placed in order to promote understanding.
The new information booklet was reviewed by virologists, haematologists, neurologists, an ophthalmologist and a trans- fusionist, who were all

authorities and experts in the field of HTLV-1. Considering the high rate of respondents who retrieved information using Internet search engines, we introduced the Ministry of Health, Labour and Welfare (MHLW) website, as well as a search map for medical institutions and attached a guide to con- sulting the HTLV-1-specialising medical institutions available in each prefecture in the Kyushu region.

As the most important issue for the improvement of the safety of blood products, we explicitly stated in the new information booklet that future blood donations from the notified recipients would be declined.

3.2 | Follow-up survey to assess comprehension after distribution of the new information booklet

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We collected the latest information for the contents of the new information booklet to address the unmet needs of notification recipi- ents as follows: the virological and epidemiological aspects of HTLV-1 virus, the routes of infection, associated diseases, transmission and prevention of transmission in normal life among the family and in the workplace, and medical institutions to consult, along with comments from and experiences of other HTLV-1 carriers. A question-and-answer format that used easy-to-understand expressions was adopted, with technical terms eliminated when possible. The illustra- tions, which were drawn by an illustrator, an HTLV-1 carrier who had also learned about the infection after donating blood, were appropri- ately placed in order to promote understanding.

The new information booklet was reviewed by virologists, haematologists, neurologists, an ophthalmologist and a trans- fusionist, who were all authorities and experts in the field of HTLV-1. Considering the high rate of respondents who retrieved information using Internet search engines, we introduced the Ministry of Health, Labour and Welfare (MHLW) website, as well as a search map for medical institutions and attached a guide to con- sulting the HTLV-1-specialising medical institutions available in each prefecture in the Kyushu region.

As the most important issue for the improvement of the safety of blood products, we explicitly stated in the new information booklet that future blood donations from the notified recipients would be declined.The reviewed and revised information booklet (available at: https:// www.bs.jrc.or.jp/bc9/bbc/special/m6_05_04_index.html) has been distributed to the HTLV-1-seropositive donors since June 2019. A follow-up survey was conducted to assess the comprehension of the notification recipients and their status of HTLV-1 infection.For the follow-up survey, we distributed a questionnaire about the notification to 233 HTLV-1-seropositive blood donors, and 58 donors (male, n = 30; female, n = 28; 24.9%) replied. The median age of the male and female respondents was 56.0 years (range, 20-64 years) and 52.5 years (range, 24-64 years), respectively; and 19 (63.3%) of the male respondents and 16 (57.1%) of the female respondents were in their 50s (Table 2). Fifty-eight respondents reported 66 impressions of the new information booklet; 33 (50.0%) found it 'easy to understand', 11 (16.7%) found it 'useful' and 14 (21.2%) found it 'difficult to understand but still comprehensive', meaning that 87.9% of the respondents were able to gather the necessary information from the contents of the new information booklet (Figure 2). By attachment of the consultation guide for available medical institutions specialising in HTLV-1 con- sultation, seven of the nine introduced hospitals confirmed that they had outpatient visits from blood donors with an HTLV- 1-seropositive notification.

The first questionnaire survey revealed that 38.8% of respondents had been notified of their HTLV-1-seropositive status before their latest blood donation. After the distribution of the new information booklet, we investigated the change in the rate of repeating donors who had already received the notification of their HTLV-1-seropositive status at their previous donation.

To evaluate the utility of the new information booklet, we assessed the re-visiting rate of notified HTLV-1-seropositive donors from January 2017 to March 2021. Among 1383 HTLV-1- seropositive

donors, 853 were identified before the distribution of the new information booklet. Among these 853 donors, 19 donations were made by 17 donors (1.99%) who had been noti- fied of their HTLV-1-seropositive status at their previous donation. Five recipients (0.59%) had re-visited for blood donation within 1 year after HTLV-1-seropositive notification. A total of 530 of 1383 received our new information booklet after the initiation of delivery in July 2019. Among these recipients, 310 were observed for more than 1 year, and none had re-visited for blood donation (Table 3).

3 | DUSCUSION

Japan is the only developed country where HTLV-1 is endemic.[4] In the Kyushu region, in particular, it was estimated that there were approximately 450 000 HTLV-1 carriers.[5]

The WHO reported that 37 countries conduct mandatory testing of all blood donors for HTLV-1 and HTLV-2 and that seven countries conduct selective testing of new donors or donors who have not been previously tested.[6] It is a worldwide consensus in blood programmes that the notification and counselling of blood donors who show seropositive test results are important to blood safety; however, there are no fixed standards for either the regulatory requirements (legally prescribed criteria for notification) or the guidelines for notifying blood donors.[7,8] Notification of HTLV-positive blood donors was reported in Canada,[9] Australia[10] and the United States[11] in the 1990s. For example, in the UK,[12] notification recipients are asked to contact the blood service to arrange a discussion about their test results and onward clinical care. In Japan, this notification program started in 1999. The notification of healthy blood donors about seropositive test results can cause confusion, anxiety, and lack of understanding. In the recent report on health-related quality of life among blood donors who were notified viral infection, cases shown anxiety and depression had been 2.67-fold in HTLV carriers comparing to the control uninfected donors.[13] However, we have not adequately followed up the outcomes of notification.

In the present study, we defined the knowledge of HTLV-1 among notified blood donors and the unmet information needs according to the findings of a questionnaire. Taking the respondents' voice into consideration, we then created a new information booklet to provide the most necessary and up-to-date information in an easy-to-understand format. In the new information booklet, with the aim of improving health-related quality of life of the notification recipients, we included phrases to mitigate their anxiety, recommended early consultation to those with any symptoms, and listed the HTLV-1-specialised medical institutions for the consultation. In addition, we conducted a questionnaire survey to investigate the comprehension of recipients. In this survey, 90% of the respondents answered that the new information booklet was understandable, indicating that their knowledge had dramatically improved thanks to the contents, which coincided with the unmet needs of the notification recipients.

No HTLV-2-seropositive individuals have been confirmed among Japanese blood donors since the start of the notification program for HTLV-1-seropositive blood donors; thus, we did not mention HTLV-2 in the latest new information booklet. However, we might need to prepare an additional description about HTLV-2 in the future, as the first case of an HTLV-2-infected Japanese pregnant woman was recently reported.[14]

HTLV-1 antibody testing became mandatory in antenatal pregnancy screening throughout the nation in 2010. Simultaneously, the recommendation for mothers with positive results to refrain from breastfeeding was implemented for the prevention of mother-to-child transmission via breast milk. Following that, the MHLW of Japan collaborated in the production of the Japanese animation series, *Cells at Work!*, to conduct a public awareness campaign about HTLV-1 in 2018.[15] Enlightenment posters using popular comic book character have been distributed to health centres throughout Japan.

In our study, regarding the knowledge of HTLV-1, 17 recipients answered that they had learned about HTLV-1 in maternity examinations and prenatal (pre-mom) classes, suggesting that the education system for pregnant women had helped to spread knowledge about HTLV-1 in Japan; however, the efforts to disseminate knowledge regarding the ways to prevent horizontal transmission via transfusion remain insufficient.

Surprisingly, despite the receipt of a HTLV-1-seropositive notification following prior donations, 15% of respondents donated blood again. Five recipients had re-visited for blood donation within 1 year after seropositive notification, suggesting that we had not provided sufficiently useful information before the distribution of the new information booklet. Continuous blood donation by notified HTLV- 1-seropositive donors poses a risk to both the donor and patients, namely; a risk of an adverse effect of unnecessary blood collection for the donor and a risk of transfusion-transmission of the virus for patients. To reduce these risks, we clearly stated in the new information booklet that blood donation by those individuals would be refused. As a result, no repeated blood donations by recipients of the new information booklet were observed, indicating that appropriate presentation of information that addressed with the unmet needs of notified donors corrected their understanding of their HTLV-1 infection status and that blood donation would be declined.

In a study conducted among blood donors in India, donors were notified of their seropositive status in order to prevent transfusion-transmission of blood-borne infectious agents (TTIs).[16] A study in Thailand[17] showed that the behaviour of blood donors could be affected by providing a deeper knowledge about their HIV status, indicating that proper notification is necessary in order to prevent repeated blood donation. These investigations demonstrated thatm donor notification is an efficient method of curtailing TTIs, which is consistent with the results of our study.

Several limitations associated with the present study should be mentioned. First, the comprehension of recipients was evaluated by self-stated answers for the questionnaire, suggesting that the understanding might not have been sufficient. Second, recipients of the new information booklet could not be tracked for a long enough period to obtain an accurate evaluation of the re-visiting rate compared with before distribution. Third, there may have been some bias, as only 26.5% of recipients participated in this survey. Thus, recipients who did not send their answer sheet might have understood less than the

participants. However, since no re-visiting donors were observed after the distribution of the new information booklet, the new infor- mation booklet might have improved their understanding of HTLV-1 infection.

We recently received an e-mail from a foreign student living in Kyushu, writing that his Japanese girlfriend had recently been notified that she was HTLV-1-seropositive and that he was strongly concerned about transmission through sexual intercourse. He was anxious to learn about infection routes and the frequency of HTLV-1 transmission, and he would like to visit a medical institution for consultation to HTLV-1-specialised doctors. A basic strategy for preventing TTIs is to notify and counsel infected blood donors. Although counselling of individuals infected with HTLV-1/2 has been recommended,[18] a nationwide consultation system has not yet been fully developed in Japan. The aforementioned international student wrote in his e-mail, 'Unfortunately I live in an HTLV-1 endemic area'. There is thus an urgent need to formulate nationally acceptable guidelines for the notification and follow-up of HTLV-1-seropositive individuals in health checks and to prevent the spread of HTLV-1, both domestically and abroad.

In this study, HTLV-1-seropositive blood donors expressed a strong wish for information about medical institutions capable of counselling HTLV-1 carriers. In response to our request, all nine certi- fied medical institutions in the Kyushu region accepted that the notifi- cation of HTLV-1 test results from the JRC would be regarded as a patient referral document and that recipients who visited the desig- nated medical institutions would be exempted from the additional fee for a first-time patient who presented no referral. Owing to the reduc- tion in the additional fee for consultation, the number of consultations for recipients of the new information booklet increased, and visits from those recipients were observed in seven of the nine designated medical institutions. In fact, visits from HTLV-1-seropositive donors increased 1.44-fold at the introduced medical institutions following the distribution of the new information booklets. The result indicated that the disclosure of available medical institutions and the reduction of medical expenses are effective measures for notified donors who are anxious about their status and who desire to visit appropriate medical institutions for consultation. The new information booklet was fruitful in two aspects: one was the facilitation of consultations of HTLV-1-seropositive notification recipients; the other was the deter- rent effect in relation to repeated donation by the recipients, leading to improvement of both the health-related quality of life of seroposi- tive blood donors and the safety of blood products.

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CONFLICT OF INTEREST

The authors have no competing interests.

AUTHOR CONTRIBUTIONS

Hitomi Nakamura and Yasuko Sagara designed this study, analysed data, edited the information booklet and wrote this manuscript. Midori Yamamoto collected data. Atae Utsunomiya and Toshiki Watanabe reviewed the information booklet and supervised this manuscript. Masahiro Satake also reviewed the information booklet, supervised this study and supervised this manuscript. Kazuo Irita supervised this study.

ORCID

Hitomi Nakamura https://orcid.org/0000-0001-5225-7295
Yasuko Sagara https://orcid.org/0000-0002-6322-7195
Atae Utsunomiya https://orcid.org/0000-0002-8843-406X
Toshiki Watanabe https://orcid.org/0000-0002-1198-3773
Masahiro Satake https://orcid.org/0000-0002-4660-6839

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The incidence of hip fractures continues to increase, along with the global expansion of aging population observed secondary to improved healthcare and quality of life.1 Subtrochanteric fractures are defined as fractures encountered between the inferior border of lesser trochanter and 5 cm distal to it.2 They represent a complex subset of injuries surrounding the hip, which are most commonly managed with intramedullary (IM) nailing.3,4 However, their moderate blood supply and being subjected to high concentration of stresses5–8 meant.

other mitigation measures resulted in a reduction in patients seeking routine preventive and screening measures, emergency services, surgical procedures, and other hospital-based care.[1-3,5,6]

Severe acute respiratory infections caused by strains of influenza or coronavirus often lead to hospitalisation and sometimes death. Symptomatic infection with SARS CoV-2 (COVID-19) has surpassed the annual global burden of death due to influenza or coronaviruses.[1] Although there are several effective vaccines for COVID-19 therapeutic treatments are still required. Patients particularly at risk are those with disorders that affect the immune system, for example, haematological malignancies or those receiving drugs that suppress an immune response, for example, after organ transplantation.[2,3]

Passive antibody therapies, including monoclonal antibody combinations have proven effective for COVID-19[4] However, the cost of these therapies is prohibitive[5] and new SARS-CoV variants may become resistant to anti-virals developed in response to previous variants.[6] Alternative and affordable responses to emerging strains of virus are needed.

Convalescent plasma (CP) is typically collected from donors with confirmed diagnosis of infection at least 2 weeks after recovery.[7] CP contains neutralising antibodies specific to the infectious agent but may also contain other immune modulators and clotting factors that can be fractionated out to produce hyperimmune-immunoglobulin (hIVIG).[8]

CP containing high titres of polyclonal antibody (Ab), has been used to treat patients hospitalised with respiratory syndromes caused by viral infections. Many studies have been poorly controlled but such series suggested decreased mortality in H1N1 Influenza infections in 1918–1920 and in 2009/2010, SARS-CoV-1 infections in 2003 and most recently COVID-19. Recent systematic reviews lacked data from RCTs and analysis did not consider the titre used within trials.[9] Moreover, there are concerns that CP may cause harm, potentially causing severe transfusion reactions such as transfusion-associated acute lung injury (TRALI) or antibody dependent enhancement of the viral infection.[10]

Prior to the COVID-19 pandemic, studies investigating the effectiveness of CP for viral infections varied in quality and the outcomes reported may not have reflected current international guidelines.[11,12]

2 | OBJECTIVE

To evaluate the evidence for the safety and effectiveness of using convalescent plasma (CP) or hyperimmune immunoglobulin (hIVIG) to treat severe respiratory disease caused by coronaviruses or influenza.

3 | METHODS

The protocol for this review was prospectively registered on PROSPERO (CRD42020176392), and the review was carried out in accordance with Cochrane methodology and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13]

3.1 | Search strategy

We searched multiple electronic databases (MEDLINE, PubMed, The Cochrane Library, Embase, Epistemonikos), ClinicalTrials.gov and WHO International Clinical Trials Registry Platform for ongoing studies, without language restriction, for all publication types on 12th October 2020 (see Appendix A1 in Data S1). We updated our search on 28th June 2021, increasing the number of databases (Cochrane COVID-19 Study Register, Transfusion Evidence Library, Web of Science). We limited the update search to systematic reviews and RCTs due to the significant number of randomised trials available at this point. Ongoing studies identified in our searches were checked on 30th November 2021 and included if published in full (peer-reviewed) by this date. We hand searched reference lists of systematic reviews and included RCTs.[11]

3.2 | Selection criteria

For assessments of effectiveness, we included RCTs comparing transfusion of CP products to any control arm with participants of any age who were admitted to hospital with severe respiratory illness. For assessments of safety, we included all study designs where patients received CP or hIVIG.

Two reviewers (CK, AL, LJG, SV) independently screened title and abstract, and then full-text using Covidence.

Where a publication was in a non-English language, we used electronic translation tools and sought the help of native speakers where appropriate (Appendix A2 in Data S1).

3.3 | Data extraction

Two of four reviewers (CK, AL, LJG, JS) independently extracted data using Covidence and Excel. Reviewers who were involved with any original trials (AL, LE) were not involved in the data extraction for those trials.

Extracted data included: details of study participants (demographic and disease characteristics), details of interventions (including titre, volume, timing of CP/hIVIG), and outcomes.

Outcomes extracted: all-cause mortality up to 30 and 90 days; need for mechanical ventilation (MV) and non-invasive ventilation (NIV) at up to 30 days; duration of MV or NIV; length of hospital stay; length of intensive care unit (ICU) stay; duration of viral detection from admission up to 30 days; transfusion-related serious adverse events (SAEs).

In a deviation from our protocol, we also assessed SAEs up to 30 days due to substantial variability in the way that SAEs were reported. For papers from the 1918 to 1920 influenza pandemic, reporting style was substantially different and, if reported, there was no grading of AEs. We recorded any potential AE described in these `publications.

Where data were not available for a particular timepoint, we extracted data to the nearest possible timepoint. We sought clarifica-

tion from trial authors where necessary.

3.4 | Risk of bias assessment

Two review authors (CK, AL, LJG, JS) independently assessed all eligible studies for risk of bias (ROB), using the Cochrane ROB tools. ROB1 for RCTs[14] and ROBINS-I for observational studies according to the Cochrane Handbook for Systematic Reviews of Interventions.[15] Reviewers who had worked on a trial (AL, LE) did not participate in ROB assessments for those studies.

Observational studies assessed as having "critical" ROB were not included in quantitative analyses.

3.5 | Data analysis

Statistical analyses were undertaken in Review Manager 5.4,[16] R[17] and the *metafor* package in R.[18] For dichotomous outcomes, we used the Mantel-Haenszel method, or Peto OR for rare events. We calculated the pooled risk ratio (RR) with a 95% confidence interval (CI), using the random effects model in RevMan5.[16] We used Tau^2 and I^2 in the assessment of heterogeneity, according to the guidelines laid out in the Cochrane handbook.[19]

We have not combined RCTs and non-RCTs and so have reported the results separately.

We planned to analyse continuous outcomes using mean difference (MD) or standardised mean difference (SMD) where different scales had been used. Continuous outcomes reported as median (IQR/range) could not be meta-analysed or pooled and have been reported narratively within tables.

Information from observational studies was collated in tables and not meta-analysed. Certainty of the evidence (based on meta-analysable data only) was assessed using GRADEPro.[20]

3.5.1 | Subgroup and sensitivity analysis

We subgrouped included trials by the type of respiratory infection.

We also subgrouped COVID-19 studies by their use of high titre or low titre/unselected plasma (see Appendix A3 in Data S1) in response to emerging research that highlighted the wide variability in CP titres used in practice.

We intended to undertake sensitivity analyses based on selection bias to examine evidence from 'low risk' studies only. However, this was not necessary for the RCTs as all included RCTs were assessed as low (or unclear) risk for mortality endpoints within this domain.

3.5.2 | *Post hoc* analysis of seropositivity

We performed a *post hoc* analysis of trials where there were sufficient data to assess the impact of SARS-CoV-2 antibody status at baseline due to emerging evidence of greater effectiveness of passive antibody therapy (monoclonal antibodies) for patients who are antibody negative at baseline.[21] Meta-regression for *post hoc* analysis of seropositivity was performed using the metafor[18] package in R.

4 | RESULTS

Our search yielded 4826 references (Figure 1 PRISMA flow diagram; for excluded studies see Appendix A4 in Data S1).

4.1 | Study Characteristics

We identified 110 completed studies (Figure 1), including 30 RCTs (four for influenza, n = 578; and 26 for COVID-19 SARS-CoV-2, *n* = 18 204).[3,7,22-49] There were no RCTs or non-randomised controlled trials identified for MERS or SARS (SARS-CoV-1) (Appendix A Supplementary Table A1 in Data S1). We included 76 non-randomised studies (Appendix B in Data S1). Of these, eleven were controlled studies, of which only two were at less than "critical" ROB[50,51] (Appendix A Supplementary Table A2 in Data S1) We included 67 uncontrolled studies: 12 assessing influenza A; two on MERS-CoV; four on SARS-CoV, and 49 on COVID-19 (SARS-CoV-2).

We also identified 143 ongoing studies (Appendix C) which were either controlled trials or single arm studies, which listed at least one safety outcome in their intended primary or secondary outcomes.

Study size in the quantitative analyses ranged from 29 to 11 555 (34 to 308 for influenza).

Of the four RCTs assessing influenza: two included children (*n* = 24/236 < 18 years)[39,45]; three RCTs[39,45,47] included pregnant women (3/270 pregnant women).

Of the 26 RCTs and 2 non-randomised studies that assessed COVID-19: one RCT included children (*n* = 26/11558 < 18 years).[3] Three RCTs[29,34,44] did not report whether they included children. Three RCTs[3,29,35] included pregnant women (*n* = 36/12575 pregnant women). Eight RCTs[22,24,30-33,36,44] did not report whether they included pregnant women.

4.2 | Comparisons

We identified four comparisons within the data that could be combined in quantitative analysis:

(1) CP versus standard care (SoC) or biologically inactive placebo (saline) (20 RCTs): 19 RCTs compared CP to SoC,[3,7,22-25,27-31,33-36,38,39] one RCT[26] compared SoC with saline placebo, and two retrospective observational studies[50,51] compared CP patients with matched controls;

(2) CP versus biologically active control (FFP or IVIG) (6 RCTs): five RCTs compared CP to non-immune FFP,[40-43,45] and one compared CP with IVIG.[44]

(3) hIVIG versus control (3 RCTs) Of these, two compared hIVIG with SoC,[46,47] one compared hIVIG with saline placebo.[48]

(4) early CP versus deferred CP (1 RCT).[49]

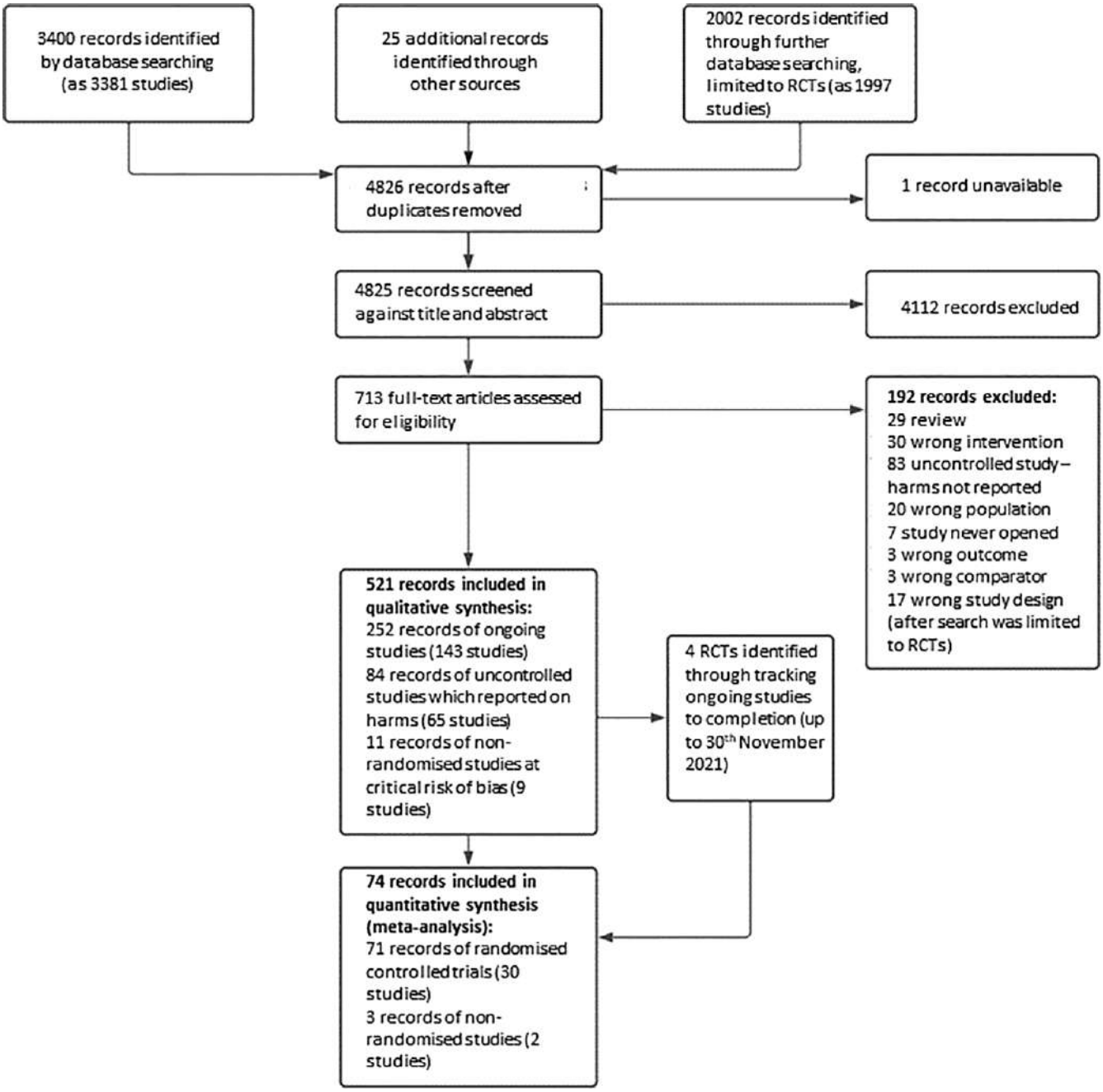

FIGURE 1 PRISMA flow diagram. Caption: The reasons for exclusion at each stage are shown with arrows to the right.

The comparators and baseline characteristics of participants in each of the thirty RCTs and two non-RCTs (retrospective observational studies)[50,51] within meta-analyses are summarised in Appendix A Table A1 in Data S1.

4.3 | Outcomes

We could only extract sufficient data to meta-analyse mortality and serious adverse events. We have presented remaining data from controlled studies in tables (Appendix A, Tables A3-A6 in Data S1). A summary of all outcomes reported is available in Appendix A5.

Most trials did not describe any method for dealing with competing risks when reporting their results. A competing risk is one which prevents the event of interest from occurring. Death is a competing risk for both (time to) mechanical ventilation and (time to) discharge. Devos 2021[28] approached competing risks using competing events analysis[52] to obtain cause-specific hazard ratios (HR). REMAP-CAP[30] used ordinal logistic regression by assigning each participant a category labelled with the number of ventilator-free days up to 21 days, with people who died up to day 90 being assigned —1, people who were on MV at

randomisation being assigned 0, and people who remained ventilator-free beyond day 21 being assigned 22. This is a useful way to compare the two groups while accounting for the very different possible outcomes but the resulting odds ratio (OR) and medians are difficult to interpret. No other trials used these methods and so we cannot combine the results but instead report the summary within Table A4 in Data S1.

Duration of viral detection was expressed as time (median IQR) to first negative test (2 RCTs).[23,36] One study,[25] reported the number of patients who had had two consecutive negative tests by day 30. See table A5 for viral detection data and table A6 for details of changes in viral loads.

4.4 | ROB in included studies

4.4.1 | RCTs (using Cochrane ROB1)

Nineteen RCTs were open-label, comparing CP to SoC, and were therefore assessed as having a high ROB for all outcomes except mortality, as knowledge of treatment allocation may have affected clinical decision-making. A summary of ROB judgements is available in Table A7 and Figure A1 in Data S1.

4.4.2 | Non-RCTs (using ROBINS-I)

Two non-RCTs[50,51] were assessed at serious RoB for selection bias and confounding at baseline. The remaining 9 studies[53-61] were at critical ROB due to baseline confounding or selection bias and were therefore not meta-analysed.

4.5 | Certainty of the evidence (GRADE)

Certainty of the evidence was GRADEd as very-low to high; primary reasons for downgrading were ROB and imprecision (wide confidence intervals and small sample size) (Tables A8-A11 in Data S1). We assessed publication bias through the generation of a funnel plot (Figure A2 in Data S1) for 30-day mortality in comparison 1, which suggests that some small studies have not been published. However, this was not significant enough to downgrade the certainty of the evidence because the analysis is dominated by two large, high-quality, and RCTs.

4.6 | Effect of the Intervention

See Table 1 for an overview of meta-analysed results.

4.6.1 | Comparison 1: CP versus SoC or biologically inactive placebo

Twenty RCTs and two retrospective studies assessed CP compared with SoC or a biologically inactive placebo.

All-cause mortality

30-day mortality data were available from 15 RCTs (30 days, 5 RCTs; 28 days, 9 RCTs; 21 days, 1 RCT) (Figure 2a); 90-day mortality data were available from 6 RCTs (56 days, 1 RCT; 60 days, 3 RCTs; 90 days, 2 RCTs) (Figure 2b).

Overall, CP did not reduce 30-day mortality (15 RCTs, n = 17 266; moderate-to-high certainty of evidence [Table A8 and footnotes in Data S1]) and there may be no effect on 90-day mortality (6 RCTs $n = 3210$; low certainty of evidence [Table A8]).

Two non-RCTs reported in-hospital mortality, and showed results consistent with the randomised evidence (2 studies, $n = 436$; very-low certainty evidence) (Figure A3A Table A8 in Data S1).

Improvement of clinical symptoms

Duration of NIV was reported in 4 studies (2 RCTs),[3,24,50,51] and duration of MV was reported by 11 studies (9 RCTs).[3,24,25,28-30,35,38,39,50,51] Two RCTs[27,31] reported any ventilatory support, but did not differentiate between MV, NIV, and passive oxygen support. One RCT[29] reported any ventilation, but also reported separately a composite outcome of patients who progressed to MV or death. Most studies reported the data as duration of support, either median (IQR) or mean (SD) (Table A4 in Data S1).

These outcomes were very variably reported, and many did not fully account for competing events, or report methods of analysis in sufficient detail. Based on what was reported, there was no apparent difference in duration of MV, NIV or ECMO support between the two groups.

Length of stay (LOS): hospital and ICU

Length of hospital stay was reported by 16 RCTs[7,23,25-28,30,31,38,39,42-47] and 1 non-RCT,[51] and length of ICU stay was reported by 9 RCTs[23,26,28,29,33,39,43,45,47] (Table A3 in Data S1). There was no evidence of an effect in length of hospital stay or length of ICU stay (Table A3 in Data S1).

Duration of viral detection from admission up to 30 days (viraemia, nasopharyngeal swabs, bronchoalveolar lavage, stool)

The 3 RCTs which reported time to negative test do not suggest any evidence of an effect (Table A5 in Data S1).

Adverse events

AEs due to transfusion were reported in 15 RCTs[3,7,22-39] (Table S10 in Data S1).

Seven RCTs reported no Grade 3 or 4 AEs due to transfusion.[22,24,26,27,31,35,39] Both non-RCTs reported AEs due to transfusion. All but one RCT[26] had SoC comparators, and therefore no transfusion-related SAEs are reported for the control group. Group comparison was not possible; results are summarised in Table A12

of in Data S1.

There was no evidence of an effect on reported SAEs[3,23-31,35,36,39] (13 RCTs, n = 16 730, very-low certainty of evidence) (Figure A3B). Data were not available on SAEs in seven RCTs.[7,22,32-34,37,38]

See forest plots Figure A3 in Data S1 and GRADE profile Table A8 in Data S1 for further detail.

4.6.2 | Comparison 2: CP versus biologically active control (FFP or IVIG)

RCTS assessed CP compared to FFP[40-43,45] or IVIG[44]

All-cause mortality

There was insufficient evidence to say whether or not there is a difference between groups in all-cause mortality at up to 30 days (5 RCTs n = 700; very-low certainty evidence, Figure A4A in Data S1), or at up to 90 days (2 RCTs, n = 264; very-low certainty evidence Figure A4B in Data S1). See forest plots Figures A4A and A4B in Data S1 and GRADE profile Table A9 in Data S1 for further detail.

Adverse events

Six RCTs reported transfusion-related Grade 3 or 4 AEs.[40-45] Events were rare (~2%) with no clear evidence of a difference (6 RCTs, n = 716; very-low certainty evidence. [Figure A4C in Data S1]). Four RCTs[40-42,45] reported SAEs up to 30 days, showing no evidence of an effect, although the rate of SAEs seems very low, given the severity of disease in hospitalised individuals (4 RCTs, n = 523; low certainty evidence, Figure A4D in Data S1). See forest plots Figure A4 and GRADE profile Table A9 in Data S1 for further detail.

Improvement of clinical symptoms

Duration of MV[40,43,45] and any ventilatory support[41] were reported as median (IQR) or mean (SD). Given the difficulties of dealing with competing events, and the small number of patients involved, it is very unclear if CP therapy had any effect on the duration of MV, NIV or ECMO support between the two groups. We have presented the data in Table A4 in Data S1 as reported by the individual studies.

Data were not available for LOS (hospital or ICU), and duration of viral load.

4.6.3 | Comparison 3: hyperimmune immunoglobulin versus control

Three assessed hIVIG compared with SoC or a biologically inactive placebo.

All-cause mortality

There was insufficient evidence to say whether or not there is an effect on mortality compared to control at up to 30 days (3 RCTs n = 392; very-low certainty evidence) (Table 1, Figure A5A, Table A10 in Data S1). There were no data for 90-day mortality.

Adverse events

Two RCTs reported transfusion-related AEs; neither reported any AEs due to transfusion in either group (2 RCTs, n = 84; very-low certainty evidence, Figure A5B in Data S1). Two RCTs reported SAES (2 RCTs n = 342; very-low certainty evidence. [Figure A5C in Data S1]). See forest plots Figure A5 and GRADE profile Table A10 in Data S1 for further detail.

Improvement of clinical symptoms

One RCT in influenza[48] reported on duration of MV and NIV. However, the data were presented using an ordinal scale that was not mappable to our outcomes or other trial results, and we were unable to extract the data.

Data were not available for LOS (hospital or ICU), and duration of viral load.

4.6.4 | Comparison 4: early CP versus deferred CP

One RCT assessed early CP compared to deferred CP.

All-cause mortality

There was insufficient evidence to say whether there is a difference in 30-day mortality between early CP and deferred CP (1 RCT n = 58; very-low certainty of evidence) (Figure A6 in Data S1). There were no data for 90-day mortality. See forest plots Figure A6 and GRADE profile Table A11 in Data S1 for further detail.

Adverse events

There were three Grade 3 or 4 transfusion-related AEs within 24 h, all in the early CP group: (1 RCT n = 58, very-low certainty evidence) (Table A12 in Data S1). SAEs were not reported. See forest plots and GRADE profile Table A11 in Data S1 for further detail.

Improvement of clinical symptoms

Duration of MV and NIV was reported as median (IQR). We have presented the data in Table A4 in Data S1 as reported by the RCT. Both groups had similar duration of ventilatory support. It is unclear if the authors accounted for competing events.

Data were not available for LOS (hospital or ICU), and duration of viral load.

4.7 | Results from uncontrolled studies (for safety only)

We identified 73 non-randomised or uncontrolled studies [49 case reports or case series] that assessed the use of CP or hIVIG in respiratory viral infection and reported AEs: 12 in influenza A, 2 in MERS-CoV, and 4 in SARS-CoV-1, and 67 in SARS-CoV-2 (COVID-19). Of the influenza studies, 10 were from the 1918 to 1920 pandemic. Fifty-one studies reported that no AEs were observed (37/49 case reports or case series). Eighteen studies reported transfusion-related AEs, and four studies reported other SAEs. These data are presented in Appendix B in Data S1.

4.8 | Post hoc subgroup analysis: seropositivity at baseline

Three RCTs,[3,30,62] including the two largest, reported 30-day mortality for subgroups defined by seropositivity at baseline. These results are shown in Figure 3.

FIGURE 3 Subgrouped by seropositivity at baseline: RCTs reporting 30-day mortality for comparison 1 (CP compared to SoC or a biologically inactive placebo)

With almost all the information coming from the two large, high-quality RCTs,[3,30] the pooled estimates from these three RCTs are: RR 1.02 (0.92 to 1.12) for people who are seropositive at baseline and 0.94 (0.86 to 1.02) for those who are seronegative. The test for interaction (subgroup difference) gives a *p*-value of 0.20 with very little heterogeneity either within or between groups.

We explored this further using meta-regression on the group of trials comparing high titre CP with SoC which reported the proportion seropositive at baseline and 30-day mortality. This analysis produced near identical results with an estimated RR at 0% seropositivity of 0.93 (0.85, 1.01) and 1.02 (0.93, 1.12) at 100% seropositivity (See Appendix A6 in Data S1. Mortality results are summarised in Table A14 in Data S1).

5 | DISCUSSION

The objective of this review was to determine the safety and effectiveness of CP or hIVIG from CP to treat patients with serious respiratory disease due to influenza or coronavirus infection. In order to increase the relevance of our findings to the COVID-19 pandemic we used the core outcome set[63] for assessing treatments for patients infected with SARS-CoV-2. We aimed to use high-quality evidence from RCTs to assess safety and effectiveness. We also used all other study designs to describe serious harms reported following transfusion with CP or hIVIG.

5.1 | Main findings

We were able to meta-analyse 32 studies for our primary outcome of 30-day mortality (30 RCTs and 2 non-RCTs). We found little evidence of any difference between the groups in either benefits or harms for patients hospitalised with a severe viral respiratory infection requiring hospital admission. Most evidence was of low or very-low certainty. The only high-certainty evidence was for the COVID high-titre sub- group in the outcome all-cause mortality at up to 30 days in CP versus SoC (Table 1).

Adverse events were variably reported. No RCTs reported a high number of transfusion-related AEs (proportion 0% to 5.67%[22-24,26,27,31,35,38,39,43,44,46,47]) (very-low to low certainty evidence). There was no evidence of an increase in harms compared with standard plasma.

5.2 | Quality (certainty) of the evidence

Where meta-analysis was possible, we used GRADE to assess our certainty in the result (Table 1). Certainty in the evidence was assessed as very-low to low certainty for all outcomes apart from mortality data in the comparison CP versus standard care.

Evidence was downgraded for serious ROB (lack of blinding, baseline imbalance, randomisation processes, missing data and unclear reporting of outcomes) and imprecision (wide confidence intervals around the effect estimate, and small sample sizes for the outcome of interest). Some of the sources of potential bias (such as patient and personnel blinding) would be hard to overcome in future trials due to the issues in finding an ethical control infusion: even saline is problematic, with the risk of volume overload, and ease with which it can be differentiated from plasma.

SAEs were also downgraded for inconsistency as the heterogeneity was significant between studies, this is likely to be due to the variation in reporting of the SAEs. This may be in part due to differing regulatory environments and different classifications of CP, requiring varying levels of AE reporting including the need to use a grading system (e.g., MedDRA[64]).

We included lower-level evidence for the assessment of safety outcomes. However, we were unable to perform quantitative analyses, and so have only presented these data as reported in Appendix B in Data S1.

There were very few endpoints reported consistently enough for meta-analysis. The difficulty in defining endpoints, especially time-to-event endpoints,[65] is discussed further in Appendix A6 in Data S1.

5.3 | Strengths and Limitations of this review

We have attempted to minimise potential bias in the review process, using Cochrane methods and PRISMA guidelines for reporting. We conducted a comprehensive search: searching data sources to ensure that all relevant studies would be captured, using multiple databases and reference lists of included studies. We included conference proceedings and included a search of clinical trial registries. We also attempted to contact authors for additional data and for clarification of their data.

There were no restrictions for the language in which the paper was originally published. We pre-specified outcomes prior to analysis and have explained the rationale for including one additional outcome (any SAEs).

We undertook duplicate screening, data extraction, and assessment of bias. Additionally, the clinical advisor (LE) was consulted for disagreements, or need for clarification.

The limitations of this review mostly arose due to gaps in the evi-

dence base, which are discussed more fully in the next section.

5.4 | Interpretation and context

A recent analysis of individual patient data (IPD) pooled from eight RCTs[9] IPD reported an OR for mortality of 0.85 at day 28 (95% credible interval, 0.62 to 1.18; posterior probability of OR <1 of 84%). These results are broadly comparable and in agreement with our own aggregate analyses for 30-day mortality. However, it should be noted that the IPD analysis included two RCTs[66,67] published after our 30th November 2021 cut-off, but did not include the two largest RCTs of CP RECOVERY[3] and REMAP-CAP[30] which we have analysed, and which together contribute 83% of sample size contributing to our analysis of 30-day mortality for CP versus SoC.

A limitation of the current evidence base is that of the 30 RCTs and two non-randomised studies included in our meta-analysis, 26 studies (24 RCTs) excluded children and 16 RCTs excluded pregnant women, with 1 RCT[39] admitting pregnant women only on the second round of recruitment. Given that children and pregnant women are both considered to be at increased risk of serious disease and death from many severe respiratory viral infections, their exclusion from trials is concerning. Of the 144 ongoing studies we identified, most trials will exclude children and pregnant women. Many ongoing studies have an upper age cut-off (of 65, 70 or 80 years), despite older age being one of the biggest risk factors for COVID-19.

The precision of our meta-analysis was affected by the different titres of CP-neutralising antibodies between trials (Table A1 in Data S1). We tried to address this by subgrouping studies based on the CP-titre reported, and whether it was considered high enough accord- ing to FDA criteria (see Appendix A3 in Data S1). However, several studies used local assays that could not be correlated with an FDA ref- erence method. Since we conducted our first search, several variants of SARS-CoV-2 have arisen worldwide and may require much higher anti- body titres measured using ELISA assays.[68] Much higher titre CP, from vaccinated convalescent donors, may be active against future variants[69] indicating that new COVID CP trials should aim to use very high titre CP standardised using internationally recognised methods.

Similarly, between trials, there was heterogeneity of patient groups and severity of illness on admission to hospital (Table 1). The RCTs in COVID may not have used the same criteria to categorise trial partici- pants at enrolment and trials designed to treat different patient groups based on comorbidities and immune states were absent. Several COVID-19 studies reported clinical improvement using the WHO ordi- nal scale. However, the scale was revised several times over the course of 2020–2021, going from an 8-point scale[70] to a 10-point scale at its latest revision[71] which have made comparisons between trials difficult.

The results of our post hoc subgroup analysis by seropositivity at baseline are very similar to the results reported by RECOVERY alone. We have not found stronger evidence of this potential interaction than that reported by RECOVERY (with a similar trend also reported by REMAP-CAP, especially for organ support-free days) but similarly, we have not found any reason to discount the possibility that there is a small but important interaction, with immunocompromised individ- uals potentially benefitting more. This hypothesis is consistent with the REGN-COV2 RECOVERY trial,[21] which has shown no benefit of monoclonal antibodies for seropositive patients who either have advanced disease or who are immunocompetent. The very high base- line risk of immunocompromised individuals might translate very small relative risks into substantial absolute risk differences. REMAP-CAP has recently reopened for immunocompromised people to test this hypothesis.[72]

5.5 | Implications for research and practice

There is currently no evidence for a benefit of CP in an unselected population of patients hospitalised with coronaviruses or influenza. It is likely that the titre of the CP and the immune response of the recipient may both be important factors affecting response to treatment.

Studies should use CP of a high enough titre to elicit a biological response, and report the actual titre used as well as the minimum as described in the protocol. Matching variants between donor and recipient may not be feasible, but viral variants circulating at the time of collection of plasma and during the study should be recorded.

Studies should assess and publish antibody status (seropositivity) at baseline in both intervention and control groups, and identify and report immunocompromised patients separately, to establish whether certain groups of patients are more likely to benefit from this intervention.

There are difficulties in designing truly blinded RCTs of CP or hIVIG (see Reference 73 for review). There are ethical problems with using a placebo which is assumed to have no clinical benefit, but has known harms.[74] One RCT[26] used a saline placebo, with potential concerns about volume overload, and six RCTs used a biologically active control, (FFP in 5 RCTs,[40–43,45] and IVIG in one[44]) which raises additional concerns about transfusion reactions.

Unless reported explicitly by investigators, it was difficult to distinguish the AEs experienced following transfusion from the symptoms of severe respiratory disease.[75] This limited the number of RCTs that we could include in our meta-analysis of AEs due to transfusion. There was also substantial variability in the way that AEs were recorded and reported in these studies. It was not always possible to determine the severity of AEs, and different studies used different criteria for SAEs. In some cases, it was hard to determine if SAE reporting was per event or per patient, making it extremely difficult to compare rates of AEs between studies. Blood components in the UK are not classified as medicines and so require a different grading system for reporting AEs to countries that classify CP as a medicine, e.g. Germany. A consensus on how AEs associated with blood products are reported in RCTs would help to address this problem.

6 | CONCLUSION

This review has highlighted several issues regarding study design and reporting which should be addressed in current and future research. A minimum titre should be established and ensured for a positive biological response to the therapy. Further research on the impact of CP/hIVIG in patients who have not produced antibodies to the virus prior to hospital admission or who are immunocompromised would be useful to target therapies at groups who will potentially benefit the most.

During April-May 2020, which marked the early COVID-19 pandemic period in the United States, RBC transfusions and corresponding whole blood donations experienced a drop, likely due to broad implementation of COVID-19 mitigation strategies. However, these were followed by a return to baseline in the following month(s). Similarly, apheresis platelet transfusions appeared to drop during March-May 2020 but rebounded thereafter.This pattern is consistent with the observed impacts of the pandemic on the healthcare system overall, in which patients initially deferred seeking medical care during the early COVID-19 risk mitigation period but subsequently resumed healthcare utilization. The findings observed in the present study are consistent with an analysis of data from the National Healthcare Safety Network Hemovigilance Module, which found a statistically significant decrease in RBC transfusions during March-April 2020, with subsequent return to baseline.8 This decline is broadly consistent with our findings, but the decrease early in the pandemic was negated throughout the rest of the year, suggesting a significant recovery in blood utilization. Interestingly, our results show that the reduced RBC transfusions during the early risk mitigation phase of the pandemic were not seen in states with high COVID-19 burden at that time. Additional research is required to determine reasons for this observation, but the findings suggest that individuals may have continued to seek therapies in some regions regardless of the adoption of COVID-19 risk mitigation measures. Ongoing communication between clinical providers and blood collection establishments to project anticipated blood demand during future pandemics may benefit preparedness and ensure adequate blood supplies as healthcare utilization returns to baseline. The FDA's Expanded Access Program (EAP) to COVID-19 convalescent plasma was initiated due to a lack of therapeutics in the early phase of the pandemic.23 Based on the findings of the present study, nearly 1 million COVID-19 convalescent plasma units were collected in the United States in 2020 and 2021. Prior case series conducted during influenza, SARS-CoV-1, and other viral infection outbreaks suggested some therapeutic benefit of convalescent plasma.24-26 Additionally, limited case reports during the early months of the pandemic suggested that convalescent plasma was safe and may also have some survival benefit in COVID-19 patients.27,28 However, widespread implementation of COVID-19 convalescent plasma occurred in the United States without robust clinical trial data on efficacy and, in many cases during 2020, without laboratory-based determination as to whether the transfused plasma products contained sufficient neutralizing antibody levels.29 Only a minority of donors who presented for convalescent plasma donation

intended for study in a clinical trial had high neutralizing antibody titers.29 Characterization of neutralizing antibody levels is complicated by discordance in measurements across different assay platforms.30 While one study suggested benefit with high titer plasma if given prior to mechanical ventilation,31 some clinical trials subsequently reported no morbidity or mortality benefit of convalescent plasma use as a therapeutic for COVID-19, particularly if used later in the clinical course of illness.32-35 Based on the findings presented here, it appears that despite evidence that convalescent plasma had minimal survival benefit outside of limited circumstances, the use of this product continued in 2021, although only 50% of estimated collections in 2021 were transfused in that year. During future pandemics, rapid and robust large scale clinical trials should be prioritized before widespread adoption of convalescent plasma as therapy.

These findings are subject to the following limitations. First, imputation and weighting were used to generate national estimates. Changes in sampling and response rates could affect comparisons to previous NBCUS estimates. Next, similar to previous iterations of the NBCUS, certain hospital types were excluded (e.g., smaller hospitals, military hospitals, and outpatient facilities), potentially resulting in underestimates. Finally, while these findings may help characterize the impact of the adoption of COVID-19 risk mitigation measures on blood supply and use in the United States, the survey did not assess the direct causality of changes in monthly blood collections or transfusions. The impact of the COVID-19 pandemic resulted in reduced blood donations and transfusions in some months during 2020, but no significant decline was seen in annualized data when compared with 2019. Future pandemic preparedness plans should include preparation for ensuring blood donations as the demand for blood products is likely to
continue during public health emergencies.

AUTHOR CONTRIBUTIONS

Catherine Kimber: screening and full text assessment, retrieved full text publications, data extraction, risk of bias assessment, entered data into RevMan and undertook subgroup analyses, performed GRADE assessments, interpreted the results, contributed to the development of the manuscript. Abigail A. Lamikanra: screening and full text assessment, retrieved full text publications, data extraction, risk of bias assessment, performed GRADE assessments, interpreted the results, contributed to the development of the manuscript. Louise J. Geneen: screening and full text assessment, retrieved full text publications, data extraction, risk of bias assessment, entered data into RevMan and undertook subgroup analyses, performed GRADE assessments, interpreted the results, contributed to the development of the manuscript. Josie Sandercock: data extraction, risk of bias assessment, and undertook all metaregression analyses, performed GRADE assessments, interpreted the results, contributed to the development of the manuscript. Carolyn Doree: developed

and performed all search strategies and de-duplication, retrieved full text publications, contributed to the development of the manuscript. Sarah J. Valk: screening and full text assessment, retrieved full text publications, contributed to the development of the manuscript. Lise J. Estcourt: developed the initial idea of the review, developed, wrote, and registered the protocol, interpreted the results, and contributed to the development of the manuscript.

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ORCID

Si-Cong Yu https://orcid.org/0000-0002-7796-9931

Yun-Tai Yao https://orcid.org/0000-0002-9287-2177 *Louise*

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Support- ing Information section at the end of this article.

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GUIDELINES

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Suggested blood donor deferral strategy regarding hepatitis B infections in China

Ling Li 1 2 [1,2] | Rui Wang 3 [3] | Jin Guo 4 [4] | Liu He [5] | Zhengmin Liu [3] | Qianqian Qin [3] | Jing Zhang [3] | Shuo Wu [3] | Liqin Huang [6] | Hongwei Ge [3] | Zhong Liu [2,5] |

[1] Department of Blood Transfusion, The Third People's Hospital of Chengdu, Affiliated Hospital of Southwest Jiaotong University, Chengdu, People's Republic of China.

[2] School of Public Health, Anhui Medical University, Hefei, People's Republic of China.

[3] Blood Screening Laboratory, Beijing Red Cross Blood Center, Beijing, People's Republic of China.

[4] Medical Affairs Department, Beijing Red Cross Blood Center, Beijing, People's Republic of China.

[5] Clinical Transfusion Research Center, Institute of Blood Transfusion, Chinese Academy of Medical Sciences & Peking Union Medical College, Chengdu, People's Republic of China.

[6] Blood Components Procession Department, Shenzhen Blood Center, Shenzhen, People's Republic of China.[1] Department of Anesthesiology, Taizhou Central Hospital (Taizhou University Hospital), Taizhou, China

Correspondence
Hongwei Ge, Blood Screening Laboratory, Beijing Red Cross Blood Center, 100088, Beijing, People's Republic of China.

Email: hwge88@163.com, liuz@ibt.pumc.edu.cn

Abstract

Background:
Hepatitis B virus (HBV) reactivity in individual immunologic and nucleic acid tests (NAT) tests does not represent the true infectious status of the blood donor. This study discusses the use of confirmatory tests to determine when deferral of blood donors is appropriate.

Methods:
HBsAg or HBV NAT reactive samples were confirmed via a neutralisation test. All the HBsAg reactive but neutralisation test negative samples were subjected to further anti-HBc testing. The receiver operating characteristic curve was used to obtain the best threshold value using signal-to-cut-off ratios of two HBsAg enzyme-linked immunosorbent assay reagents.

Results:
Of the 780 HBV reactive samples collected, there were 467 HBsAg reactive but HBV DNA negative samples, of which 65 (13.92%) and 402 (86.08%) were neutralisation test positive and negative, respectively. Of the 402, 91 samples (30% of tested samples) were anti-HBc reactive. HBV DNA positive specimens negative by virus neutralisation were >80% HBcAg positive. A screening strategy was proposed for Chinese blood collection agencies.

Conclusion:
These findings suggest that adopting a screening algorithm for deferring HBV reactive blood donors based on HBsAg and NAT testing followed with HBsAg S/CO consideration and HBcAg testing can be both safe and feasible in China.

Keywords: HBV DNA; HBsAg; ROC; blood donor deferral; neutralisation test.

1 | INTRODUCTION

In 2020, the emergence of the severe acute respiratory syndrome Coronavirus 2 (SARS CoV-2) resulted in significant disruption to the US healthcare system. During March April 2020 and extending through 2020, mitigation measures intended to control virus transmission resulted in reduced utilization of healthcare services.1-3 The Centers for Medicare & Medicaid Services (CMS) issued recommendations to delay all nonessential medical procedures.4 Subsequently, this recommendation along with the implementation of

other mitigation measures resulted in a reduction in patients seeking routine preventive and screening measures, emergency services, surgical procedures, and other hospital-based care.[1-3,5,6]

Severe acute respiratory infections caused by strains of influenza or coronavirus often lead to hospitalisation and sometimes death. Symptomatic infection with SARS CoV-2 (COVID-19) has surpassed the annual global burden of death due to influenza or coronaviruses.[1] Although there are several effective vaccines for COVID-19 therapeutic treatments are still required. Patients particularly at risk are those with disorders that affect the immune system, for example, haematological malignancies or those receiving drugs that suppress an immune response, for example, after organ transplantation.[2,3]

Passive antibody therapies, including monoclonal antibody combinations have proven effective for COVID-19[4] However, the cost of these therapies is prohibitive[5] and new SARS-CoV variants may become resistant to anti-virals developed in response to previous variants.[6] Alternative and affordable responses to emerging strains of virus are needed.

Convalescent plasma (CP) is typically collected from donors with confirmed diagnosis of infection at least 2 weeks after recovery.[7] CP contains neutralising antibodies specific to the infectious agent but may also contain other immune modulators and clotting factors that can be fractionated out to produce hyperimmune-immunoglobulin (hIVIG).[8]

CP containing high titres of polyclonal antibody (Ab), has been used to treat patients hospitalised with respiratory syndromes caused by viral infections. Many studies have been poorly controlled but such series suggested decreased mortality in H1N1 Influenza infections in 1918–1920 and in 2009/2010, SARS-CoV-1 infections in 2003 and most recently COVID-19. Recent systematic reviews lacked data from RCTs and analysis did not consider the titre used within trials.[9] Moreover, there are concerns that CP may cause harm, potentially causing severe transfusion reactions such as transfusion-associated acute lung injury (TRALI) or antibody dependent enhancement of the viral infection.[10]

Prior to the COVID-19 pandemic, studies investigating the effectiveness of CP for viral infections varied in quality and the outcomes reported may not have reflected current international guidelines.[11,12]

2 | OBJECTIVE

To evaluate the evidence for the safety and effectiveness of using convalescent plasma (CP) or hyperimmune immunoglobulin (hIVIG) to treat severe respiratory disease caused by coronaviruses or influenza.

3 | METHODS

The protocol for this review was prospectively registered on PROSPERO (CRD42020176392), and the review was carried out in accordance with Cochrane methodology and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13]

3.1 | Search strategy

We searched multiple electronic databases (MEDLINE, PubMed, The Cochrane Library, Embase, Epistemonikos), ClinicalTrials.gov and WHO International Clinical Trials Registry Platform for ongoing studies, without language restriction, for all publication types on 12th October 2020 (see Appendix A1 in Data S1). We updated our search on 28th June 2021, increasing the number of databases (Cochrane COVID-19 Study Register, Transfusion Evidence Library, Web of Science). We limited the update search to systematic reviews and RCTs due to the significant number of randomised trials available at this point. Ongoing studies identified in our searches were checked on 30th November 2021 and included if published in full (peer-reviewed) by this date. We hand searched reference lists of systematic reviews and included RCTs.[11]

3.2 | Selection criteria

For assessments of effectiveness, we included RCTs comparing transfusion of CP products to any control arm with participants of any age who were admitted to hospital with severe respiratory illness. For assessments of safety, we included all study designs where patients received CP or hIVIG.

Two reviewers (CK, AL, LJG, SV) independently screened title and abstract, and then full-text using Covidence.

Where a publication was in a non-English language, we used electronic translation tools and sought the help of native speakers where appropriate (Appendix A2 in Data S1).

3.3 | Data extraction

Two of four reviewers (CK, AL, LJG, JS) independently extracted data using Covidence and Excel. Reviewers who were involved with any original trials (AL, LE) were not involved in the data extraction for those trials.

Extracted data included: details of study participants (demographic and disease characteristics), details of interventions (including titre, volume, timing of CP/hIVIG), and outcomes.

Outcomes extracted: all-cause mortality up to 30 and 90 days; need for mechanical ventilation (MV) and non-invasive ventilation (NIV) at up to 30 days; duration of MV or NIV; length of hospital stay; length of intensive care unit (ICU) stay; duration of viral detection from admission up to 30 days; transfusion-related serious adverse events (SAEs).

In a deviation from our protocol, we also assessed SAEs up to 30 days due to substantial variability in the way that SAEs were reported. For papers from the 1918 to 1920 influenza pandemic, reporting style was substantially different and, if reported, there was no grading of AEs. We recorded any potential AE described in these `publications.

Where data were not available for a particular timepoint, we extracted data to the nearest possible timepoint. We sought clarifica-

tion from trial authors where necessary.

3.4 | Risk of bias assessment

Two review authors (CK, AL, LJG, JS) independently assessed all eligible studies for risk of bias (ROB), using the Cochrane ROB tools. ROB1 for RCTs[14] and ROBINS-I for observational studies according to the Cochrane Handbook for Systematic Reviews of Interventions.[15] Reviewers who had worked on a trial (AL, LE) did not participate in ROB assessments for those studies.

Observational studies assessed as having "critical" ROB were not included in quantitative analyses.

3.5 | Data analysis

Statistical analyses were undertaken in Review Manager 5.4,[16] R[17] and the *metafor* package in R.[18] For dichotomous outcomes, we used the Mantel-Haenszel method, or Peto OR for rare events. We calculated the pooled risk ratio (RR) with a 95% confidence interval (CI), using the random effects model in RevMan5.[16] We used Tau^2 and I^2 in the assessment of heterogeneity, according to the guidelines laid out in the Cochrane handbook.[19]

We have not combined RCTs and non-RCTs and so have reported the results separately.

We planned to analyse continuous outcomes using mean difference (MD) or standardised mean difference (SMD) where different scales had been used. Continuous outcomes reported as median (IQR/range) could not be meta-analysed or pooled and have been reported narratively within tables.

Information from observational studies was collated in tables and not meta-analysed. Certainty of the evidence (based on meta-analysable data only) was assessed using GRADEPro.[20]

4 | RESULTS

Our search yielded 4826 references (Figure 1 PRISMA flow diagram; for excluded studies see Appendix A4 in Data S1).

4.1 | Study Characteristics

We identified 110 completed studies (Figure 1), including 30 RCTs (four for influenza, n = 578; and 26 for COVID-19 SARS-CoV-2, n = 18 204).[3,7,22-49] There were no RCTs or non-randomised controlled trials identified for MERS or SARS (SARS-CoV-1) (Appendix A Supplementary Table A1 in Data S1). We included 76 non-randomised studies (Appendix B in Data S1). Of these, eleven were controlled studies, of which only two were at less than "critical" ROB[50,51] (Appendix A Supplementary Table A2 in Data S1) We included 67 uncontrolled studies: 12 assessing influenza A; two on MERS-CoV; four on SARS-CoV, and 49 on COVID-19 (SARS-CoV-2).

We also identified 143 ongoing studies (Appendix C) which were either controlled trials or single arm studies, which listed at least one safety outcome in their intended primary or secondary outcomes.

Study size in the quantitative analyses ranged from 29 to 11 555 (34 to 308 for influenza).

Of the four RCTs assessing influenza: two included children (n = 24/236 < 18 years)[39,45]; three RCTs[39,45,47] included pregnant women (3/270 pregnant women).

Of the 26 RCTs and 2 non-randomised studies that assessed COVID-19: one RCT included children (n = 26/11558 < 18 years).[3] Three RCTs[29,34,44] did not report whether they included children. Three RCTs[3,29,35] included pregnant women (n = 36/12575 pregnant women). Eight RCTs[22,24,30-33,36,44] did not report whether they included pregnant women.

4.2 | Comparisons

We identified four comparisons within the data that could be combined in quantitative analysis:

(1) CP versus standard care (SoC) or biologically inactive placebo (saline) (20 RCTs): 19 RCTs compared CP to SoC,[3,7,22-25,27-31,33-36,38,39] one RCT[26] compared SoC with saline placebo, and two retrospective observational studies[50,51] compared CP patients with matched controls;

(2) CP versus biologically active control (FFP or IVIG) (6 RCTs): five RCTs compared CP to non-immune FFP,[40-43,45] and one compared CP with IVIG.[44]

(3) hIVIG versus control (3 RCTs) Of these, two compared hIVIG with SoC,[46,47] one compared hIVIG with saline placebo.[48]

(4) early CP versus deferred CP (1 RCT).[49]

4.3 | Outcomes

We could only extract sufficient data to meta-analyse mortality and serious adverse events. We have presented remaining data from controlled studies in tables (Appendix A, Tables A3-A6 in Data S1). A summary of all outcomes reported is available in Appendix A5.

Most trials did not describe any method for dealing with competing risks when reporting their results. A competing risk is one which prevents the event of interest from occurring. Death is a competing risk for both (time to) mechanical ventilation and (time to) discharge. Devos 2021[28] approached competing risks using competing events analysis[52] to obtain cause-specific hazard ratios (HR). REMAP-CAP[30] used ordinal logistic regression by assigning each participant a category labelled with the number of ventilator-free days up to 21 days, with people who died up to day 90 being assigned —1, people who were on MV at

5 | DISCUSSION

The objective of this review was to determine the safety and effectiveness of CP or hIVIG from CP to treat patients with serious respiratory disease due to influenza or coronavirus infection. In order to increase the relevance of our findings to the COVID-19 pandemic we

used the core outcome set[63] for assessing treatments for patients infected with SARS-CoV-2. We aimed to use high-quality evidence from RCTs to assess safety and effectiveness. We also used all other study designs to describe serious harms reported following transfusion with CP or hIVIG.

5.1 | Main findings

We were able to meta-analyse 32 studies for our primary outcome of 30-day mortality (30 RCTs and 2 non-RCTs). We found little evidence of any difference between the groups in either benefits or harms for patients hospitalised with a severe viral respiratory infection requiring hospital admission. Most evidence was of low or very-low certainty. The only high-certainty evidence was for the COVID high-titre sub- group in the outcome all-cause mortality at up to 30 days in CP versus SoC (Table 1).

Adverse events were variably reported. No RCTs reported a high number of transfusion-related AEs (proportion 0% to 5.67%[22-24,26,27,31,35,38,39,43,44,46,47]) (very-low to low certainty evidence). There was no evidence of an increase in harms compared with standard plasma.

5.2 | Quality (certainty) of the evidence

Where meta-analysis was possible, we used GRADE to assess our cer- tainty in the result (Table 1). Certainty in the evidence was assessed as very-low to low certainty for all outcomes apart from mortality data in the comparison CP versus standard care.

Evidence was downgraded for serious ROB (lack of blinding, baseline imbalance, randomisation processes, missing data and unclear reporting of outcomes) and imprecision (wide confidence intervals around the effect estimate, and small sample sizes for the outcome of interest). Some of the sources of potential bias (such as patient and personnel blinding) would be hard to overcome in future trials due to the issues in finding an ethical control infusion: even saline is problem- atic, with the risk of volume overload, and ease with which it can be differentiated from plasma.

SAEs were also downgraded for inconsistency as the heterogene- ity was significant between studies, this is likely to be due to the vari- ation in reporting of the SAEs. This may be in part due to differing regulatory environments and different classifications of CP, requiring varying levels of AE reporting including the need to use a grading system (e.g., MedDRA[64]).

We included lower-level evidence for the assessment of safety outcomes. However, we were unable to perform quantitative analyses, and so have only presented these data as reported in Appendix B in Data S1.

There were very few endpoints reported consistently enough for meta-analysis. The difficulty in defining endpoints, especially time-to-event endpoints,[65] is discussed further in Appendix A6 in Data S1.

5.3 | Strengths and Limitations of this review

We have attempted to minimise potential bias in the review process, using Cochrane methods and PRISMA guidelines for reporting. We conducted a comprehensive search: searching data sources to ensure that all relevant studies would be captured, using multiple databases and reference lists of included studies. We included conference proceedings and included a search of clinical trial registries. We also attempted to contact authors for additional data and for clarification of their data.

There were no restrictions for the language in which the paper was originally published. We pre-specified outcomes prior to analysis and have explained the rationale for including one additional outcome (any SAEs).

We undertook duplicate screening, data extraction, and assessment of bias. Additionally, the clinical advisor (LE) was consulted for disagreements, or need for clarification.

The limitations of this review mostly arose due to gaps in the evidence base, which are discussed more fully in the next section.

5.4 | Interpretation and context

A recent analysis of individual patient data (IPD) pooled from eight RCTs[9] IPD reported an OR for mortality of 0.85 at day 28 (95% credible interval, 0.62 to 1.18; posterior probability of OR <1 of 84%). These results are broadly comparable and in agreement with our own aggregate analyses for 30-day mortality. However, it should be noted that the IPD analysis included two RCTs[66,67] published after our 30th November 2021 cut-off, but did not include the two largest RCTs of CP RECOVERY[3] and REMAP-CAP[30] which we have analysed, and which together contribute 83% of sample size contributing to our analysis of 30-day mortality for CP versus SoC.

A limitation of the current evidence base is that of the 30 RCTs and two non-randomised studies included in our meta-analysis, 26 studies (24 RCTs) excluded children and 16 RCTs excluded pregnant women, with 1 RCT[39] admitting pregnant women only on the second round of recruitment. Given that children and pregnant women are both considered to be at increased risk of serious disease and death from many severe respiratory viral infections, their exclusion from trials is concerning. Of the 144 ongoing studies we identified, most trials will exclude children and pregnant women. Many ongoing studies have an upper age cut-off (of 65, 70 or 80 years), despite older age being one of the biggest risk factors for COVID-19.

The precision of our meta-analysis was affected by the different titres of CP-neutralising antibodies between trials (Table A1 in Data S1). We tried to address this by subgrouping studies based on the CP-titre reported, and whether it was considered high enough according to FDA criteria (see Appendix A3 in Data S1). However, several studies used local assays that could not be correlated with an FDA reference method. Since we conducted our first search, several variants of

SARS-CoV-2 have arisen worldwide and may require much higher anti- body titres measured using ELISA assays.[68] Much higher titre CP, from vaccinated convalescent donors, may be active against future variants[69] indicating that new COVID CP trials should aim to use very high titre CP standardised using internationally recognised methods.

5.5 | Implications for research and practice

There is currently no evidence for a benefit of CP in an unselected population of patients hospitalised with coronaviruses or influenza. It is likely that the titre of the CP and the immune response of the recip- ient may both be important factors affecting response to treatment.

Studies should use CP of a high enough titre to elicit a biological response, and report the actual titre used as well as the minimum as described in the protocol. Matching variants between donor and recipient may not be feasible, but viral variants circulating at the time of collection of plasma and during the study should be recorded.

Studies should assess and publish antibody status (seropositivity) at baseline in both intervention and control groups, and identify and

report immunocompromised patients separately, to establish whether certain groups of patients are more likely to benefit from this intervention.

There are difficulties in designing truly blinded RCTs of CP or hIVIG (see Reference 73 for review). There are ethical problems with using a placebo which is assumed to have no clinical benefit, but has known harms.[74] One RCT[26] used a saline placebo, with potential concerns about volume overload, and six RCTs used a biologically active control, (FFP in 5 RCTs,[40-43,45] and IVIG in one[44]) which raises additional concerns about transfusion reactions.

Unless reported explicitly by investigators, it was difficult to distinguish the AEs experienced following transfusion from the symptoms of severe respiratory disease.[75] This limited the number of RCTs that we could include in our meta-analysis of AEs due to transfusion. There was also substantial variability in the way that AEs were recorded and reported in these studies. It was not always possible to determine the severity of AEs, and different studies used different criteria for SAEs. In some cases, it was hard to determine if SAE reporting was per event or per patient, making it extremely difficult to compare rates of AEs between studies. Blood components in the UK are not classified as medicines and so require a different grading system for reporting AEs to countries that classify CP as a medicine, e.g. Germany. A consensus on how AEs associated with blood products are reported in RCTs would help to address this problem.

6 | CONCLUSION

This review has highlighted several issues regarding study design and reporting which should be addressed in current and future research. A minimum titre should be established and ensured for a positive biological response to the therapy. Further research on the impact of CP/hIVIG in patients who have not produced antibodies to the virus prior to hospital admission or who are immunocompromised would be useful to target therapies at groups who will potentially benefit the most.

This pattern is consistent with the observed impacts of the pandemic on the healthcare system overall, in which patients initially deferred seeking medical care during the early COVID-19 risk mitigation period but subsequently resumed healthcare utilization. The findings observed in the present study are consistent with an analysis of data from the National Healthcare Safety Network Hemovigilance Module, which found a statistically significant decrease in RBC transfusions during March-April 2020, with subsequent return to baseline.8 This decline is broadly consistent with our findings, but the decrease early in the pandemic was negated throughout the rest of the year, suggesting a significant recovery in blood utilization. Interestingly, our results show that the reduced RBC transfusions during the early risk mitigation phase of the pandemic were not seen in states with high COVID-19 burden at that time. Additional research is required to determine reasons for this observation, but the findings suggest that individuals may have continued to seek therapies in some regions regardless of the adoption of COVID-19 risk mitigation measures. Ongoing communication between clinical providers and blood collection establishments to project anticipated blood demand during future pandemics may benefit preparedness and ensure adequate blood supplies as healthcare utilization returns to baseline. The FDA's Expanded Access Program (EAP) to COVID-19 convalescent plasma was initiated due to a lack of therapeutics in the early phase of the pandemic.23 Based on the findings of the present study, nearly 1 million COVID-19 convalescent plasma units were collected in the United States in 2020 and 2021. Prior case series conducted during influenza, SARS-CoV-1, and other viral infection outbreaks suggested some therapeutic benefit of convalescent plasma.24-26 Additionally, limited case reports during the early months of the pandemic suggested that convalescent plasma was safe and may also have some survival benefit in COVID-19 patients.27,28 However, widespread implementation of COVID-19 convalescent plasma occurred in the United States without robust clinical trial data on efficacy and, in many cases during 2020, without laboratory-based determination as to whether the transfused plasma products contained sufficient neutralizing antibody levels.29 Only a minority of donors who presented for convalescent plasma donation

intended for study in a clinical trial had high neutralizing antibody titers.29 Characterization of neutralizing antibody levels is complicated by discordance in measurements across different assay platforms.30 While one study suggested benefit with high titer plasma if given prior to mechanical ventilation,31 some clinical trials subsequently reported no morbidity or mortality benefit of convalescent plasma use as a therapeutic for COVID-19, particularly if used later in the clinical course of illness.32-35 Based on the

findings presented here, it appears that despite evidence that convalescent plasma had minimal survival benefit outside of limited circumstances, the use of this product continued in 2021, although only 50% of estimated collections in 2021 were transfused in that year. During future pandemics, rapid and robust large scale clinical trials should be prioritized before widespread adoption of convalescent plasma as therapy.

ORCID

Si-Cong Yu https://orcid.org/0000-0002-7796-9931

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28. i

SUPPORTING INFORMATION

Additional supporting information can be found online in the Support- ing Information section at the end of this article.

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ORIGINAL ARTICLE

TRANSFUSION MEDICINE WILEY

Analysis of a 5-year, evidenced-based, rational blood utilisation project in a South African regional hospital

Robert Wise[1,2,3] | Kirsten Hood[4] | David Bishop[1] | Gary Sharp[5] | Reitze Rodseth[6,7] | Saving Blood Saving Lives Working Group

[1]Discipline of Anaesthesiology and Critical Care, School of Clinical Medicine, University of KwaZulu-Natal, Durban, South Africa

[2]Adult Intensive Care Unit, John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

[3]Faculty Medicine and Pharmacy, Vrije Universiteit Brussel (VUB), Brussels, Belgium

[4]Department of Anaesthesia and Perioperative Medicine, Groote Schuur Hospital and University of Cape Town, Cape Town, South Africa

[5]Statistics Department, Nelson Mandela University, South Campus, Port Elizabeth, South Africa

[6]Department of Anaesthetics, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Pietermaritzburg, South Africa

[7]Netcare Limited, Sandton, South Africa

Correspondence
Robert Wise, Discipline of Anaesthesiology and Critical Care, School of Clinical Medicine, University of KwaZulu-Natal, 718 Umbilo Road (Room 420), Durban, South Africa.
Email: robwiseicu@gmail.com

Abstract

Background: Blood products are a lifesaving but limited resource, particularly in resource-limited settings. Evidence-based transfusion criteria tailored to local hospitals have shown great promise in reducing costs, minimising shortages, and ameliorating the morbidity and mortality associated with liberal blood product usage. We implemented the "Saving Blood, Saving Lives" project to: promote responsible blood product use and reduce blood product ordering inefficiencies and expenditure.

Methods: A comprehensive change management programme, preceded by 3 months of clinical department consultation and training, was implemented. A new evidence-based protocol for blood product utilisation was developed, together with an accountability form. This form was used in monthly audit meetings to refine policies, identify new problems, improve communication, and to drive hospital staff accountability and training. The primary measure of the programme's success was the change in the number of red cell concentrate units ordered.

Results: Project implementation required minimal time and no additional budget or staff. Annual red cell concentrate usage reduced from 7211 units in year one to 4077 units in year 5 ($p < 0.001$). Similar reductions were seen in freeze-dried plasma and platelet usage, as well as administrative costs. Total project saving, adjusted to baseline admission numbers, amounted to over R46 million ($2.5 million).

Conclusions: As a change management programme centred the "Saving Blood, Saving Lives" project, was able to significantly reduce blood product-related administration and expenditure by implementing evidence-based transfusion criteria. The programme is simple, replicable and cost effective, making it ideally suited for use in resource-constrained environments.

KEYWORDS
patient blood management, South Africa, transfusion

1 | INTRODUCTION

Blood products are a lifesaving but costly and limited resource. Their careful management is critical to all healthcare systems and more so

The members of Saving Blood Saving Lives Working Group are listed in Appendix A.

in resource-limited settings, where demand may often exceed supply.[1] The last two decades have yielded significant insight into the timing and manner of blood product administration, with most guidelines advocating a restrictive transfusion strategy. New guidelines aim to decrease unnecessary use of blood products and protect patients against the risks of unnecessary transfusions.[2,3] Transfusions carry numerous risks including increasing length of hospital stay, morbidity and mortality.[4] Authors have advised that low- and middle-income countries (LMIC) establish systems to encourage the appropriate and consistent use of blood products according to evidence-based principles.[5]

In South Africa, blood products are supplied by the South African National Blood Service (SANBS) and the Western Cape Blood Service, which require 3500 donations a day to maintain an adequate national supply. The country has a heavy burden of trauma, HIV, chronic medical conditions and a rapidly growing population. The donor pool is both ageing and is heavily reliant on university students, often resulting in inadequate blood stock.[6]

Harry Gwala Regional Hospital (formerly Edendale Hospital) has over 900 beds and serves a population of 1.4 million people in KwaZulu-Natal, South Africa. In 2012, the hospital was identified as one of the worst provincial performers in terms of rational usage and wastage of blood products. The hospital's poor performance in rational blood product utilisation, together with the national pressure on available blood product resources, formed the basis for the motivation behind the development of the "Saving Blood, Saving Lives" patient blood management system.[7]

Various evidence-based approaches to blood product utilisation have been applied in high-income country (HIC) healthcare settings.[8,9] However, these strategies require technological infrastructure, expertise, funding, and staffing that is not available in most resource-limited environments. The objective of the "Saving Blood, Saving Lives" project was to improve performance at the hospital by implementing a management system that would encourage rational blood product utilisation, provide education, support behavioural change, and enable continuous clinical auditing without increasing cost or requiring additional staff.

The system aimed to achieve:

i. Rational blood product utilisation by improving responsible blood product usage, thus saving blood products for appropriate clinical situations and avoiding complications associated with unnecessary transfusions.
ii. Improved blood bank services by decreasing the number of unnecessary blood products and tests ordered, reducing waste, laboratory work and provincial system inefficiencies.
iii. Financial efficiency by reducing unnecessary blood product expenditure.

In this article, we describe this system and its implementation and conduct a retrospective analysis comparing blood product utilisation and costs before and after implementation. We hypothesised that we would see significant reductions in both metrics. We conducted this analysis over a 5-year period to assess the durability and sustainability of the implemented system.

2 | METHODS

2.1 | Strategy and system outline

A new evidence-based hospital protocol for blood product utilisation was drafted. All key role-players (both clinical and non-clinical) were involved to ensure every discipline and department in the hospital had the opportunity to debate and contribute to the new protocol and system. This process facilitated knowledge translation and encouraged departmental buy-in. An innovative system using a blood accountability form was developed (Figure 1). This additional form would accompany every blood product request and was designed to guide the medical practitioner's decision-making and facilitate audit of decision-making processes. It captured basic demographic details, the reason for ordering the blood product/s based on evidence-based criteria, whether there were any special clinical considerations, and the names of those involved in the decision-making. This form enabled ongoing clinical governance of the system, captured transfusion indications, and was used to hold healthcare practitioners accountable for their decisions. This form was regularly revised and updated with clinician feedback and as new evidence emerged from the literature.

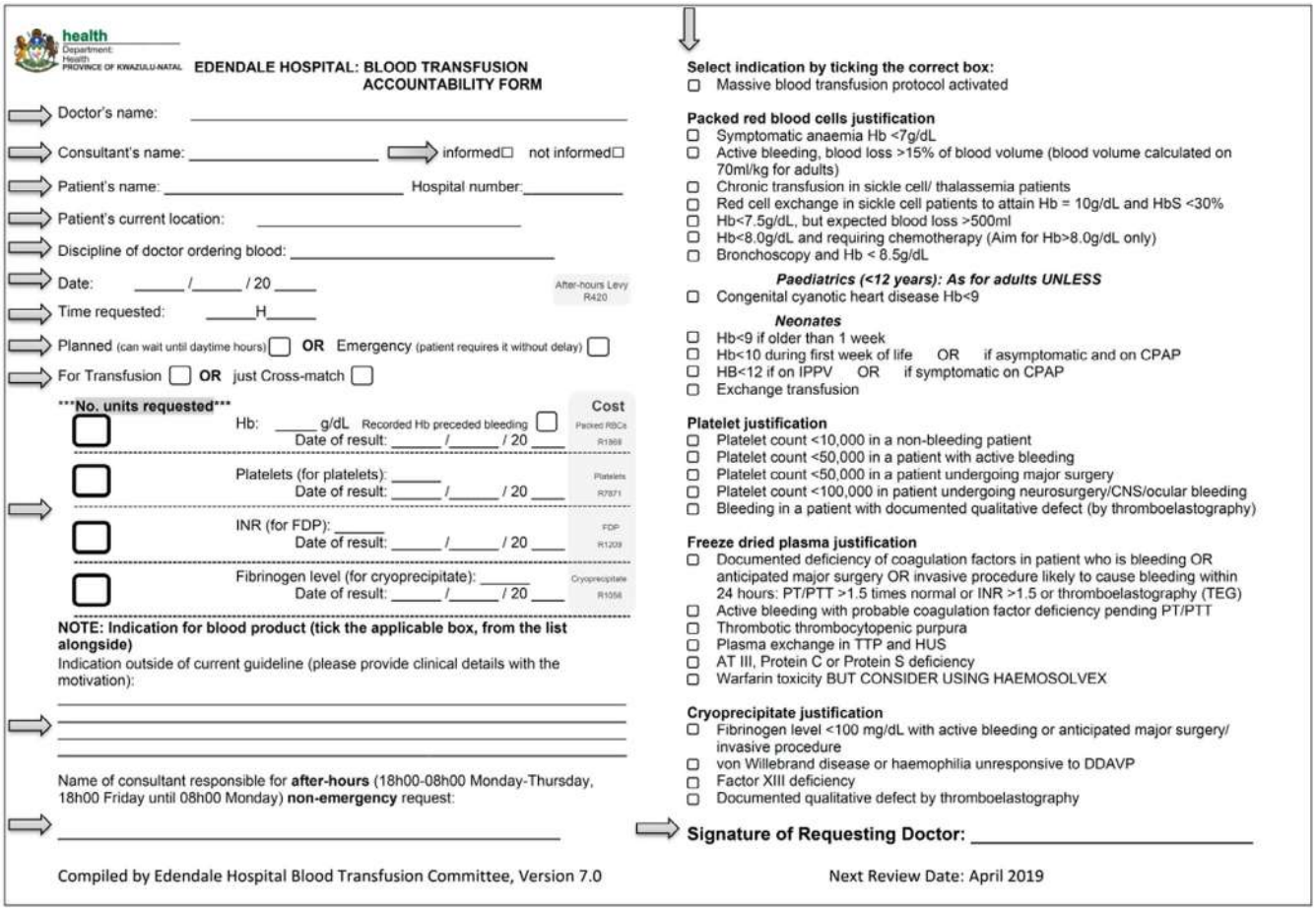
After finalisation of the protocol and accountability form, a pre-recorded video presentation was produced. The 12-minute-long presentation detailed the need for change and outlined the new management system. It was regularly shown at departmental meetings and to all new staff joining the hospital, thereby ensuring clear and consistent communication. The Hospital Transfusion Committee (HTC) was revitalised with support from hospital management. The committee was responsible for ongoing clinical governance and auditing, addressing new publications and research, involving other stakeholders and challenging previously conceived blood product use ideas that were not evidence-based.

2.2 | Implementation

Implementation of the project was preceded by 3 months of preparation, during which clinical leadership of departments were given time to provide input on the new protocol. Education regarding the new blood product utilisation protocol was completed for all teams involved with prescribing and administering blood products. The following principles were prioritised:

a. Inclusion—involvement of all medical, support and managerial structures within the hospital, to create a culture of responsible blood product usage.
b. Transparency—regarding goals, implementation plans and progress, and plans for allocation of savings.
c. Flexibility—willingness to change with new information, evidence and ideas.

The project was launched in April 2014, and specific areas of rational blood product utilisation were targeted as these were deemed easier to correct. These included the use of red cell concentrate



health
Department: Health
PROVINCE OF KWAZULU-NATAL

EDENDALE HOSPITAL: BLOOD TRANSFUSION ACCOUNTABILITY FORM

Doctor's name: _____

Consultant's name: _____ informed☐ not informed☐

Patient's name: _____ Hospital number: _____

Patient's current location: _____

Discipline of doctor ordering blood: _____

Date: _____/_____/ 20 ____ After-hours Levy R420

Time requested: _____H_____

Planned (can wait until daytime hours)☐ **OR** Emergency (patient requires it without delay)☐

For Transfusion☐ **OR** just Cross-match☐

No. units requested Cost

☐ Hb: _____g/dL Recorded Hb preceded bleeding☐ Date of result: _____/_____/ 20 ____ Packed RBCs R1968

☐ Platelets (for platelets): _____ Date of result: _____/_____/ 20 ____ Platelets R7871

☐ INR (for FDP): _____ Date of result: _____/_____/ 20 ____ FDP R1209

☐ Fibrinogen level (for cryoprecipitate): _____ Date of result: _____/_____/ 20 ____ Cryoprecipitate R1056

NOTE: Indication for blood product (tick the applicable box, from the list alongside)

Indication outside of current guideline (please provide clinical details with the motivation):

_____

_____

_____

_____

Name of consultant responsible for **after-hours** (18h00-08h00 Monday-Thursday, 18h00 Friday until 08h00 Monday) **non-emergency** request:

_____

Select indication by ticking the correct box:

☐ Massive blood transfusion protocol activated

Packed red blood cells justification

☐ Symptomatic anaemia Hb <7g/dL
☐ Active bleeding, blood loss >15% of blood volume (blood volume calculated on 70ml/kg for adults)
☐ Chronic transfusion in sickle cell/ thalassemia patients
☐ Red cell exchange in sickle cell patients to attain Hb = 10g/dL and HbS <30%
☐ Hb<7.5g/dL, but expected blood loss >500ml
☐ Hb<8.0g/dL and requiring chemotherapy (Aim for Hb>8.0g/dL only)
☐ Bronchoscopy and Hb < 8.5g/dL

Paediatrics (<12 years): As for adults UNLESS

☐ Congenital cyanotic heart disease Hb<9

Neonates

☐ Hb<9 if older than 1 week
☐ Hb<10 during first week of life OR if asymptomatic and on CPAP
☐ HB<12 if on IPPV OR if symptomatic on CPAP
☐ Exchange transfusion

Platelet justification

☐ Platelet count <10,000 in a non-bleeding patient
☐ Platelet count <50,000 in a patient with active bleeding
☐ Platelet count <50,000 in a patient undergoing major surgery
☐ Platelet count <100,000 in patient undergoing neurosurgery/CNS/ocular bleeding
☐ Bleeding in a patient with documented qualitative defect (by thromboelastography)

Freeze dried plasma justification

☐ Documented deficiency of coagulation factors in patient who is bleeding OR anticipated major surgery OR invasive procedure likely to cause bleeding within 24 hours: PT/PTT >1.5 times normal or INR >1.5 or thromboelastography (TEG)
☐ Active bleeding with probable coagulation factor deficiency pending PT/PTT
☐ Thrombotic thrombocytopenic purpura
☐ Plasma exchange in TTP and HUS
☐ AT III, Protein C or Protein S deficiency
☐ Warfarin toxicity BUT CONSIDER USING HAEMOSOLVEX

Cryoprecipitate justification

☐ Fibrinogen level <100 mg/dL with active bleeding or anticipated major surgery/ invasive procedure
☐ von Willebrand disease or haemophilia unresponsive to DDAVP
☐ Factor XIII deficiency
☐ Documented qualitative defect by thromboelastography

Signature of Requesting Doctor: _____

Compiled by Edendale Hospital Blood Transfusion Committee, Version 7.0

Next Review Date: April 2019

FIGURE 1 Example of an earlier blood transfusion accountability form (April 2019).

(RCC), type and screen testing, after-hours levies, and the use of freeze-dried plasma (FDP). Criteria for blood product use (RCC, FDP, platelets and cryoprecipitate) were adjusted according to published evidence (Table 1). Although recent evidence suggests a symptomatic haemoglobin trigger of 7 g/dL for most patients,[10] the accountability form allowed for deviation from the transfusion criteria in certain clinical situations when adequate explanation could be provided.

The accountability form went through multiple design and content iterations after pilot runs during the preparation period. Importantly, a gatekeeper system for the accountability forms was enabled via the SANBS blood bank, whose inclusion in all processes before and during implementation of the project was essential. Imperatively, the standard SANBS blood product request forms would not be accepted without a compulsory corresponding accountability form. Thus, uptake of the use of the form was 100 per cent (forms were kept at the blood bank for those that forgot to pre-emptively complete one). Monthly HTC meetings facilitated the auditing of accountability forms and the review of SANBS statistics. These meetings helped refine policies, identify new problems and improve communication between departments. The HTC consisted of a specialist from each clinical department, and representatives from pharmacy, nursing, hospital management and the blood bank. The accountability forms were analysed by a committee member prior to the meeting. The findings were presented in a spreadsheet and deviations from the protocol were discussed. Each member of the committee would feedback the results (together with the analysed forms) to their respective departments. Accountability, training of individuals deviating from protocol and feedback to hospital staff were key performance improvement measures applied to problems identified through the accountability forms and progress assessments. Nurses played an important role as gatekeepers to accessing FDP after-hours, and distribution and printing of accountability forms.

2.3 | Outcomes

We aimed to conduct a retrospective analysis comparing blood product utilisation and costs before and after implementation of the programme. The primary outcome was the change in the historical baseline number of RCC ordered and the ensuing years after implementing the programme. Secondary outcomes included the number of FDP, platelets, and cryoprecipitate used, the number of after-hours and emergency crossmatch levies charged, and the number of transfusion crossmatch and type and screen orders. Data included number of units requested, cost per unit, basic demographic details, as well as information pertaining to the reason for ordering the blood product/s

TABLE 1 Harry Gwala Regional Hospital transfusion criteria.

Red cell concentrate justification
Symptomatic anaemia Hb <7 g/dL
Active bleeding, blood loss >15% of blood volume (TBV: 70 mL/kg for adults)
Chronic transfusion in sickle cell/thalassemia patients
Red cell exchange in sickle cell patients to attain Hb = 10 g/dL and HbS <30%
Hb <7.5 g/dL, but expected blood loss >500 mL
Hb <8.0 g/dL and requiring chemotherapy (Aim for Hb >8.0 g/dL only)
Bronchoscopy and Hb <8.5 g/dL
Paediatrics (<12 years): as for adults UNLESS
Congenital cyanotic heart disease Hb <9 g/dL
Neonates
Hb <9 g/dL if older than 1 week
Hb <10 g/dL during first week of life OR if asymptomatic and on CPAP
HB <12 g/dL if on IPPV OR if symptomatic on CPAP
Exchange transfusion
Platelet justification
Platelet count <10 × 10^9/L in a non-bleeding patient
Platelet count <50 × 10^9/L in a patient with active bleeding
Platelet count <50 × 10^9/L in a patient undergoing major surgery
Platelet count <100 × 10^9/L in patient undergoing neurosurgery/CNS/ocular bleeding
Bleeding in a patient with documented qualitative defect (by TEG)
Freeze dried plasma justification
Documented deficiency of coagulation factors in patient who is bleeding OR anticipated major surgery OR invasive procedure likely to cause bleeding within 24 h: PT/PTT >1.5 times normal OR INR >1.5 OR abnormal TEG
Active bleeding with probable coagulation factor deficiency pending PT/PTT
Thrombotic thrombocytopenic purpura
Plasma exchange in TTP and HUS
AT III, Protein C or Protein S deficiency
Warfarin toxicity but consider using Haemosolvex[a]
Cryoprecipitate justification
Fibrinogen level <100 mg/dL with active bleeding or anticipated major surgery/ invasive procedure
von Willebrand disease or haemophilia unresponsive to DDAVP
Factor XIII deficiency
Documented qualitative defect by TEG (decreased alpha angle)

Abbreviations: AT III: antithrombin III; CNS: central nervous system; CPAP: continuous positive airway pressure; DDAVP: desmopressin; FDP: freeze-dried plasma; Hb: haemoglobin; HbS: haemoglobin S; HUS: hemolytic uremic syndrome; INR: international normalised ratio; IPPV: intermittent positive pressure ventilation; PT: prothrombin time; PTT: partial thromboplastin time; TBV: total blood volume; TEG: thromboelastography; TTP: thrombotic thrombocytopenic purpura.

[a]Haemosolvex is a reconstituted prothrombin complex concentrate, produced by the National Blood Institute. Each vial contains factor IX 500iu, factor II >400iu, factor VII >65iu and factor X >400iu.

based on evidence-based criteria, if there were any special considerations, who was involved in the decision-making, and when the decision was made.

Data for the 12 months before implementation of the project (April 2013–March 2014) were used as the comparator baseline (Year 0). Data were collected prospectively for 5 years after implementation of the project, with the last year of data collection being April 2018–March 2019 (Year 5). The number of units used, and unit costs were standardised according to the number of hospital admissions in each year relative to the baseline Year 0. Savings were calculated relative to Year 0 prices and adjusted for inflation.

2.4 | Statistical analysis

Graphical and numerical descriptive statistics were reported to demonstrate trends, whilst inferential statistics were used to assess significance of findings. For all analyses, a *p*-value <0.05 was defined as

statistically significant. The sample size was determined by the amount of data available for the pre-defined period. The overarching assumption of these analyses was that all variables were normally distributed, and the Shapiro–Wilks test was used to confirm this (see Table S1).

Ethical approval for the study was obtained from the SANBS Human Ethics Research Committee (clearance certificate 2015/27) and the KwaZulu-Natal Department of Health, Health Research Committee (KZ_2015RP26_313).

3 | RESULTS

Over the 5-year period, there was a significant reduction in the primary study outcome—the number of RCC and blood bank levies (Figure 2). The same reduction can be seen for the secondary outcomes—use of platelets (Figure 2), cryoprecipitate and FDPs (Figure 3). RCC use and blood bank levies were reduced in the first year of the programme and continued to do so over the study period. Both platelet and FDP use were reduced in the first year of the programme but appeared to stabilise over the next 4 years. Over the 5-year period there was a progressive increase in the amount of cryoprecipitate used (Figure 3).

One-way ANOVA of the mean monthly orders (RCC, platelets, FDP, cryoprecipitate and number of levies) across the six time periods (Year 0 to Year 5) identified that at least one of these periods differs statistically from the other periods for all five variables (F-statistic RCC = 58.75, $p < 0.001$; platelets = 10.95, $p < 0.001$; cryoprecipitate = 2.96, $p < 0.001$; FDP = 4.85, $p < 0.001$; number of levies charged = 289.8, $p < 0.001$).

Using Tukey's method, *post hoc* comparison of the mean monthly orders of RCC found that Years 1–5 all differed from Year 0. This is observed in Figure 4 where a plot of the monthly mean differences for the periods of year one to five minus year zero is shown. All five plots indicate that the 95% confidence mean differences are well below zero, thereby indicating significant differences from year zero (see Figure S1). Similar *post hoc* analyses for platelets, cryoprecipitate, FDP and number of levies charged were conducted and are reported in the Supporting Information.

The annual impact on blood product expenditure and levy cost is shown in Figures 5 and 6, respectively. The data and projections can be found in Tables S2 and S3. Figures 5 and 6 illustrate that there is a noticeable difference between the patterns observed in the base period versus the other five yearly periods, lending support to the benefit of the project.

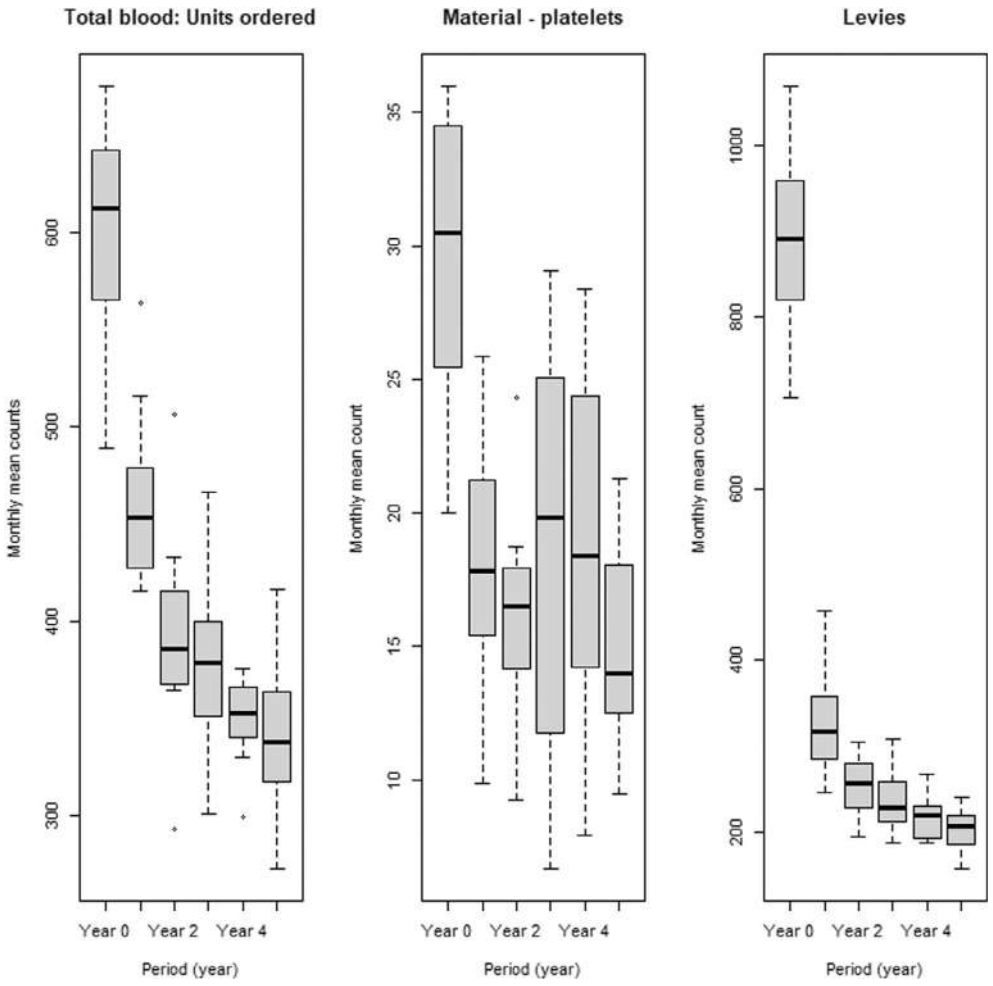


FIGURE 2 The average number of orders received each year for red cell concentrate, platelets and levies charged, over the 5-year period assessed.

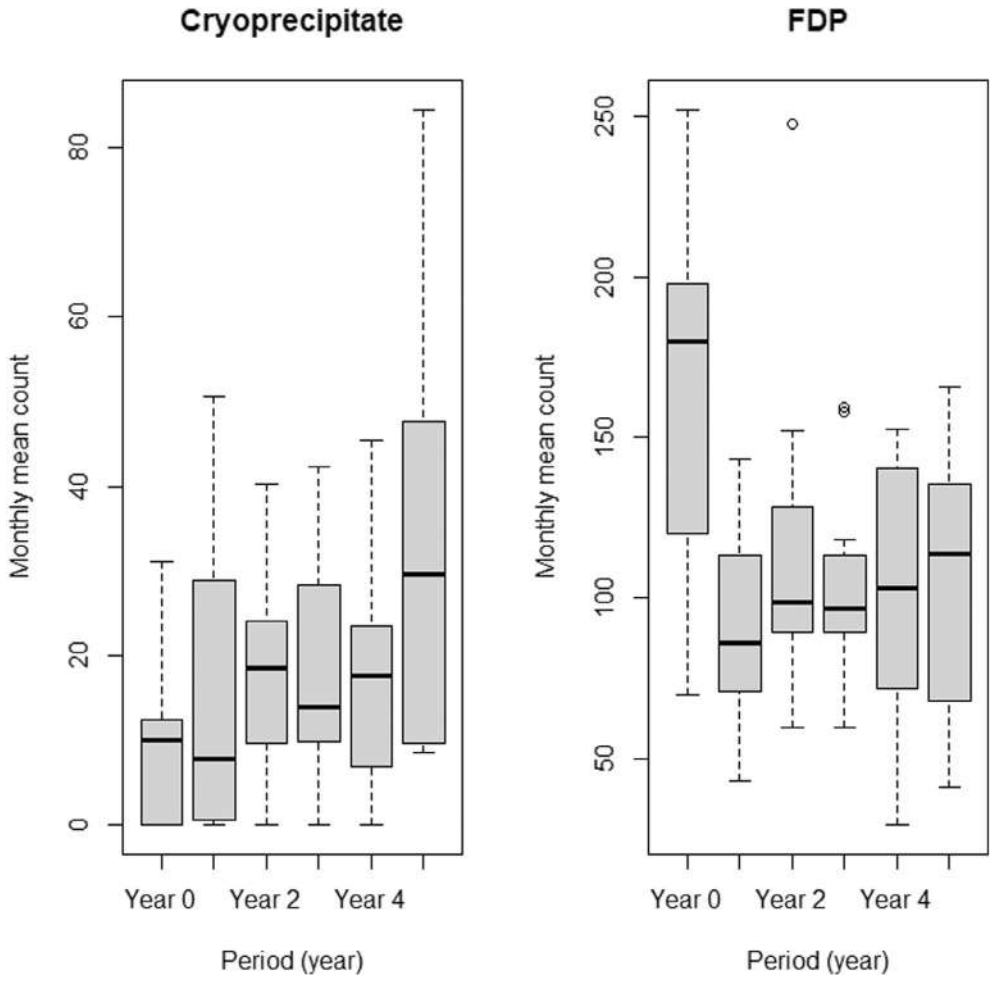


FIGURE 3 The average number of orders received each year for cryoprecipitate (D) and freeze-dried plasma (E), for the 5-year period assessed.

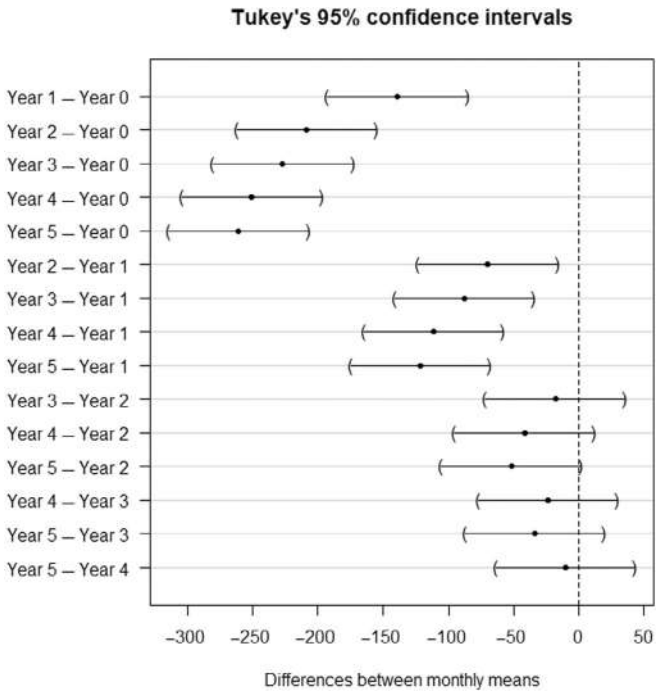


FIGURE 4 95% Confidence interval plot for comparison of means for red cell concentrate.

The number of products ordered annually over the study period is summarised in Table 2, showing a reduction in three of the four blood products over the study period (see Figure S2). FDP and platelet use plateaued whilst cryoprecipitate use increased due to practise changes.

We also conducted analysis on secondary outcomes linked to administrative costs and tests, such as after-hours levies, emergency crossmatch costs (as opposed to standard crossmatch) and type and screen test costs (Table 3). After-hours levy orders reduced from 4102 to 1339, emergency crossmatch orders from 1039 to 787, standard crossmatch orders from 1591 to 252, and type and screen orders from 3971 to 40 between year 1 and 5, respectively.

The total 5-year project savings, when adjusted to baseline admission numbers and for inflation, amounted to over R46 000 000 (USD: $2 458 000)—an overall saving of 44% compared with the forecast expenditure based on Year 0 ordering rates (see Table S3). Further cost details are provided in Tables S4–S6. Cost savings are likely underestimated due to unaccounted labour cost savings associated with the blood bank staff, doctors and nurses, as well as expenses for supplies, such as reagents, and possible decreased hospital stays that were not accounted for in the calculations. During the study period, institutional inpatient mortality rates were unchanged (see Table S7).

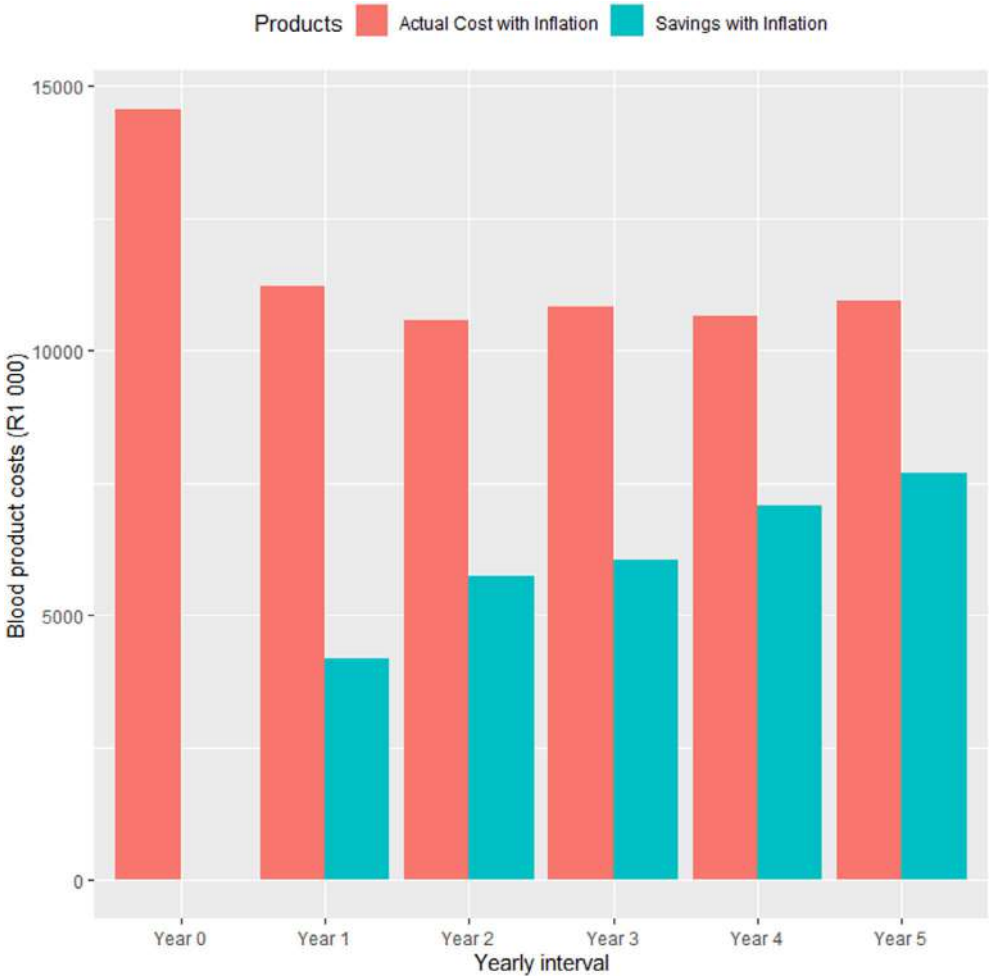


FIGURE 5 Blood product cost savings (2013–2018).

4 | DISCUSSION

Blood products are expensive, scarce and over-prescribed in many under-resourced countries, including South Africa. We introduced an education and accountability-based system designed to reduce unnecessary blood transfusions by encouraging the use of restrictive evidence-based criteria aimed at improving patient safety and outcomes.[7] This analysis has demonstrated that the 'Saving Blood, Saving Lives' system resulted in a significant reduction in blood product utilisation, administrative costs and overall expenditure. These benefits persisted over time and were contingent on a functional and motivated blood transfusion committee, with hospital managerial support.

Patient blood management systems describe a patient-centred approach to addressing anaemia, coagulopathy and the need for blood transfusions.[11,12] This broad approach is based on three 'pillars',[8] namely:

1. Optimization of haematopoiesis and red cell mass
2. Minimising blood loss and bleeding
3. Optimising physiological tolerance of anaemia

A key component of these systems is rational blood usage, which ensures the appropriate use of blood transfusions in a context-sensitive manner. We developed hospital transfusion criteria based on current evidence and adopted the principle that restrictive transfusion thresholds should generally be applied, unless there was specific evidence to suggest otherwise.[10] We also encouraged single-unit transfusions, with assessment of haemoglobin levels between units, unless lifesaving, large volume resuscitation was required.[13] These institutional guidelines were discussed regularly in multidisciplinary meetings with regular updates based on changing evidence. These monthly forums established consensus on guidelines, and measured ongoing compliance with hospital policies, in collaboration with the SANBS as a gatekeeper to regulate blood product usage.

Patient blood management systems have been successfully introduced in HIC settings.[14] These programmes have adopted similar strategies, where a system is applied at a local level, and subsequently applied at national level. These approaches have been more successful in HICs, despite access to blood products being easier, and LMICs in general have failed to replicate these successes.[15,16] Differing staffing ratios and resource-limitations require LMICs to implement approaches that can be incorporated into the daily workflow of healthcare professionals without a significant time–cost, and which do not rely on functional haematology services or on-site expertise. Our system required the completion of a single additional form, and

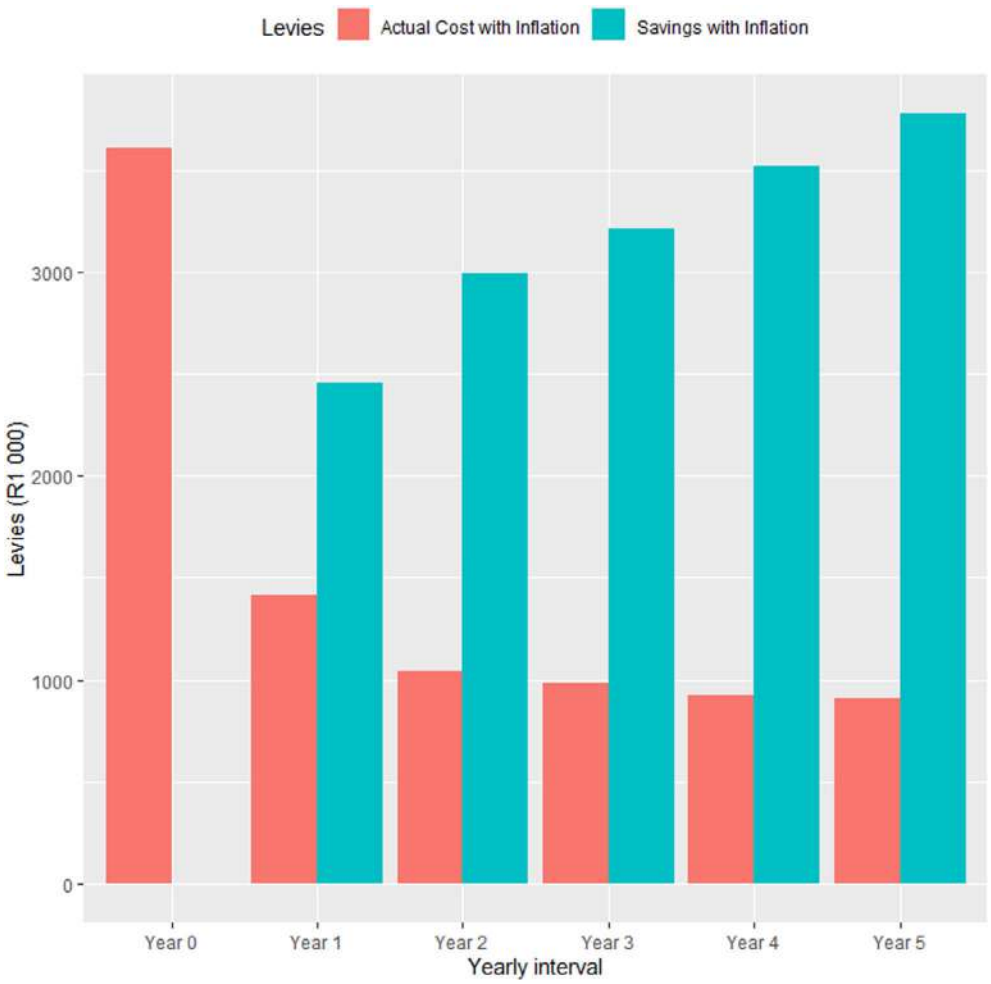


FIGURE 6 Blood product levies savings (2013–2018).

TABLE 2 Blood products ordered per year.

	Year 0 (baseline)	Year 1	Year 2	Year 3	Year 4	Year 5
RCC	7211	5530	4696	4481	4204	4077
Platelets	356	220	192	226	225	182
Cryoprecipitate	115	173	207	208	201	389
FDP	1966	1080	1394	1248	1203	1263

TABLE 3 Changes in testing and administrative levies.

Number of orders	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
After-hours levy	4102	2080	1804	1556	1404	1339
Emergency crossmatch	1039	913	830	874	868	787
Standard crossmatch	1591	787	370	336	261	252
Type and screen	3971	101	35	82	81	40

participation in a monthly meeting from a departmental representative. This was preceded by a 3-month education programme designed to encourage maximal departmental participation.

Some of the individual effects of our system warrant further discussion. The project showed substantial decreases in the amount of blood products transfused almost immediately during Year 1 and continued throughout the project. Blood product usage began to plateau towards the end of the project, suggesting that a practise of consistently ordering only necessary blood products had been established. Because of the reduced workload for the hospital blood bank, both standard and emergency requests for blood were processed faster. The workload of the blood bank was almost halved by the large reduction in unnecessary type and screen requests.

The decrease in blood product usage during the monitoring years resulted in significant cost savings that were re-allocated to improving patient care. This amount is likely underestimated as the cost savings

related to decreased consumables, blood bank and hospital staff workload, and decreased hospital length of stay, were not accounted for in calculations.

The use of cryoprecipitate did not reduce over the 5-year period and may even have increased slightly. This is likely due to a change in hospital policy regarding the use of cryoprecipitate in response to obstetric haemorrhage. Prior to 2014, cryoprecipitate was empirically indicated in massive obstetric transfusion following the use of RCC, FDP and platelets. Ongoing research challenged this notion and suggested that fibrinogen should be given earlier in massive obstetric haemorrhage.[17,18] Consequently, the use of cryoprecipitate increased significantly in obstetric theatres and is thought to account for the change in usage of this product.

The calculations above do not account for activity-based transfusion costs. Other studies have demonstrated how the full cost of blood product transfusions are much more than the cost of just the blood products used.[19] Our system has generated impact and sustainability and it has been successfully replicated in at least 7 other hospitals across different provinces in South Africa. Please see Appendix B for further details on the change management strategies employed during the project.

Our study has limitations. The poor overall performance of the hospital in 2012 in comparison to other provincial hospitals suggests that improvements may not be as dramatic in other settings. However, it is encouraging that our programme could be implemented even in these circumstances. A further limitation is that patient cases were not analysed on an individual level regarding adverse events and morbidity, due to limited resources and poor ward record-keeping. Whilst there was no change in institutional mortality rates, these rates are likely due to many factors and data are not available to determine the exact impact of our programme on those statistics. The success of the project was dependent on the support and compliance of doctors and blood bank staff involved as well as medical management support. Our data does not address whether the changes in doctors' behaviour and blood product usage would continue if the accountability forms were discontinued. We standardised annual blood usage and costs using the number of hospital admissions in the baseline year (Year 1). Statistically, this standardisation is imperfect because of inaccuracies in admissions data, and blood product use is not directly related to total patient admissions. However, this does provide a rough measure of the steady increase in hospital admissions and standardises the data for the year-to-year comparisons. We did not have data on the number of single-unit transfusions. The accountability forms were analysed for this, and if multiple units were ordered when a single-unit would suffice, then this was addressed at the Hospital Transfusion Committee meeting and the individuals involved were re-educated regarding correct practises.

5 | CONCLUSION

The "Saving Blood, Saving Lives" project reduced blood product expenditure by almost half, saving in excess of R46 million ($2 458 000) over 5 years. It decreased RCC, platelets and FDP usage by over 40% each by year 5 of implementation, with even greater reductions in other ordering practises. This illustrated the implementation of successful, cost-effective, reproducible solutions to address service delivery challenges facing South Africa. Project success was possible with effective teamwork, communication and cooperation. The project also demonstrated the power of creating a culture within a community of healthcare professionals to change behaviour. The "Saving Blood, Saving Lives" Project, which requires no budget, could dramatically improve the national blood shortage problem if adopted on a broad scale.

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CONFLICT OF INTEREST STATEMENT

Robert Wise has provided lectures and taught on behalf of the South African National Blood Service. All other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data is available upon request.

ORCID

Robert Wise https://orcid.org/0000-0001-5237-5582
David Bishop https://orcid.org/0000-0001-9861-3646
Gary Sharp https://orcid.org/0000-0003-0321-8067
Reitze Rodseth https://orcid.org/0000-0002-3779-7805

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX A: SAVING BLOOD SAVING LIVES WORKING GROUP

Robert Wise: Discipline of Anaesthesiology and Critical Care, School of Clinical Medicine, University of KwaZulu-Natal, Durban, South Africa; Adult Intensive Care Unit, John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, UK; Faculty Medicine and Pharmacy, Vrije, Netherlands. David Bishop: Discipline of Anaesthesiology and Critical Care, School of Clinical Medicine, University of KwaZulu-Natal, Durban, South Africa. Nikki Allorto: Discipline of General Surgery, School of Clinical Medicine, University of KwaZulu-Natal, Durban, South Africa. Saleem Haffejee: Discipline of Obstetrics and Gynaecology, School of Clinical Medicine, University of KwaZulu-Natal, Durban, South Africa. Charles Serfontein: Discipline of Orthopaedic Surgery, School of Clinical Medicine, University of KwaZulu-Natal, Durban, South Africa. Nafeesa Hansa: Harry Gwala Hospital, Pharamcy, Department of Health, Kwazulu Natal, Pietermaritzburg, South Africa. Amanda Gangaloo: Discipline of Internal Medicine, School of Clinical Medicine, University of KwaZulu-Natal, Durban, South Africa. Ash Vather: Discipline of Paediatrics and Child Health, School of Clinical Medicine, University of KwaZulu-Natal, Durban, South Africa. Shireen Singh: Harry Gwala Hospital, Nursing Division, Department of Health, Kwazulu Natal, Pietermaritzburg, South Africa. Thopo Chamane: Harry Gwala Hospital, Nursing Division, Department of Health, Kwazulu Natal, Pietermaritzburg, South Africa. Moffat Mabhida: South African National Blood Service, Harry Gwala Hospital, Pietermaritzburg, South Africa.

APPENDIX B

The "Saving Blood, Saving Lives" project required neither large budgets nor sophisticated technology to be successful. Rather, it required teamwork, co-operation, and flexibility to adapt to changing and difficult environments. Several assumptions and principles were established at the outset of the project:

1. Healthcare professionals want to make the correct decisions and do what is right for their patients. Many healthcare structures rely on junior staff for service delivery in busy and stressful working environments. Consequently, difficult decision-making compounded by fatigue, can lead to incorrect choices. However, if the system for ordering blood provides decision-making guidance, then correct decision proportions would increase. The "accountability form" aimed to provide this guidance, with a list of indications.
2. Healthcare professionals require motivation to change their behaviour. Behaviour change was one of the project's fundamental challenges. Project adopting principles were used throughout implementation, including:
   a. Giving people a reason why they needed to change.
   b. Providing a means to change and not just giving instructions.
   c. Making the message emotive and appealing to peoples' values and ethics.
3. Teamwork is possible within large organisations and was achieved by:
   a. Inclusion of all role-players and clear communication of the plan before initiation of the project.
   b. Allowing even the most junior staff to contribute to improving the system and gaining support from all leaders within the hospital.
   c. Ensuring support from the most senior hospital management from the outset.
4. Continued communication and feedback to everyone involved in ordering blood products within the hospital. This was done through verbal feedback, written reports and posters. The members of the Hospital Transfusion Committee enabled department-wide communication.
5. It was important to prioritise strong, unambiguous, and consistent leadership in a revitalised hospital transfusion committee, a clear succession plan in the leadership, and maintaining a mandate to hold each other accountable for every blood product ordered. Importantly, the financial savings from the project were used to improve patient care. This motivated and encouraged clinical staff to continue their efforts and was an important driver in results pursuit between the first and second years after implementation.
6. Educating all staff involved in the blood ordering process in a clear, consistent and repetitive manner was integral to the success of the project. The system plans and explanation of the need for change was distributed via a pre-recorded 12-minute video presentation shown at departmental meetings and to all new staff joining the hospital. We used simple software available on most computers, and it proved an effective way to educate everyone whilst minimising time and staff spent on this process.