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FOREWORD

This document has been produced by the Customer Service Patient Blood Management (PBM) Practitioner Team within NHS Blood and Transplant (NHSBT). It follows on from 'A Drop of Knowledge – Guidance for New and Developing Transfusion Practitioners' and contains information on more specialised areas of transfusion to help Transfusion Practitioners to develop a broader knowledge base. References and further information guide the reader to other documents and websites with greater detail. It is designed to be used in conjunction with 'A Drop of Knowledge – Guidance for New and Developing Transfusion Practitioners' where an "acronym and abbreviation buster" can be found.

The authors have taken care to ensure the information contained in this document is accurate and up to date at the time of print; however we do not accept any legal responsibility for any errors or omissions. The content will be updated regularly. I would very much welcome your feedback on this document and would be grateful to hear from you if you have any comments or suggestions for future versions.

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CONTENTS

1. Blood Components

Whole blood is now rarely used for transfusion. Blood component therapy makes clinical sense as most patients require a specific element of blood (Norfolk, 2013). Blood components include red cell concentrates, platelet concentrates, fresh frozen plasma and cryoprecipitate. Plasma derivatives include albumin, coagulation factors and immunoglobulins and are referred to as blood products.

1.1 Blood Collection, Processing, Testing and Issue

Blood collected at static and mobile collection sites is returned to the blood centre's laboratories for processing and testing.
Generally blood is processed into its separate components. This practice has been developed as a response to clinical demand and it is a more efficient use of blood because it means that more than one patient can be treated from a single blood donation and only the blood component required is given.

The processing department is responsible for:
- Blood component production
- Quality monitoring of the components

The department routinely produces:
- Red cells
- Platelet concentrates
- Fresh Frozen Plasma / Cryoprecipitate

Collection
Blood is collected from the donor into a multiple blood pack collection system within a 15 minute bleed time. There are different types and configurations of pack depending on which components are going to be prepared from the donor's blood. This will be determined by donor blood group, stock requirements and the time of day it is collected (certain blood groups may be required for platelets and the time of day may be important if the blood has to get back to the processing department in time for platelet production).
A donation of 450mls (+/- 10%) is required to ensure the final red cell component meets the specification as outlined in 'Guidelines for the Blood Transfusion Services in the United Kingdom', 8th Edition 2013, also known as 'The Red Book'. In general 470-475ml of blood, excluding samples, is collected into the main pack. Three blood samples are also collected, taken for testing and all bar code labelled at the same time.

Processing
Processing begins with centrifugation of the donation, which accelerates separation of blood into its component parts. Red cells being heavier will settle at the bottom of the bag, white cells and platelets in the middle (often called the buffy coat) and plasma at the top. Under pressure in automated presses, the components are then expressed into the different satellite bags. Bags are then separated by heat sealing the tubing. Labelling of the components is done as part of the process and all the critical stages of processing are under computer control to minimise the risk of human error.
Since 1999 all components are routinely leucocyte depleted by filtration to a white cell count of $<5x10^6$ per unit to minimise the risk of variant Creutzfeldt-Jakob Disease (vCJD) transmission. The point in the process at which filtration occurs, depends on which component is being produced (see section on Filtration).

Red cell components are usually routinely processed 'off the shelf' components, with a shelf life of 35 days. They must be stored at a temperature of 4°C (± 2°C) and all blood service storage fridges are fitted with temperature monitoring devices with audible alarm systems.

Platelet concentrates can be made from the pooling of platelets from four blood donations or can be collected from a single donor using a cell separator machine (apheresis).

The usual dose unit for an adult is referred to as an 'adult dose unit' or 'adult therapeutic dose' (ATD). It should contain more than $240x10^9$ platelets per unit.

A single platelet apheresis procedure can provide 2 or 3 adult dose units from a single donor.

Pooled platelets - In order to pool together the platelets from four blood donations, the four units of separated platelets (all of the same blood group) are connected using a sterile connecting device. The platelets can then be expressed through a leucodepletion filter into a special platelet pack that allows gaseous exchange to occur so the platelets can 'breathe'.

These pooled platelets are a routinely produced 'off the shelf' component with a shelf life span of 5 to 7 days. The recent introduction of automated bacterial screening has allowed some Blood Services to extend the shelf life from 5 to 7 days after donation. They are stored at a controlled temperature of 22°C (± 2°C) in a platelet agitator cabinet. Keeping the platelets moving helps to stop them clumping together during storage. Platelets must never be stored in a refrigerator.

Fresh frozen plasma (FFP) in the UK is prepared from a single blood donation. The plasma must be processed and frozen to -30°C within 2 hours of being separated from whole blood. It has a shelf life of up to 36 months if kept at –25°C or colder. Once thawed the component must not be refrozen and should be transfused as soon as possible or within 4 hours. It can be stored for 24 hours at 4°C (± 2°C).
Methylene Blue treated FFP (MBFFP) is a single donor pathogen reduced component available from UK Blood Services.

Cryoprecipitate is produced by the controlled thawing of FFP at 4°C (± 2°C) after which the precipitate can be isolated and re-frozen (within 2 hours) in a small volume of the plasma. It is re-frozen to a temperature of –30°C and then has a shelf life of 36 months at –25°C or colder. Use within 4 hours once thawed.

A typical adult dose is two 5-donor pools (equivalent to 10 single donor units) containing 3-6g fibrinogen in a volume of 200 - 500ml. One such treatment administered to an adult would typically raise the plasma fibrinogen level by about 1g/L (Norfolk, 2013).

Testing

Of the three samples taken from the donor at the time of donation and returned to the testing laboratory, two of these are used to routinely screen the blood for mandatory markers:

- Hepatitis B - HBsAg and HBV NAT
- Human Immunodeficiency Virus – anti -HIV-1 and 2 and HIV NAT (nucleic acid testing)
- Human T-cell lymphotrophic virus – anti HTLV 1 and 2
- Hepatitis C – anti HCV and HCV NAT
- Syphilis – syphilis antibodies

Any donation with a positive result to any of the above screening tests is destroyed and the donor is contacted for further confirmatory testing.
Other tests may be performed e.g. malarial antibody test if travel has exposed the donor to this risk.
Some donations are tested for Cytomegalovirus (CMV) to meet the needs of specific patients.

The third sample is a grouping sample to test:

- ABO group

On known donors this is tested and compared against historical records to confirm donor identity. New donors are tested twice using different sets of reagents.

- Rh D group

Every donation is Rh D typed. Many donations are Rh phenotyped (tested for Rh CDE) so that donations can be selected for patients with specific requirements.

- Antibody screening

All donations are tested for red cell allo antibodies.

Quality Monitoring of Blood Components

1% of each component type is sampled and tested to ensure that specifications from national guidelines are met. There is a minimum requirement for 75% compliance (See the Guidelines for the Blood Transfusion Services in the UK ('the Red Book') and also the Donor Selection Guidelines at http://www.transfusionguidelines.org).
Checks are made for correct volume requirements, function of component, storage and contamination. There are also various in-process controls: worker assessments, equipment calibration and monitoring and reagent control. The quality monitoring information then becomes the basis of statistical analysis, which is routinely used to measure performance, compliance and trends.
The testing and processing of blood donations is subject to regular self-inspection and audit via the blood service quality department. It is also subject to external inspection by the Medicines and Healthcare products Regulatory Agency (MHRA).

Issue - Validation and Release of Blood Components

Computers are used to control both blood grouping and blood pack labelling. The system depends on the use of machine-readable (bar code) labels.

All donating, testing and processing stages of blood component production are computer controlled. There must be physical separation of all components that are under preparation from those which are ready for issue. All components must be stored in secure areas.

The release of blood components is also computer controlled with an automatic production of an issue report, which requires a signature from the individuals who packed it, collected it for transport and receive the components.

Licensing

Blood components are produced under licence from the MHRA, the authority responsible for ensuing compliance with the 'Blood Safety and Quality Regulations 2005' (and amended).

The MHRA carries out inspections of Blood Establishments every two years. A Blood Establishment is defined by the regulations as, 'Any structure or body that is responsible for any aspect of the collection and testing of human blood or blood components, whatever their intended purpose and their processing, storage, and distribution when intended for transfusion'. This includes blood service centres and some hospital transfusion laboratories.

Production is also subject to the requirements of Good Manufacturing Practice (GMP). GMP can be defined as, 'that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards and appropriate to their intended use'.

Guidelines for the Blood Transfusion Services in the UK (2013)(the Red Book), state that 'the application of GMP is the cornerstone of an effective Quality Management System'.

The 'Orange Guide' published by the MHRA under the title 'Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2014,' gives the guidelines for GMP under several separate headings.

The processing of blood is inspected and audited by the MHRA against the 'Orange Guide' as well as the Blood Safety and Quality Regulations 2005.

The NHS Blood and Transplant's training department offer tours of the Blood Centres for anyone wishing to gain an overview of the service and the workings of a Blood Centre.

They also offer a one-day 'Core Knowledge' course aimed at improving basic knowledge of NHS Blood and Transplant. See:

http://hospital.blood.co.uk/training/index.asp

Further Information:

Guidelines for the Blood Transfusion Services in the United Kingdom 8th Edition (2013)
http://www.transfusionguidelines.org.uk/index.aspx?Publication=RB

Norfolk D (Ed) (2013) Handbook of Transfusion Medicine 5th Edition, The Stationary Office
ISBN 9780117068469
http://www.transfusionguidelines.org.uk/transfusion-handbook

Rules and Guidance for Pharmaceutical Manufacturers and Distributors 8th Edition (2014)
http://www.mhra.gov.uk/Publications/Regulatoryguidance/Medicines/Othermedicinesregulatoryguidance/CON2030291

1.2 Explanation of a Blood Pack Label

The design, content and use of labels for blood components should conform to the specification in the Red Book (Guidelines for the Blood Transfusion Services in the UK 2013).

The following diagrams show what the various numbers and codes mean on the blood bags. These diagrams are available as training laminates or on PowerPoint slides from your local Patient Blood Management Practitioner.

All blood components have labels applied by NHS Blood and Transplant (NHSBT) which give important information for staff that issue and administer it.

These labels also allow for the origin of the component to be traced.

Unique donation number:
This is in the top left hand corner. This number is assigned to each pack at donation and allows traceability from donor to patient. ALL the digits, including the final check digit must be recorded.

Blood Component:
This describes the blood component contained in the bag and gives instructions on storage conditions and use.

Safety information:
A reminder to check the patient identity, the component compatibility and to highlight the risk of adverse reaction/ infection including vCJD.

Blood Group:
The ABO and RhD group of the unit is shown here.
It does not have to be identical with the patient's blood group but must be compatible.
The expiry date is shown below the blood group. The transfusion must be completed by midnight on this date.

Additional Information:
Results of additional blood tests are shown here so that the unit can be matched to a patient's specific requirements. It also details the centre at which the blood was processed and the date of donation.

Irradiated blood label:
A Rad-Sure 'Irradiated' label (only present on irradiated blood*) is stuck onto the bag beneath the main label before irradiation and indicates whether the component has been irradiated (which helps protect vulnerable patients from Transfusion-Associated Graft-versus-Host Disease).
*this is present on all components irradiated by NHSBT - components irradiated locally may have a different indicator / label

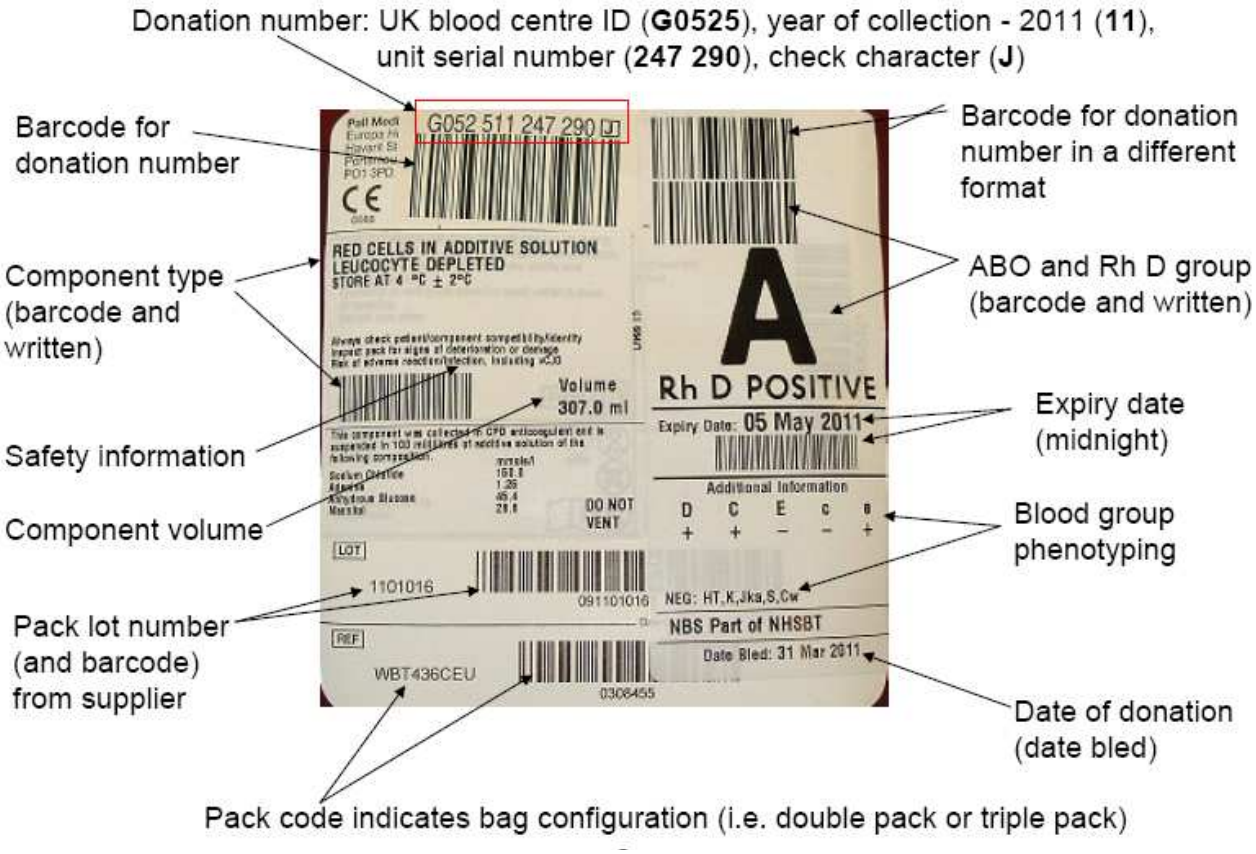
Blood selected for a specific patient by the hospital transfusion laboratory should **have an additional label affixed to it bearing that patient's details.**

The final patient identity check **must** be done at the patient's side.

The information on the blood **must** match the information on the patient's identity band (or photo ID) and the prescription sheet.
Identity **must** be confirmed by asking the patient their full name and date of birth whenever possible.

If there are any discrepancies DO NOT PROCEED WITH THE TRANSFUSION and contact the hospital transfusion laboratory.

What do all the numbers and barcodes mean?



1.3 Specific Requirements

Some patients may have specific requirements to minimise complications of transfusion. It is necessary to inform the hospital transfusion laboratory as soon as it is recognised the patient has specific requirements, even if they do not immediately require a blood transfusion, so the information can be added to the patient's record. Under the Blood Safety and Quality Regulations 2005 and as part of the quality structure, the MHRA has indicated that there should be a Standard Operating Procedure (SOP) in place to cover this process.
Specific requirements include:

Irradiated Blood Components
Irradiated blood components are needed to minimise the risk of Transfusion-Associated Graft-versus-Host Disease (TA-GvHD). This can develop following the transfusion of lymphocytes present in donated blood components to immunosuppressed recipients. The patient's impaired immune system is unable to reject these foreign lymphocytes, which engraft and initiate TA-GvHD. Patients develop skin rash, diarrhoea and abnormal liver function and deteriorate with bone marrow failure. Death from infection usually occurs within two to three weeks of transfusion.
Irradiating the component is the treatment of choice, as leucocyte depletion cannot be considered enough to remove the risk of TA-GvHD. Those patients requiring irradiated blood components should be given an information leaflet and card, which is available from blood centres or through the Patient Blood Management Team. They should be encouraged to show it whenever they need a blood transfusion and the hospital notes 'flagged' in some way to alert hospital staff. It is not necessary to irradiate FFP, cryoprecipitate or fractionated plasma products.

A factsheet on Irradiated Blood Components has been produced by the Patient Blood Management Team and is available to healthcare professionals:
http://hospital.blood.co.uk/media/2992/9c334f23-78be-4176-b789-e2750dbd473c.pdf
Hard copies are available from the Customer Service Administration office, email:
NHSBT.customerservice@nhsbt.nhs.uk Tel: 01865 38 1010

For a list of the types of patients considered to be at risk of TA-GvHD see:

- British Committee for Standards in Haematology (BCSH) Blood Transfusion Taskforce Guidelines on the use of irradiated blood components.
  British Journal of Haematology (2010) 152:35-51
  http://www.bcshguidelines.com/4_HAEMATOLOGY_GUIDELINES.html
- Norfolk D (Ed) (2013) The Handbook of Transfusion Medicine 5th Edition, The Stationary Office ISBN 9780117068469 Chapter 8, page 102
  http://www.transfusionguidelines.org.uk/transfusion-handbook
- NHS Blood and Transplant Information Document - Transfusion Associated Graft versus Host Disease (2012)
  http://hospital.blood.co.uk/media/2129/4b4c5eba-2721-420b-813b-007f0947110f.pdf

CMV Negative Blood Components
Cytomegalovirus (CMV) is a white cell-associated virus transmissible by transfusion which can cause serious infection in fetuses, neonates and immunocompromised CMV negative patients. Historically, although there has been debate about the efficacy of leucodepletion to prevent CMV transmission, this risk has been minimised by the use of CMV antibody negative (seronegative) blood components. In 2012, the Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) undertook a review of the requirement for CMV negative blood components and produced an evidence-based position statement which (in summary) recommended:

- CMV seronegative red cells and platelets should be provided for intrauterine transfusions and neonates (up to 28 days after expected delivery date).
- CMV seronegative granulocytes should be provided for CMV seronegative recipients.
- CMV seronegative red cells and platelets should be provided, where possible, for pregnant women. In an emergency, such as major haemorrhage, standard leucodepleted components should be given to avoid delay.
- Standard pre-storage leucodepleted components are suitable for all other transfusion recipients, including haemopoietic stem cell transplant patients, organ transplant patients and immune deficient patients, including those with HIV.

A full SaBTO report is available at:
https://www.gov.uk/government/publications/sabto-report-of-the-cytomegalovirus-steering-group

HLA Matched Platelets

Human Leucocyte Antigens (HLA) are found on most cells in the body including platelets. Matching for HLA is important for some patients undergoing a transplant. HLA typing is a measure of the unique (genetic) tissue type of a person and HLA matched platelets are more closely matched to a patient's own HLA type than 'standard' platelets. HLA matched platelets are used to treat patients who have a poor response to 'standard' platelet transfusions due to HLA antibodies. Some patients produce HLA antibodies during pregnancy, after transfusion or transplant and the presence of these antibodies may affect the survival of the transfused platelets. HLA matching reduces the risk of the patient's own HLA antibodies destroying the transfused platelets. HLA matched red cells are also available for specific indications related to renal transplantation.

NHS Blood and Transplant searches its database for donors who match a specific patient's HLA type and then a panel of HLA typed donors is co-ordinated to ensure a regular supply of matched platelets to meet hospital requests. To check the transfused platelets have been effective, NHS Blood and Transplant must be informed of the patient's platelet count pre and post transfusion. NHS Blood and Transplant 'HLA Selected Platelets - Follow Up' form must be completed and returned after each transfusion episode. This helps ensure that the most effective platelets are selected for subsequent transfusions. Failure to monitor a patient's response to HLA platelets may compromise their treatment.

A poster, created by the NHSBT Patient Blood Management Team, has been developed to raise awareness amongst clinical staff in haematology units and wards of this important issue:
http://hospital.blood.co.uk/patient-services/patient-blood-management/platelet-resources/
Hard copies are available from the Customer Service Administration Office, email:
NHSBT.customerservice@nhsbt.nhs.uk Tel: 01865 38 1010

Virus Inactivated FFP

In 2002, the UK Departments of Health issued a recommendation that FFP for patients born after 1 January 1996 be sourced from areas where BSE and vCJD are of low endemicity. Individuals born since this date and living in the UK have benefitted from regulations enacted by the Food Standards Agency affecting meat quality, which keep infected material out of the human food supply. These are the 'Specified Bovine Materials Ban' and the 'Over Thirty Months Rule'. The effect of these bans has reduced the risk of such individuals contracting vCJD from their diet to levels which may well be lower than the risk of them contracting vCJD from transfused blood donated by UK donors who, although showing no signs of vCJD, may be incubating it.

Sourcing materials for FFP production from donors residing in areas where BSE and vCJD are of low endemicity may introduce other risks e.g. if prevalence of transfusion-transmissible diseases caused by known organisms is relatively high. However, most of these diseases can be effectively eliminated from plasma by 'pathogen reduction' procedures. Although these procedures do not inactivate prions, by applying them to imported plasma, the overall risks of transmitting infection from treated components will be reduced.
At present two virus-inactivated FFP preparations are licensed and available in the UK:

- Methylene Blue (MB) treated FFP
- Solvent detergent (SD) treated FFP (available commercially as 'Octaplas').

Both methods are associated with 15-20% loss of labile clotting factors. Each type has certain potential drawbacks that may influence the clinical decision on which to use. In 2006 the DH recommended using SD FFP for plasma exchange in TTP.

- **MB FFP**

MB treatment can be applied to single unpooled units of plasma and requires prior removal of white blood cells by filtration or freeze-thawing. The MB is contained in or added to, the integral pack system, mixed with the plasma, then exposed to white light to generate reactive oxygen species which damage nucleic acids, preventing viral replication (Murphy and Pamphilon 2001).
MB FFP is available from NHS Blood and Transplant and is currently sourced from Europe, from a country with a lower risk of vCJD than the UK.

- **SD FFP**

SD treatment can be applied only to large pools of ABO-identical units. Exposure to SD destroys the lipid envelope of the HIV, Hepatitis B and C viruses. Non-lipid-coated viruses such as Parvovirus B19 and Hepatitis A are not specifically inactivated, but their titre may be reduced in downstream processing. In addition, plasma pools contain levels of antibodies to these viruses, which may be at least partially protective. No increase in clinical cases of Parvovirus B19 in SD FFP recipients is evident. Genome testing for these viruses is now performed (Murphy and Pamphilon 2001).

As SDFFP is a pooled product the plasma must be sourced from outside the UK (e.g.USA), a prion reduction process may be included, to meet the Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) stipulation of a 4-5 log reduction in vCJD risk.

Further Information:

British Committee for Standards in Haematology (BCSH) Blood Transfusion Taskforce Guidelines on the use of irradiated blood components. British Journal of Haematology (2010) 152:35-51
http://www.bcshguidelines.com/4_HAEMATOLOGY_GUIDELINES.html
Contreras M (2009) ABC of Transfusion 4th edition, BMJ books London
ISBN-10: 1405156465

Murphy MF, Pamphilon DH, Heddle, NM (Eds) (2013) Practical Transfusion Medicine 4th Edition, Blackwell Science Ltd
ISBN 0470670517

NHS Blood and Transplant (2011) Pathogen inactivated fresh frozen plasma: solvent-detergent (SDFFP) and methylene blue (MBFFP)
http://hospital.blood.co.uk/products/plasma-components/

NHS Blood and Transplant (2012) Patient Information Leaflet: Will your child need a plasma transfusion?
http://hospital.blood.co.uk/patient-services/patient-blood-management/patient-information-leaflets/

Norfolk D (Ed) (2013) Handbook of Transfusion Medicine 5th Edition, The Stationary Office
ISBN 978 0 11 706846 9
http://www.transfusionguidelines.org.uk/transfusion-handbook

SaBTO Publications and Recommendations:
https://www.gov.uk/government/policy-advisory-groups/advisory-committee-on-the-safety-of-blood-tissues-and-organs

Williamson LM, Cardigan R, Prowse PV (2003) Methylene-blue treated fresh-frozen plasma: what is its contribution to blood safety? Transfusion 43 (9) 1322 – 1329

1.4 Buffy Coats and Granulocytes

Properly functioning white blood cells are necessary for the body's defence against infection. Leucocytes in general and granulocytes in particular, are vital for protection against bacterial and fungal infection. When patients are neutropenic (low neutrophil count), they run an increased risk of severe infection. They usually become neutropenic as a result of disease which involves the bone marrow (such as leukaemia) or as a response to drug therapy which impairs bone marrow function (such as chemotherapy). There are also patients with congenital disorders affecting neutrophil function that may develop severe bacterial or fungal infections.
When these patients develop severe infections, antibiotics and antifungal drugs seem to be of limited use unless the neutrophil count can also be raised. Granulocyte transfusions may be indicated to treat these patients. Granulocyte transfusions may also be given prophylactically to cover anticipated periods of neutropaenia in high-risk patients.

Source of Granulocytes

- **Buffy Coats**

Produced from a unit of blood, buffy coats are the white cells and platelets left behind when red cells and plasma are removed. The recommended dose is ten buffy coats or two pooled buffy coats daily for adults (10-20mL/Kg for smaller children and infants).
Each buffy coat is approximately 50 ml in volume, with a high haematocrit of 60%. After a buffy coat infusion, patients will have a rise in haematocrit and platelet count as well as neutrophil count. This may be a problem in small children.
Buffy coats are irradiated to reduce the risk of Transfusion Associated Graft versus Host Disease (TA-GvHD) and they are cross-matched in the hospital transfusion laboratory because of the high haematocrit.

- **Apheresis Granulocyte Collections**

These can be collected from selected volunteer apheresis donors. These donors are not 'stimulated' to produce granulocytes and these donations only contain low numbers of granulocytes. These donations are therefore, only suitable for use in small children under 30kg in weight.
'Stimulated' granulocyte collections can be obtained from relatives and friends of the patient. In these cases Granulocyte Colony Stimulating Factor (GCSF) is used to stimulate production of granulocytes by the donor,

together with steroids. NHS Blood and Transplant does not stimulate donors by GCSF or steroids and is only involved with the collection of granulocytes after a donor has been given these at the hospital or clinic which has referred them. The collections of granulocytes from these donors will contain significantly higher numbers of granulocytes than those collected from unstimulated donors.

Further Information:

M Elebute (Convenor), E Massey, S Benjamin, S Stanworth, C Navarrete and G Lucas. Revised by Edwin Massey December 2006, 2010 and 2012. Clinical Guidelines for the use of Granulocyte Transfusions Prepared by the Granulocyte Working Group
http://hospital.blood.co.uk/media/27068/inf276-clinical-guidelines-for-the-use-of-granulocyte-transfusions.pdf

1.5 Lymphocytes

Lymphocytes are small white blood cells, which play a major part in carrying out the activities of the human body's immune system. They are collected by apheresis from donors who have already donated Peripheral Blood Stem Cells (PBSC) as either a sibling or an unrelated donor. Donor Lymphocyte Infusion (DLI) is given as a treatment to stimulate or restore the immune response in those cases where the patient needs a 'top-up' transplant, either because they are in early stages of relapse, or because they have developed a mixture of donor/patient bone marrow cells (mixed chimerism).

The lymphocytes can be collected some months or even years after the initial transplant. The lymphocytes that are collected are divided into doses of varying sizes. One dose is given fresh; the others are cryopreserved and given to the patients at three-month intervals. Hopefully the treatment will cause the patient to go into remission or at least show signs of Graft versus Host Disease (GvHD) which means there will also be some Graft versus Leukaemia effect.

Further Information:

European Blood and Marrow Transplantation (UK) Nurses and Allied Professions Group:
http://www.ebmt.co.uk/

1.6 Stem Cells

Stem cells are immature blood cells, which develop in the bone marrow. From these immature cells all the blood cells will develop. These cells have 2 important characteristics; one is the ability to reproduce themselves at a rapid rate, the other is the ability to develop into any blood cell as required. Most stem cells are present in the bone marrow.

Sometimes the patient has their own cells harvested (autologous donation) but where this is not possible, cells from a donor are used. Transplants from sibling donors are usually the most successful transplants but not all patients have siblings with the same or similar tissue types. In this event, unrelated donors are sought using bone marrow donor databases e.g. British Bone Marrow Registry or Anthony Nolan Trust.

Patients and donors may have stem cells collected from the peripheral blood by doing a 'Peripheral Blood Stem Cell (PBSC) Harvest'. Peripheral blood stem cells can be collected using a cell separator machine, like the one used for donor platelet apheresis. Only a few stem cells are present in peripheral blood under normal circumstances, so these patients or donors need to undergo a priming regime to encourage the production of stem cells so that more of them will be pushed out into the circulating blood. For patients, this regime (conditioning) usually consists of a combination of chemotherapy and injections of Granulocyte Colony Stimulating Factor (GCSF). Donors who are primed for PBSC harvest are only given GCSF and not chemotherapy.

Patients or donors who have had this conditioning/priming are then monitored to see if they have sufficient numbers of stem cells appearing in peripheral blood. After a specified number of days (usually 5 days for donors but variable for patients dependent on conditioning regime) a blood sample is taken daily and tested for CD34 cell markers. These cell markers will indicate a rise in the number of circulating stem cells. Once the required number of stem cells has been reached, the harvest can take place. The patient or donor will be attached to the apheresis machine for between 3 and 4 hours. Often the patient or donor will have to be harvested more than once, on consecutive days, until sufficient cells are obtained to do a viable transplant.

Once collected in this way, PBSCs are returned to the stem cell laboratory for processing and freezing (if required). They are frozen using a controlled-rate freezing machine. They can then be stored in liquid nitrogen vapour for several years if necessary until the patient requires them. Donor stem cells are often given fresh.

Some patients or donors will have stem cells harvested via a 'Bone Marrow Harvest' done under a general anaesthetic. Bone marrow cells are collected from the hip bone. The bone marrow is then returned to the stem cell laboratory for processing and freezing.

The purpose of stem cell harvest, by either of the methods described above, is as a bone marrow rescue. Some patients have malignant conditions, which will not respond to conventional doses of chemotherapy treatment. There are high-dose chemotherapy regimes, which may be successful in either curing or slowing down the disease but, the high doses of chemotherapy required would destroy the bone marrow and therefore kill the patient. If sufficient numbers of stem cells can be harvested and stored prior to high dose chemotherapy treatment, they can then be re-infused into the patient afterwards. These cells will then re-establish haemopoiesis and after a period of immunosuppression the patient will recover. This treatment is not without significant risk.

Another strategy is to use smaller doses of chemotherapy and use the graft-versus-host effect for disease control. This is called reduced intensity conditioning.
Sometimes the patient has high dose chemotherapy straight away and the stem cells are only stored for a short time before being given to the patient. In other cases the stem cells are harvested from the patients themselves while in remission and stored in case the patient suffers a relapse at a later date.

Where donor and recipient are not of the same blood group, blood components for the transplant must be compatible with both and blood grouping data reassessed six month post transplant.

Definitions

Allograft	An allograft or allogeneic transplant or homograft is a transplant in which transplanted cells, tissues or organs are sourced from a genetically non-identical member of the same species. Most human tissue and organ transplants are allografts.
Autograft	Autograft is the transplantation of tissue from one part of the body to another in the same individual.
Autologous donation	Transfusion to an individual of blood collected from themselves.
BMT (Bone Marrow Transplant)	This involves taking a healthy sample of stem cells from bone marrow belonging to a healthy donor and then injecting them into a recipient's bone marrow. The new stem cells take over the production of the blood cells. http://www.nhs.uk/Conditions/Bone-marrow-transplant/Pages/Introduction.aspx
DLI (Donor lymphocyte infusion)	A form of immunotherapy used after stem cell transplantation. Lymphocytes from the original stem cell donor are infused, after the transplant, to augment an anti-tumor immune response or ensure that the donor stem cells remain engrafted. Complications of DLI include acute and chronic graft versus host disease and bone marrow aplasia resulting in immunosuppression and susceptibility to opportunistic infections.
EPO	The abbreviation for recombinant human erythropoietin, which is a hormone produced by the kidney that stimulates red cell production by bone marrow.
GCSF (Granulocyte-colony stimulating factor)	A haematopoietic growth factor. It stimulates the bone marrow to produce more white blood cells. Growth factors are special proteins which are produced naturally in the body. http://www.macmillan.org.uk/Cancerinformation/Cancertreatment/Treatmenttypes/Supportivetherapies/HaematopoieticGrowthFactors.aspx
HLA (Human Leukocyte Antigens)	To reduce the risk of the body rejecting the donated stem cells (graft rejection), the donor's tissue type has to be closely matched to the recipient. The matching process involves a blood test, and is done by looking for specific proteins known as markers on the surface of the cells. The markers are called human leukocyte antigens (HLAs). Once the HLA type of the recipient's bone marrow has been found, donors can be tested to see whether their bone marrow and stem cells match.
MUD (Matched Unrelated Donor)	If the intended recipient has no suitable relatives it may be possible to find a matched unrelated donor (MUD). The National Blood Service in England and Wales, the National Blood Transfusion Service (Scotland) and some charities have lists of volunteer unrelated donors. Recipients will have access to these registries through their consultants who can initiate searches for a close match for them. It may be very difficult and time-consuming to find a good match. Overall, only about 1 in 10 searches

	will find a closely matched, unrelated donor. People from minority ethnic groups often have difficulty finding a good match from the volunteer registries. This is because most people who register as potential bone marrow donors are from the white population, and tissue types rarely match across different ethnic groups. http://www.nhsbt.nhs.uk/download/uk_stem_cell_strategic_forum_report.pdf
PBSC (Peripheral Blood Stem Cells)	Stimulating hormones can be injected into the donor's blood which causes their stem cells to proliferate and filter out of their bone marrow and into their bloodstream. An amount of their blood can then be taken out of their body and given to a matched recipient. This procedure is known as a peripheral blood stem cell (PBSC) donation. The advantage of a PBSC is that the donor does not need to have a general anaesthetic.
RIC (Radiation Induced Cytotoxicity)	Radiation Induced Cytotoxicity While radiotherapy can destroy cancer cells, it can also have an effect on some of the surrounding normal cells. There are many side effects causing various symptoms, the severity of which will depend on the dose of radiation as well as the individual, thus making it difficult to predict. Most side effects of radiotherapy disappear gradually once the course of treatment is over. http://www.macmillan.org.uk/Cancerinformation/Cancertreatment/Treatmenttypes/Radiotherapy/Sideeffects/General.aspx
TA–GvHD (Transfusion-Associated Graft-versus-Host Disease)	Transfusion-Associated Graft-versus-Host Disease is a rare but serious complication, due to the engraftment and proliferation of transfused donor lymphocytes.

Further Information:

Blood Matters issue no 18 summer edition 2005:
http://hospital.blood.co.uk/media/27145/bm18.pdf

European Blood and Marrow Transplantation (UK) Nurses and Allied Professions Group:
http://www.ebmt.co.uk/

Guidelines for the Blood Transfusion Services in the United Kingdom 8th Edition (2013) The Stationery Office, ISBN 0 11 703371 5:
http://www.transfusionguidelines.org.uk/

Macmillan Cancer Support:
http://www.macmillan.org.uk/

NHS Blood and Transplant Hospitals & Science website:
http://hospital.blood.co.uk/

1.7 Cord Blood

The first successful sibling cord blood transplant was performed in 1988 and since then there have been more than 20,000 related and unrelated cord blood transplants performed throughout the world. Cord blood is rich in stem cells, easy to collect, readily available, has low rates of transmission of CMV and other latent viruses and is especially suitable for children. A disadvantage of cord blood is the low volume of blood collected at donation. Related and unrelated cord blood transplants have resulted in good outcomes for children with malignancy, immune deficiencies and some congenital conditions.

Cord blood is banked from those donors whose mothers have met the criteria in the Cord Blood Donor Selection Guidelines. It is a regulatory requirement that both maternal and cord blood samples are taken at between day 0 and 7 of donation, and undergo mandatory and any additional discretionary tests. Mandatory infectious disease testing includes screening for HIV-1 and HIV-2, HBV, HCV, HTLV and syphilis. A donation sample must also be tested for bacterial and fungal contamination.
Collection takes place at selected hospitals only. These hospitals have obtained ethical permission and have a service level agreement in place with a licensed processing and storage facility. All prospective donor mothers are interviewed for suitability under the terms of the donor selection criteria (UKBTS Medical Assessment of Donors of Tissues). Informed, written consent is obtained for the testing and use of the donation.

Cord blood is stored for a maximum of 24 hours prior to processing. The volume is then reduced by removal of plasma and red cells, leaving only the buffy coat component which is then cryopreserved. Throughout the process, samples are obtained for testing, quality monitoring and for archiving purposes.
After processing and freezing the donations are subject to medical review and then, subject to Quality Assurance release, they are made available to the searchable database. If matched, the donation then undergoes assessment by a Medical Consultant as to its suitability for the prospective patient. Confirmatory tests are performed on archived samples as are any additional testing which the requesting Transplant Centre may require.

Cord blood may need to be stored for indefinite time periods, and transported for long distances; this is done at a temperature less than -130°C in validated containers, which contain a temperature monitoring device.

Further Information:

Blood and Transplant Matters, Winter 2009, Issue 29:
http://hospital.blood.co.uk/media/27157/bm29.pdf

NHS Blood and Transplant Hospitals & Science website:
http://hospital.blood.co.uk/diagnostic_services/stem_cell_immunotherapy_services/cord_blood/index.asp

NHS Cord Blood Bank
http://www.nhsbt.nhs.uk/cordblood/index.asp

Royal College of Obstetricians and Gynaecologist – Umbilical Cord Blood Banking:
http://www.rcog.org.uk/womens-health/clinical-guidance/cord-blood-banking-information-parents

1.8 Blood Cell Separators and Apheresis

The On-line Medical Dictionary published at the Department of Medical Oncology, at the University of Newcastle-upon-Tyne describes apheresis as:
"A haematology procedure. A technique in which blood components are separated … and the desired elements collected and the rest returned to the donor"
Apheresis procedures can be carried out on a donor or a patient.

Components that can be separated from whole blood are:
- Red cells
- Platelets
- Plasma
- White cells - granulocytes
- White cells - lymphocytes
- Stem cells

Various manufacturers make apheresis machines, the major ones include:
Terumo BCT https://www.terumobct.com
Fresenius KABI http://www.fresenius-kabi.com/
Fresenius Medical http://www.freseniusmedicalcare.com/
Haemonetics U.K. http://www.haemonetics.com/

The majority of machines are suitable for many different procedures. Different disposable kits are available for different procedures.

How Does Apheresis Work?
Most therapeutic (patient) machines are set up with a single use 'Dual Needle' kit. The patient has a wide bore (16-gauge) fixed-wing needle inserted into a large vein, (usually the antecubital fossa) and a smaller 19-gauge needle inserted into a vein on the hand/arm on the opposite side (an appropriately sized patent cannula that is already insitu may be used for this instead).
Blood is drawn from the patient through the 16-gauge needle into the machine where it is centrifuged, separating it into its component parts, the required component is drawn off and the rest returned, with or without replacement fluid, to the patient. Where peripheral venous access is problematic, an apheresis central venous catheter can be used.

Donor Procedures
Donor procedures are carried out on volunteers donating blood components for therapeutic use. When collecting platelets by apheresis, two or three complete 'adult therapeutic doses' (ATDs) can be taken from one donor, as opposed to the 'pool' of 3 or 4 buffy coats from whole blood donations which is required to make just one ATD. It is also possible to collect 'double-doses' of red cells from donors by apheresis.

Patient Procedures
Patient procedures are carried out on patients with haematological, renal, neurological or other autoimmune conditions for whom separation/removal of a blood component is desired as part of their treatment.

The major types of therapeutic (patient) procedures are:

Stem Cell Harvest
Stem cells are collected from the patient's blood for storage and re-infusion at a later date, usually after a course of chemotherapy. Approximately 200mls of stem cells are collected, and no replacement fluid is required. Stem cells can also be harvested from family members or volunteer donors.

Plasma Exchange
The patient's plasma is removed (2-6 litres depending on the weight and haematocrit of the patient) and at the same time replaced either with FFP (usually SDFFP) or Albumin (4.5%). Plasma exchange can be carried out for patients with blood diseases such as Thrombotic Thrombocytopenic Purpura (TTP) or Waldenstrom's Macroglobulinaemia.

Red Cell Exchange
The patient's red cells are removed and replaced simultaneously with donor red cells (6-20 units depending on the patient's weight, HbS level and haematocrit). Red cell exchange can be carried out on patients with Sickle Cell Disease, for example, who may be 'in crisis', prior to having surgery or for primary stroke prevention.

Further Information:

American Society for Apheresis:
http://www.apheresis.org/

BCSH Guideline on the clinical use of apheresis procedures for the treatment of patients and the collection of cellular therapy products (2015)
http://onlinelibrary.wiley.com/doi/10.1111/tme.12205/epdf

NHS Blood and Transplant Hospitals & Science website:
http://hospital.blood.co.uk/therapeutic_apheresis_services/

Thrombotic Thrombocytopenic Purpura Network:
http://www.ttpnetwork.org.uk/

Photograph of a Terumo Optia Apheresis machine

1.9 Artificial Blood

The search for a blood substitute, or artificial blood, has been going on for over half a century. The need for such a substance is based on the established limitations in the use of allogeneic blood.
These include:

- A limited shelf life of 42 days (maximum)
- The limitations on storage and handling imposed by ‘cold chain’
- The restrictions on use presented by blood group compatibility
- The risk of viral and bacterial infection transmission
- The limited oxygen-transport capacity of banked blood during the initial hours following transfusion
- Availability of donated blood.

The ideal blood substitute should not require compatibility testing or refrigeration, which would allow routine use in pre-hospital care. More importantly it should have a long shelf life and be disease free. The term blood substitutes is a technical misnomer given the variety of functions carried out by this ‘liquid organ’ and a more

appropriate term is ‘red cell substitutes’ or the more generic term ‘oxygen therapeutics’ (Robert Bartlett - Transfusion Free Medicine and Surgery. Edited by Nicolas Jabbour 2005).

Currently, there are several companies working on the production of a safe and effective artificial blood substitute. The various blood substitutes all suffer from certain limitations. For example, most of the hemoglobin-based products last no more than 20-30h in the body. This compares to transfusions of whole blood that lasts 34 days. Also, these blood substitutes do not mimic the blood's ability to fight diseases and clot. Consequently, the current artificial blood technology will be limited to short-term blood replacement applications. In the future, it is anticipated that new materials to carry oxygen in the body will be found. Additionally, longer lasting products should be developed, as well as products that perform the other functions of blood.

Oxygen therapeutics could offer advantages over red blood cells in their natural state, one significant property they may be able to offer is the ability to perfuse and oxygenate compromised capillary beds which cannot be reached by a red blood cell with its 7 microns diameter.

There are four broad categories of oxygen therapeutics under consideration:

- Haemoglobin-based oxygen carriers, which are chemically modified derivatives of haemoglobin or recombinant DNA derivatives of haemoglobin
- Perfluorocarbons, which have a high solubility coefficient for oxygen
- Synthetic allosteric modifiers, which shift the oxyhemoglobin dissociation curve to the right, producing a greater release of oxygen in the capillary beds
- Hyperbaric oxygen, which exploits the natural gas laws to dissolve large volumes of oxygen in plasma.

Because the four classes have different delivery mechanisms and side-effect profiles, each can be expected to have its own unique clinical applications as the characteristics of the individually designed products are better understood.

Two distinctly different classes of oxygen carriers are being developed, each capable of transporting and delivering oxygen to peripheral tissues. The delivery of oxygen by these two methodologies may have both benefits and risks unique to its class.
(Leone BJ (1998) Artificial blood: What is it? Will I use it? Jacksonville Medicine)

With research, development, prototypes and animal modelling abound, it appears that much work remains on perfecting an oxygen therapy that will meet the myriad requirements and complexities of the human body. None are licensed for use in the UK at present.

Further Information:

Jabbour N (Ed) (2005) Transfusion Free Medicine and Surgery, Blackwell Publishing
ISBN 1405121 59 9

Leone BJ (1998) Artificial Blood: What is it? Will I use it? Jacksonville Medicine

Sarkar S (2008) Artificial Blood. Indian J Crit Care Med, Jul-Sept; 12(3): 140-144

Simoni J. (2012) Artificial Oxygen Carriers: Renewed Commercial Interest and Scientific/Technological Advances. Artificial Organs, 36: 123–126.

Thomas D, Thompson J, Ridler B (Eds) (2005) A Manual for Blood Conservation, Tfm publishing
ISBN 1 903378 24 9

Vandegriff K. D., Young M. A., Keipert P. E. and Winslow R. M. (2007), The safety profile of Hemospan®: a new oxygen therapeutic designed using maleimide poly(ethylene) glycol conjugation to human hemoglobin. Transfusion Alternatives in Transfusion Medicine, 9: 213–225.

2. Filtration of Blood Components

All blood components (red blood cells, platelets and FFP) should be administered through a giving set with an integral filter to remove clots and other debris. A 170-200 micron screen filter is the norm in Blood Component administration sets.

Leucocyte Reduction Filters

Leucocyte reduction filters are absorption filters which are designed to remove most of the white blood cells. Universal leucodepletion for all blood components in the UK was mandated by the Department of Health in 1998 to try to reduce the risk of transmission of variant Creutzfeldt–Jakob Disease (vCJD) by blood transfusion. Implementation was completed by November 1999 and since then all blood components in England have been leucodepleted to less than 5×10^6 leucocytes per unit in 99% component and less than 1×10^6 leucocytes per unit in 90% components. Leucodepletion at source means that bedside leucodepletion filters are no longer required.

Further Information:

Sheila McClellan (2006) What has leucodepletion done for patients? Blood Matters Issue 19
http://hospital.blood.co.uk/media/27147/bm19.pdf

Microaggregate Filters

Microaggregate filters have a very small pore size (20-40 microns) to filter out microscopic debris (clumps of dead cells and fibrin strands) in stored blood.

The clinical value of microaggregate filters is uncertain. They were previously thought to protect patients from developing occlusion of pulmonary capillaries by transfused cellular debris. However, current literature suggests that such complications are not attributable to blood component administration and that these filters provide no advantage over use of a standard screen (170-200 microns) filter integral in Blood Component giving sets for routine transfusion. There are some studies that suggest microaggregate filters may be indicated during cardio bypass surgery or in patients with impaired pulmonary function, although even in these situations their use is controversial.

The routine use of microaggregate filters for neonatal transfusion is also not warranted since to date no convincing studies exist to indicate efficacy and the relatively fresh red cell components used for most neonatal transfusion contain minimal amounts of microaggregates.

The available literature suggests, however, that microaggregate filters have some intrinsic disadvantages. Of particular concern is the administration of platelet components through microaggregate filters. A portion of the platelets themselves will be trapped by microaggregate filters, diminishing the therapeutic value of the transfusion and thereby ultimately increasing the patient's transfusion requirement and donor exposure.

If they are used for blood in circumstances where there are no 170-200 micron filters, they will not cause harm, but may slow the rate of transfusion.

Microaggregate filters must not be used for granulocyte transfusions.

Further Information:

Puget Sound Blood Centre Administration Guidelines:
http://www.psbc.org/bcrm/pdf/King_County_SectionB_123_RevA.pdf

Filtering Requirements for Salvaged Blood

In cell salvage where washing is employed, the only specific filter recommended for use is the RS LeukoGuard for use in obstetrics and malignancy.

The American Association of Blood Banks (AABB) guidelines state that all salvaged blood should be filtered to remove potentially harmful contaminates. All types of blood administration sets should incorporate a screen filter and for the majority of users this would appear sufficient.

There is an argument for the use of microaggregate/leucocyte reduction filters in the cardiac setting where the reinfusion of activated neutrophils may exacerbate reperfusion injury. The evidence for this however is not that robust.

There is also a theoretical concern in orthopaedic surgery that fat globules released from the bone marrow may be reinfused resulting in fat embolism syndrome, but again there is no supporting evidence. If this is a concern for your clinicians it can be addressed by not infusing the last few mls of the salvaged blood as the fat should form a layer at the top of the salvaged unit.

Use of the LeukoGuard RS is advocated in obstetrics and malignancy, however there are limitations with their use – the flow rate is very slow and the maximum capacity per filter is around 450ml. This filter however is the only one that has been shown to effectively remove contaminants specific to these settings. Further research may give us more options in the future.

Further Information:

Factsheet 7 on UKCSAG Toolkit on Transfusion Guidelines website:
http://www.transfusionguidelines.org.uk/transfusion-practice/uk-cell-salvage-action-group/technical-factsheets-and-frequently-asked-questions-faq

Blest A and Roberts M et al (2008): How often should a red blood cell administration set be changed while a patient is being transfused? A commentary and a review of the literature. Transfusion Medicine 18 pp 121-133.

NICE (2005) Intraoperative blood cell salvage in obstetrics:
http://www.nice.org.uk/guidance/index.jsp?action=byID&r=true&o=11038

In-line Bacterial Filters

The following is taken from Guidelines for the Prevention of Intravascular Catheter-Related Infections from the Centres for Disease Control and Prevention:
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5110a1.htm

In-line filters reduce the incidence of infusion-related phlebitis. No data support their efficacy in preventing infections associated with intravascular catheters and infusion systems. Proponents of these filters cite several potential benefits to using them, including:

- reducing the risk for infection from contaminated infusate or proximal contamination (i.e. introduced proximal to the filter)
- reducing the risk for phlebitis in patients who require high doses of medication or in those in whom infusion-related phlebitis already has occurred
- removing particulate matter that might contaminate IV fluids
- filtering endotoxin produced by gram-negative organisms in contaminated infusate.

These theoretical advantages should be tempered by the knowledge that infusate-related blood stream infection is rare and that filtration of medications or infusates in the pharmacy is a more practical and less costly way to remove the majority of particulates. Furthermore, in-line filters might become blocked, especially with certain solutions (e.g. dextran, lipids, and mannitol); thereby increasing the number of line manipulations and decreasing the availability of administered drugs.
Thus, for reducing the risk for catheter related bloodstream infection, no strong recommendation can be made in favour of using this type of in-line filters.

Prion Filters

Prion removal filters for use in the processing of blood are being developed and piloted as an approach to reducing the risk of transmission of prions by blood transfusion. However, these filters lead to an increase in red cell (and/or platelet) loss, possibly increasing the number of units of red cells/platelets needed for a therapeutic dose. This in turn will require increased collection targets and result in increased donor exposure for recipients.

Further Information:

Joint UKBTS/HPA Professional Advisory Committee
Evaluation of Efficacy of Prion Removal Filters Version 2 (April 2012)
http://www.transfusionguidelines.org/document-library/documents/evaluation-of-efficacy-of-prion-removal-filters

Teljeur C et al (2012) Cost Effectiveness of prion filtration of red blood cells to reduce the risk of transfusion-transmitted variant Creutzfeldt-Jacob disease in the Republic of Ireland.
Transfusion; 52(11):2285-93

Use of Prion filters also results in a reduction in levels of coagulation factors.
(Hewitt P (2006) Impact of vCJD on the UK Blood Supply, Blood Matters 19, p12-13)
http://hospital.blood.co.uk/media/27147/bm19.pdf

3. Normal Blood Values

Haematology tests determine specific blood parameters and are useful in diagnosing disorders such as anaemia, leukaemia and infection. Staff should refer to the normal ranges as published within their organisation as these may be different due to the individual technologies used in the labs.

Normal Adult Blood Volume

The normal healthy adult Total blood volume (TBV) is approximately 70 ml/kg body weight e.g. TBV of a 70 kg adult is 4.9 litres.

Haemoglobin
Haemoglobin transports oxygen. It is the main component of red blood cells (RBCs) and a good indicator of anaemia.

Men:	140 -170 g/L
Women:	120 -160 g/L
Children:	120 -140 g/L
Newborn:	140 - 240 g/L

Haematocrit (Hct) or packed cell volume (PCV)
The Hct reflects the proportion of blood occupied by RBCs by measuring the percentage volume of packed RBCs.

Men:	Hct	45%	(Range 38 - 51%)
Women:	Hct	40%	(Range 36 - 47%)

Mean Corpuscular Volume (MCV)
The MCV is the average volume of red cells, calculated from the haematocrit and the red cell count, in erythrocyte indices.

MCV	76 - 100 cu µm

White blood cell count (WBC) and differential
WBC can be used to diagnose infection and inflammation, and to monitor response to chemotherapy or radiotherapy. White cell differential provides more specific information about the immune system. There are 5 major types of WBC:

Total white blood cells (WBC)	4.0 - 11.0 x10^9/L

Differential counts (x10^9/L) - given as an absolute value or as a percentage

Neutrophils	2.0 - 7.5	60 - 70%
Lymphocytes	1.0 - 4.0	25 - 30%
Monocytes	0.0 - 0.8	5 - 10%
Eosinophils	0.0 - 0.5	1 - 4%
Basophils	0.0 - 0.2	up to 1%

These values are sometimes higher in neonates and infants.

Platelets
Platelets are produced in the bone morrow from cells called megakaryocytes. They circulate for approximately one week, and are then destroyed by the spleen. The main function of platelets is to arrest bleeding. Platelets are primarily activated when brought into contact with collagen, when the endothelial blood vessel lining is damaged. However there are several other activating factors. Once activated, they release a number of different coagulation factors and platelet activating factors. Platelets go through a process of aggregation and adhesion to form a platelet plug to stop bleeding. A low platelet count is called thrombocytopenia.

Platelet count	150,000-400,000/mL or 150-400 x10^9/L

Clotting
Clotting tests include International Normalised Ratio (INR) used to monitor oral anticoagulation; Prothrombin Time (PT) measures 'extrinsic' system plus final common pathway and Activated Partial Thromboplastin Time (APTT) measures 'intrinsic' system plus final common pathway. Different machines/techniques give different results for clotting tests; therefore they are often expressed as a ratio against a 'control' (normal) plasma.
Normal clotting ratios are around 1.0.

Coagulation problems may occur in patients because of:

a) loss of haemostatic factors
b) consumption in clot formation
c) dilution with blood components and volume expanders
d) depletion of coagulation factors due to inadequate synthesis
e) over anticoagulation with Warfarin, for example.

Dilutional Coagulopathy

Clotting factors – As a guide, when red cells in additive solution are transfused, a prothrombin time ratio (PTR) of >1.5 (clotting factors approximately 50% of normal) will be reached after replacement of 1 - 1.5 x blood volume, or transfusion of 8 - 12 units of red cells.

A PTR of >1.8 (clotting factors approximately 30% of normal) will be reached after replacement of 2 x blood volume.

Fibrinogen - As a guide fibrinogen is likely to fall to < 1g/l after replacement of 12 units of red cells or 1.5 x blood volume.

The platelet count will halve for every 1 x blood volume replaced and depending on the starting count, will usually fall to 50 - 100 x 10^9/l after 2 blood volume replacement.

Further Information:

BCSH Guidelines (2008), Guidelines on the assessment of bleeding risk prior to surgery or invasive procedures.
http://www.bcshguidelines.com/documents/bleeding_risk_surgery_bjh_2008.pdf

BCSH Guidelines (2004), Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant.
http://www.bcshguidelines.com/documents/FFP_28020604.pdf
http://www.bcshguidelines.com/documents/FFP_Amendments__09122005.pdf

Norfolk D (Ed) (2013) Handbook of Transfusion Medicine, 5th Edition. The Stationary Office ISBN 9780117068469
http://www.transfusionguidelines.org/transfusion-handbook

Practical Transfusion Medicine, 2nd Edition, Edited by Michael F. Murphy and Derwood H. Pamphilon, Blackwell Publishing.

4. Appropriate Use of Blood

4.1 Patient Consent for Blood Transfusion

The Advisory Committee for Blood, Tissue and Organs, (SaBTO) initiated a public consultation questionnaire in March 2010 on patient consent for transfusion with key stakeholders. The consultation had the following key objectives:

- ***Identify the preferred option for recording consent***
- ***Explore the potential operational impact of implementing a standardised form of consent for transfusion***
- ***Confirm what type of information patients should receive***

The consultation process identified keys issues in transfusion practice and resulted in 14 recommendations.

Key Issues:

- Patients are not being given information on risks, benefits, and alternatives to transfusion, or the right to refuse transfusion
- Patients may not be aware they have received a transfusion
- Patients who receive blood may go on to donate blood, without realising that they should not
- There is inconsistent practice across the UK.

Recommendations:

1. Valid consent for blood transfusion should be obtained and documented in the patient's clinical record by the healthcare professional.

2. There should be a modified form of consent for long term multi-transfused patients, details of which should be explicit in an organisation's consent policy.

3. There should be a standardised information resource for clinicians indicating the key issues to be discussed by the healthcare professional when obtaining valid consent from a patient for a blood transfusion: http://www.transfusionguidelines.org/transfusion-practice/consent-for-blood-transfusion

4. The consent standard developed by Health Improvement Scotland (formerly NHS Quality Improvement Scotland) should be adopted throughout the UK for consent for blood transfusion. http://www.transfusionguidelines.org/transfusion-practice/consent-for-blood-transfusion

5. The Care Quality Commission (CQC), NHS Litigation Authority (NHSLA) and equivalent organisations in the Devolved Administrations should be aware of the SaBTO consent standard for blood transfusion.

6. A UK comparative audit of consent for transfusion should be carried out, facilitated by the National Comparative Audit of Blood Transfusion (a collaborative between the Royal College of Physicians and NHS Blood and Transplant).

7. Depending on the role envisaged for Healthwatch, the potential role of patient groups in providing an active oversight should be explored.

8. There should be a standardised source of information for patients who may receive a transfusion in the UK.

9. Patients who have received a blood transfusion and who were not able to give valid consent prior to the transfusion should be provided with information retrospectively.

10. SaBTO consent working group should produce good practice guidance to help identify the most effective way of providing information retrospectively when patients were unable to give prior consent. http://www.transfusionguidelines.org/transfusion-practice/consent-for-blood-transfusion

11. UK Blood Services should have an ongoing programme for educating patients and the public about blood transfusion as part of their respective 'Better Blood Transfusion' strategies.
12. Use of the LearnBloodTransfusion e-learning package should be promoted by the UK Blood Services and Royal Colleges for all staff involved in the blood transfusion process. A module on

consent has been developed and is now available on the LearnBloodTransfusion website: http://www.learnbloodtransfusion.org.uk/

13. The UK Better Blood Transfusion Network should explore the feasibility of developing a new module specific to consent and blood transfusion as part of its 2012/13 work plan.
14. Completion of the LearnBloodTransfusion e-learning package should be included in all undergraduate curricula. Reference to consent for blood transfusion should be included in the undergraduate curriculum as part of the learning objectives outlined for the principles of consent.

A SaBTO approved action plan to support the delivery of these recommendations is available at: http://www.transfusionguidelines.org/transfusion-practice/consent-for-blood-transfusion

The 'Patients' Charter 1992' states that we all have the right "To be given a clear explanation of any treatment proposed, including any risks and any alternatives before you decide whether you will agree to the treatment." The Health Service Circular (2007/001) Better Blood Transfusion requires hospitals to ensure patients who are likely to receive blood transfusion are informed of their choices. This is echoed by Patient Blood Management initiatives, which puts the patient at the heart of decisions made about blood transfusion to ensure they receive the best treatment and avoid the inappropriate use of blood and blood components. However, it is not mandatory in this country for patients to sign a consent form before receiving a transfusion, but may be a local requirement.

The need for consent must not prevent or delay essential or urgent transfusion, but the presence of a valid Advance Decision Document declining transfusions should always be respected (See section 4.2).

Change to the consent law in 2015
The law relating to informed consent has recently changed and there is now an increased duty for a clinician to provide a patient with accurate, up to date information about the proposed medical or surgical procedure. Patients are better informed and the courts now endorse and indeed expect a collaborative approach to consent. What amounted to good clinical practice has now become necessary clinical practice.

For more information:
Update on the UK Law on Consent:
http://www.bmj.com/content/350/bmj.h1481

Types of Consent

Implied Consent e.g. a patient is told they need a blood test and willingly holds out their arm for the test to be completed, no discussion of risks and benefits usually takes place.

Written/verbal Consent e.g. some dialogue takes place between the health professional and the patient, the patient either verbally states they are happy to proceed or they sign to the same effect.

Informed Consent e.g. discussion with the patient regarding the relevant risks, benefits and alternatives to proposed treatment. The information should be given in a timely manner to enable alternatives to be considered and to ensure the information is understood, giving time for the patient to ask questions.
"It is advisable to inform the patient of any material or significant risk in the proposed treatment, any alternatives to it and the risks incurred by doing nothing" (DH 2001).

Valid Consent - for consent to be valid, it must be voluntary and informed, and the person consenting must have the capacity to make the decision (NHS Choices, 2012).

Further Information:
Patient Information Leaflets and further patient information can be found at;

Transfusion Practice section of the Transfusion Guidelines website:
http://www.transfusionguidelines.org.uk/transfusion-practice/consent-for-blood-transfusion-1

British Medical Association:
http://bma.org.uk/practical-support-at-work/ethics/consent

Department of Health:
https://www.gov.uk/government/publications/reference-guide-to-consent-for-examination-or-treatment-second-edition

NHS Choices:
http://www.nhs.uk/conditions/consent-to-treatment/pages/introduction.aspx

Norfolk D (Ed) (2013) Handbook of Transfusion Medicine, 5th Edition, The Stationary Office
ISBN 9780117068469
http://www.transfusionguidelines.org/transfusion-handbook

The RCN consent bibliography:
http://www.rcn.org.uk/development/researchanddevelopment/rs/publications_and_position_statements/informed_consent

UK Clinical Ethics Network:
http://www.ukcen.net/index.php/main/policies_guidelines/consent

Web based access for ordering patient information leaflets:
https://hospital.nhsbtleaflets.co.uk/

PDFs of NHSBT's patient information leaflets:
http://hospital.blood.co.uk/patient-services/patient-blood-management/patient-information-leaflets/

Patient information from NHSBT:
http://www.nhsbt.nhs.uk/what-we-do/blood-transfusion/

4.2 Refusal of Blood Transfusion

Patient Blood Management puts the patient at the heart of the decisions made about blood transfusion and it is possible, after understanding the risks and benefits of a transfusion, that some patients may refuse blood. In these circumstances, following one of the actions of the HSC 2007/001 Better Blood Transfusion, Trusts should ensure that procedures are in place for managing patients who refuse blood. Patients who refuse a blood transfusion do so for various reasons and may not necessarily be a Jehovah's Witness. It is important that the patient understands the consequences of not having a blood transfusion and wherever possible is offered an alternative.
Refusing a blood transfusion should be documented in the medical notes and brought to the attention of all medical professionals involved in the care of the patient. The medical professionals need to clarify with the patient which blood components and products, if any, they would be willing to accept.
Patients that are Jehovah's Witnesses should be invited to lodge a copy of their Advance Decision Document to be included with their medical notes. This will serve to document some information regarding the patient's personal views on autologous procedures and blood components.

Jehovah's Witnesses have a countrywide network of Hospital Liaison Committees (HLCs). They are available 24 hours a day to assist with difficulties, either at the request of the treating team or the patient. Contact information for these committees is available from a central co-ordinating office, Hospital Information Services (020 8906 2211 or email his.gb@jw.org)

Further Information:

Transfusion Practice section of the Transfusion Guidelines website:
http://www.transfusionguidelines.org.uk/transfusion-practice/consent-for-blood-transfusion-1

Norfolk D (Ed) (2013) Handbook of Transfusion Medicine, 5th Edition The Stationary Office
ISBN 9780117068469
http://www.transfusionguidelines.org.uk/transfusion-handbook

4.3 Transfusion Indication Codes

The decision to transfuse any blood component must be made on the basis of a clear clinical indication and should be a balance between the known risks of transfusion and the intended benefit.

Studies of the use of red cell transfusion suggest that morbidity, mortality, haemodynamic, pulmonary and oxygen transport variables do not differ between restrictive strategies employing a haemoglobin trigger of 70-80g/l and more liberal strategies (trigger of 100g/l). A restrictive strategy may be associated with decreased adverse outcomes in younger, less sick, critical care patients.

Most guidelines note that red cell transfusion is rarely indicated when the haemoglobin is greater than 100g/l in healthy stable patients and is almost always indicated when below 60g/l.

The National Blood Transfusion Committee (NBTC) *Indication codes for transfusion – an audit tool* draws together indications for red cell concentrates, fresh frozen plasma, cryoprecipitate and platelet concentrates from available transfusion guidelines and evidence into one short document to support clinician's decision to transfuse. The indications set out are centred around the clinical situation and relevant clinical results. However it is also acknowledged that "Clinical judgement plays an essential part in the decision to transfuse or not".

Further Information:

Association of Anaesthetists of Great Britain and Ireland. Blood transfusion and the anaesthetist: red cell transfusion 2, 2008:
http://www.aagbi.org/sites/default/files/red_cell_08.pdf

British Committee for Standards in Haematology.(2012) Guidelines on the management of anaemia and red cell transfusion in adult critically ill patients:
http://onlinelibrary.wiley.com/doi/10.1111/bjh.12143/pdf

British Committee for Standards in Haematology (2004)..Guidelines for the use of Fresh Frozen Plasma, Cryoprecipitate and Cryosupernatant:
http://www.bcshguidelines.com/documents/FFP_28020604.pdf
http://www.bcshguidelines.com/documents/FFP_Amendments__09122005.pdf

British Committee for Standards in Haematology.(2003) Guidelines for the use of platelet transfusions:
http://www.bcshguidelines.com/documents/platelettrans_bjh_04072003.pdf

National Blood Transfusion Committee (2013) Indication codes for transfusion – an audit tool:
http://www.transfusionguidelines.org.uk/document-library/documents/indication-codes-for-transfusion-an-audit-tool

4.4 Maximum Surgical Blood Order Schedule

Maximum Surgical Blood Order Schedule (MSBOS), is a protocol designed to promote the efficient use of blood resources and minimise component wastage. MSBOS is list of surgical procedures and the recommended maximum number of units of red cells which should be requested to be cross-matched for each procedure. Recommendation could include 'no blood required', 'group and save' or 'cross-match'. This schedule will be agreed and set at hospital/Trust level.
Some hospitals may not have a MSBOS as they may use electronic Issue for some blood components. Electronic issue involves the selection and issuing of units without the direct serological testing between the patient and the donor red cells. Electronic issue is not suitable for all patients, those hospitals using electronic issue must comply with the British Committee for Standards in Haematology (BCSH) national guidelines (2006) 'The specification and use of information technology systems in blood transfusion practice'.

The Implementation of a (M)SBOS will:
- Minimise unnecessary cross-matching and therefore, unnecessary workload in the hospital transfusion laboratory
- Promote efficient utilisation of the hospital transfusion laboratory blood stock, ensuring blood is available for those most in need
- Optimise the shelf life of the blood and reduce wastage
- Ensure patients attending theatre have sufficient blood 'cover'.

A Successful (M)SBOS should be:
- Evidence based (cross-match to transfusion ratio considered) and audited regularly to ensure it is kept in-line with changing practice
- Widely consulted – developing/updating a (M)SBOS requires wide consultation between the Hospital Transfusion Team, surgeons, anaesthetists as well as the co-operation of all junior medical staff
- Regularly reviewed and updated
- Disseminated well within the organisation.

Factors which influence the agreed tariff for a surgical procedure include:
- Local, regional and national audit
- Cross-match to transfusion ratio
- The use of alternatives such as cell salvage, iron optimisation, tranexamic acid
- Consultation with surgeons and anaesthetists

- The proximity of the hospital transfusion laboratory to the operating theatres
- Surgical techniques and advances
- Electronic issue
- Accessibility of blood promptly when there is unexpected blood loss
- Guidelines.

Consideration should be given to the time taken to acquire and cross-match antigen-negative blood in patients with red cell alloantibodies.

Flexibility using a (M)SBOS is necessary but when orders are in excess of the agreed tariff, the clinician should have valid rationale.

Further Information:

Norfolk D (Ed) (2013) Handbook of Transfusion Medicine (5th edition), The Stationary Office
TSO ISBN 9780117068469
http://www.transfusionguidelines.org.uk/transfusion-handbook

4.5 Near Patient/Point of Care Testing (POCT)

Near patient testing, also known as 'point of care' testing or 'bedside' testing, allows a range of tests to be performed quickly and simply at the patient's side. Used within a variety of clinical settings, near patient testing can give quick results that can help optimise effective clinical decision-making. This section will concentrate on near patient testing commonly used to provide results that may influence the decision to transfuse.

There are two key types of point of care testing for transfusion practice: bench top analysers and hand-held devices.
The bench top systems are smaller versions of laboratory machines, where the testing process is automated. An example of this is viscoelastic measurement, often referred to as thromboelastography (TEG) or thromboelastometry (TEM).
These techniques are used to monitor blood clot formation, in real time, which is a complex interaction of plasma proteins (clotting factors), blood cells and other factors which may have an effect on clotting (e.g. drugs). Unlike clotting assays, they measure not only the clotting time (speed), but also clot formation characteristics such as strength and clot stability and breakdown. Using different reagents, complex clinical cases can be analysed and provide rapid results.
TEG/ ROTEM are used to guide the use of platelets, FFP and cryoprecipitate, especially in the bleeding patient.

Hand-held systems include the HemoCue® haemoglobin analyser, a portable and quick method of measuring haemoglobin at the bedside. It is particularly useful in acute clinical situations to inform and support clinical assessment of red cell transfusion requirements. The HemoCue® system consists of disposable microcuvettes, which contain reagents in dried form. A patient blood sample is drawn into the microcuvette, which is then placed into the portable unit where a photometer determines the haemoglobin.

Another portable system for measuring haemoglobin, using a non-invasive process, is the Masimo Rainbow® System. These SpHb® devices can perform continuous or intermittent measurement and work using similar technology to SpO_2 (oxygen saturation) monitors.

It is important to note that reliable results can only be achieved if the preparation and correct procedure for use of these machines is correctly followed. Establishments using these systems should ensure that a robust training programme and quality control process is in place.

In order to ensure POCT is carried out correctly and gives reliable results, the BCSH General Haematology Taskforce issued *Guidelines for Point Of Care Testing: Haematology* in July 2008.

Key recommendations from these guidelines:

- The purpose, nature and potential benefits of POCT at any site should be defined before initiating the service

- An NHS Trust POCT committee should be appointed to take responsibility for all POCT and ensure it is appropriate and credible

- The advice of an accredited clinical laboratory should be sought in order to achieve optimum quality and cost effectiveness
- It is sensible to co-opt the local Consultant Haematologist and relevant laboratory managers onto the POCT committee to be involved in any ongoing provision of POCT
- The POCT committee should be clear as to the purpose of the test: is it for diagnosis, screening, monitoring or treatment?
- The POCT committee should investigate the full cost of the service including purchase, running costs, staff training etc
- The POCT environment should be clean and well lit and may require temperature control. Risk assessments must be carried out
- Blood and contaminated disposables must be disposed of according to guidelines
- Accurate documentation must be kept detailing patient ID, staff ID, date of test, result of test, lot numbers of equipment, reagents, calibrant and quality control material
- All staff using the equipment must be trained and competent to do so
- Internal quality control and external quality assurance programmes must be put in place
- Possible litigation for erroneous results and the legal responsibilities should be considered.

Further Information:

British Committee for Standards in Haematology (2008) Guidelines for point of care testing: haematology
http://www.bcshguidelines.com/documents/pont_of_care_bjh_2008.pdf

Price CP, John AS, Hicks MH (Eds) (2001) Point of care testing, Amer Assn for Clinical Chemistry
ISBN: 159425012X

4.6 Emergency Planning and Business Continuity

- **Blood Shortage Plan**

There exists the ever possible risk of reduced stocks and blood shortages, although this is rare in the UK the National Blood Transfusion Committee (NBTC) sub group on contingency planning, released an integrated plan listing actions to be taken by the National Blood Services and Hospitals in times of shortages.

A summary of the original plan was issued via the NHS gateway to Chief Executives of Trusts on 23rd July 2004 (gateway reference 3344). On 25th November 2009, the plan was updated (gateway reference 12810).

The objective is to ensure that patients who need blood can receive a transfusion regardless of their geographical location. The arrangements are designed to ensure that:

- Blood is available for all essential transfusions to patients equally across the country
- Overall blood usage is reduced to ensure the most urgent cases receive the supply which is available.

The plan is designed to operate at all times, using appropriate use initiatives which may prevent activation of formal blood shortage arrangements.

- **Platelet Shortage Plan**

A second plan to address platelet shortages was issued to Chief Executives in September 2006 via the NHS gateway (Gateway reference 6514).

Both the blood and platelet shortage plans are available at:
http://hospital.blood.co.uk/business-continuity/contingency-planning/

- **Recommendations for Organisations of Hospital Transfusion Services following the July 2005 London Bombings**

The NBTC established an Emergency Planning Working Group to review the lessons learned in relation to organisation of transfusion services following the 7th July London Bombings. The recommendations were issued in December 2006 from the NBTC. Copies can be obtained from the NBTC website.

http://transfusionguidelines.org/uk-transfusion-committees/national-blood-transfusion-committee/responses-and-recommendations/recommendations

http://hospital.blood.co.uk/media/3009/cb82386f-890d-4e75-81cd-82c57fab2dd0.pdf

- **Flu Planning**

The NHS has prepared plans to mitigate the impact of a flu pandemic. UK Blood Services have prepared their own plans which concentrates on the impact a pandemic could have on them and the action necessary to mitigate the impact.

Further Information:

A copy of the top level NHSBT pandemic flu plan can be found at:
http://hospital.blood.co.uk/business-continuity/contingency-planning/

See also Blood Matters Autumn 2006 'Pandemic Influenza and the blood supply' Issue 20
http://hospital.blood.co.uk/media/27148/bm20.pdf

4.7 Nurse Authorisation

A collaborative project was undertaken by NHS Blood and Transplant and The Scottish National Blood Transfusion Service (SNBTS) to investigate the "prescribing" or more properly "authorisation" of blood transfusions by nurses and midwives. Section 130 of the 1968 Medicines Act has been amended by Section 25 of the Blood Safety and Quality Regulations (BSQR) 2005 (SI2005 No 50). In effect this means that blood and blood components are excluded from the legal definition of medicinal products and therefore, cannot be "prescribed" by a practitioner. There is therefore no legal barrier to nurses authorising blood transfusions, provided it is within their scope of practice and that they are appropriately trained and deemed competent.
The nurse undertaking the role requires skills to assess a patient, take a history, make a decision, understand the principles of consent and also have the clinical knowledge and expertise to respond to adverse events in a timely manner. For these reasons, this role development is generally limited to advanced nurse practitioners. The hospital policy must state which staff groups are covered to authorise blood components, how they can be supported, and what additional training is required.
The Independent and Supplementary Prescribing for Nurses and Midwives and Supplementary Prescribing for Allied Health Professionals (V300) course does not include the authorisation of blood components.

It is also acknowledged that for this role development to be successful, a high level of medical consultant support is required. It is essential for all key stakeholders to be consulted and that the service provided is in the best interests of the patient.

Further Information:
Green J and Pirie L (2009) A Framework to Support Nurses and Midwives Making the Clinical Decision and Providing the Written Instruction for Blood Component Transfusion.
http://transfusionguidelines.org/document-library/documents/bt-framework

Nursing and Midwifery Council (2006), Standards of proficiency for nurse and midwife prescribers
http://www.nmc-uk.org/Publications/Standards/

4.8 Home Transfusions

For many patients with certain disorders blood transfusion support is essential to maintain life and relieve symptoms. Transfusion support may be required for an intermediate or long term basis and as a number of these patients may have a reduced life expectancy, it is essential that hospital services intervene no more than is necessary. There is a desire to minimise the intrusion of hospital care for these patients however, organising a safe, efficient blood transfusion service involves the coordination of many personnel performing different tasks.

The aim of a home/community transfusion service is to:

- Maintain the patients lifestyle with the minimum of disruption to their daily activities
- To provide a safe, efficient and cost effective service
- To increase the patients control and independence for those who wish it.

The out of acute hospital setting refers to:

- The patients own home
- Residential and nursing homes
- Hospices
- Renal satellite units
- Local treatment centres
- All other areas where blood components are administered that are not covered by local acute hospital protocols.

Further Information:

Green J and Pirie L (2012) Framework for the Provision of Blood Transfusion Out of the Acute Hospital Setting (3rd edition)
http://hospital.blood.co.uk/media/27199/home_tx_framework_post-shot-2013.pdf

5. Patient Blood Management

Patient Blood Management (PBM) is an evidence-based, multi-disciplinary approach to optimising the care of patients who might require a blood transfusion. It builds on the success of the previous Better Blood Transfusion Health Service Circular Initiatives by putting the patient at the heart of decisions made about blood transfusion to ensure they receive the best treatment. PBM was launched in June 2012 and focussed on:

- Pre, intra and post operative management
- Identification and management of anaemia
- Avoidance of blood transfusions if alternatives are available
- Use of pharmacological agents.

The role of the Transfusion Practitioner (TP) in patient blood management will be dependant upon the individual TP's background and the support and functionality of the Hospital Transfusion Team and Hospital Transfusion Committee.
The TP is often seen as the key person to deliver the blood conservation message and provide or facilitate training and education. However, PBM is also aimed at those responsible for deciding clinical priorities within their Trusts.

5.1 Pre-operative Preparation

All patients should be suitably prepared for the surgery they require. The NHS Plan (DH 2000) recommended the setting up of "preparing patients for surgery" clinics which should also explore those aspects of patient health relevant to their requirements for blood transfusion (both autologous and allogeneic). The National Institute for Health and Clinical Excellence (NICE) has published guidance on preoperative tests. Local haematologists and clinics need to work together to produce protocols, which should include the blood tests to be carried out depending upon the medical history of the patient.

The West Midland Regional Transfusion Committee has produced guidelines for the management of anaemia in pre-operative assessment clinics:
http://www.transfusionguidelines.org/uk-transfusion-committees/regional-transfusion-committees/west-midlands/education-resources

The Enhanced Recovery Programme is about improving patient outcomes and speeding up a patient's recovery after surgery. It also aims to ensure that patients always receive evidenced based care at the right time. The pre-operative assessment optimisation of Hb plays an important role in this.

Assessment of Patients with Regard to Blood Conservation Should Include:

- Investigation, diagnosis and treatment of anaemia, including correction of iron deficiency anaemia
- Investigation, diagnosis and treatment of any bleeding disorder or haemoglobin defect e.g. sickle or thalassaemia
- Assessment of the patient's current medication, its potential for increasing bleeding and whether it is safe to stop this prior to surgery to reduce the risk of bleeding
- Identification of problems which may require specialist intervention
- Patient beliefs in relation to blood transfusion e.g. Jehovah's Witnesses and other patients who may decline donated blood components.

Further Information:

Association for peri-operative practice:
http://www.afpp.org.uk/

Department of Health (2000) NHS Plan*:* A plan for investment. A plan for reform. The Stationary Office, London

James V (2004) A National Blood Conservation Strategy for NBTC and NBS Report from the Working Party on Autologous Transfusion and the Working Party on Alternatives to Transfusion of the NBS Sub-Group on Appropriate Use of Blood. NBTC, London

March JC, Bevan DH (2002) Haematological care of the Jehovah's Witness patient. Br J Haematol, 119 (1), 25-37, Review

NHS Institute for Innovation and Improvement (now closed but several tools still available at time of print)
http://www.institute.nhs.uk/quality_and_service_improvement_tools/quality_and_service_improvement_tools/enhanced_recovery_programme.html

NHS Improving Quality
http://www.nhsiq.nhs.uk/

NICE (2003) The use of routine preoperative tests for elective surgery
https://www.nice.org.uk/search?=+The+use+of+routine+preoperative+tests+for+elective+surgery

NICE (2015) Blood Transfusion
http://www.nice.org.uk/guidance/ng24/

Pre-operative assessment and patient preparation. Association of Anaesthetists of Great Britain and Ireland.
http://www.aagbi.org/sites/default/files/preop2010.pdf

Preoperative association:
http://www.pre-op.org/

5.2 Autologous Blood Use

Autologous donation means 'blood and blood components collected from an individual and intended solely for subsequent transfusion or other human application to the same individual' (adapted from the Blood Safety and Quality Regulations 2005).

Pre-deposit Autologous Donation (PAD)
It is possible, under certain special circumstances, for patients to pre-donate blood for their own use. Up to three units of blood can be collected in advance of their planned surgery, which may be stored for up to 35 days in standard blood bank conditions. Iron supplements and sometimes erythropoietin, may be given, to patients, to prevent anaemia or allow a larger number of units to be collected.

PAD can only be performed by a licensed 'Blood Establishment' (Blood Safety and Quality Regulations 2005). This blood has to be tested, processed, labelled and stored to exactly the same standards as donor blood and is subject to the same requirements for traceability. However, it must be clearly identified as being autologous blood for an intended recipient and stored separately from homologous donations. If autologous blood is not used for the patient who donated it, it cannot be used for another patient (as PAD donors have underlying medical conditions), therefore, it will be wasted.

Before the blood is re-transfused it must undergo viral testing; be ABO and D grouped and have compatibility checks done with a sample of the patient's blood, to avoid possible errors in issuing the blood to the wrong person.

Although PAD may reduce exposure to donor blood it does not reduce exposure to the overall transfusion process and the risks associated with identification errors; this, in addition to the fact that the risk of viral transmission by donor blood is remote, undermines the rationale for PAD. Many Jehovah's Witnesses will decline PAD and many patients will not be suitable for PAD due to existing health problems.
Therefore the BCSH guideline on PAD recommends its use only in exceptional circumstances (BCSH, 2007), these include:

- Patients with rare blood groups or multiple antibodies where allogenic blood is difficult to obtain
- Children with scoliosis (in practice other blood conservation methods are more commonly used)
- Patients who refuse allogenic blood transfusion but will accept PAD
- Patients at serious psychiatric risk associated with anxiety about exposure to donor blood

In addition certain criteria should be met (BCSH 2007) and PAD should only be considered:

- Before elective surgery that has a high likelihood of requiring transfusion
- When the date of operation is guaranteed
- If the patient is able to donate safely (assessed by a competent clinician)

For these reasons, PAD is not available from NHS Blood and Transplant except for patients with rare antibodies for whom it would be difficult to find suitable allogeneic blood.

Acute Normovolaemic Haemodilution (ANH)
Acute Normovolaemic Haemodilution (ANH) entails the withdrawal of blood from a patient, shortly before anticipated blood loss i.e. either immediately before or shortly after induction of anaesthesia, with simultaneous volume replacement by crystalloid and/or colloid (to maintain the circulating volume). The blood is stored at room temperature (in the operating theatre) and reinfused at the end of surgery or as indicated by intra-operative blood loss.

The maximum volume of blood that can be withdrawn during haemodilution depends on the preoperative haemoglobin, the lowest acceptable intra-operative haemoglobin and the estimated blood volume. Mathematical formulas are available to help calculate this amount. It is suggested that ANH is (or would be) most effective, in reducing donor blood component demand, in surgery with anticipated major blood loss and where the immediate transfusion of fresh whole blood containing platelets and clotting factors is seen as an advantage. However systematic reviews of trials have found no significant reduction in exposure to donor transfusions (Norfolk, 2013).

Examples of reported incidents associated with ANH include:

- Fluid overload
- Cardiac ischaemia
- Wrong blood to patient errors.

PAD and ANH are not currently recommended.

References

Boulton FE, James V (2007) Guidelines for policies on alternatives to allogeneic blood transfusion. 1.Predeposit autologous blood donation and transfusion. British Committee for Standards in Haematology (BCSH) Transfusion Medicine 17 (5) 354-365
http://www.bcshguidelines.com/documents/alt_allogeneic_blood_transfusion_1_pad_bjh_2007.pdf

Norfolk D (Ed). (2013) Handbook of Transfusion Medicine, 5th edition. TSO. Ch 6.
http://www.transfusionguidelines.org.uk/transfusion-handbook

Intra-operative Cell Salvage (ICS)

"Access to 24-h cell salvage support should be available in cardiac, obstetric, trauma and vascular centres" (BCSH, 2015)

This is a procedure by which the patient's own blood, that is shed during surgery, can be collected and then washed and processed in a cell salvage machine. The packed red cells which are produced can then be returned to the patient either during or shortly after surgery. Intra-operative cell salvage is used in many different types of surgery and means that the patient should require fewer red cell transfusions than would have been necessary if the procedure had not been used. Many Jehovah's Witness patients find this acceptable if a closed circuit system is set up. The UK Cell Salvage Action Group (UKCSAG) have produced a fact sheet for patients and educational material for staff.

Anticoagulant is fed in and mixed immediately with the shed blood. The anticoagulated blood is then drawn, via suction, into a sterile reservoir where it is filtered to remove large clots and debris. This blood is then washed with a saline solution during centrifugation to separate the red cells from white cells and platelets, plasma and other waste. The red cells are collected and re-suspended in normal saline in a re-infusion bag. During surgery, blood spillage collected on swabs can also be added to the cell salvage reservoir. The swabs are weighed, rinsed in a solution of saline and the resulting blood mixture can be drawn into the reservoir for processing. This ensures that as much blood as possible is salvaged back for the patient. A factsheet on swab washing has been produced by the UKCSAG.

The collected red blood cells can then either be re-infused immediately, or they may be taken to recovery with the patient to begin re-infusion. There is a time limit of four hours from collection in which to re-infuse the red cells, after which they must be discarded because of the possibility of bacterial proliferation. The bags of autologous red cells must be clearly labelled with the patient's name, date of birth and hospital/NHS number and these details must be checked against the details on the patient's identity band before they are administered. The date and time of collection must also be recorded on the bag, so that the time of four hours from collection to re-infusion is not exceeded. The UKCSAG have produced an autologous blood label for such use, which has been endorsed by all the major cell salvage equipment providers. The red cells are transfused through a 200μm filter (standard blood administration set) unless a leucodepletion filter is indicated.

Indications for ICS include:

- Surgery where there is significant anticipated blood loss
- Surgery in patients with bleeding risk factors or low preoperative haemoglobin
- Major haemorrhage
- Patients for whom it may be difficult to provide donor blood e.g. rare blood groups

- Patients who refuse donor blood but consent to ICS.

ICS is contraindicated when there is contamination of the surgical field from bowel contents, infection and other contaminants; a full list is available on Factsheet 9 at:
http://www.transfusionguidelines.org.uk/transfusion-practice/uk-cell-salvage-action-group

In addition, manufacturers do not recommend ICS in surgery for malignant disease. However, clinical experience suggests that if a leucodepletion filter is used the risk of malignant cell reinfusion and spread is not significant. Leucodepletion filters are also recommended in ICS for caesarean section. Concerns regarding amniotic fluid embolism have not been realised although significant fluid contamination should be aspirated before commencing blood collection.

Post-operative Cell Salvage
Post-operative cell salvage is the collection and re-infusion of the patient's own blood which has been collected by means of wound drainage after an operation. The blood collection takes place in theatre, recovery or back on the ward. Post-operative drains are commonly used in some types of cardiac and orthopaedic surgery.

The blood shed in the post-operative period can be collected in specially designed wound drains. This blood can then be filtered and returned to the patient. Some devices also wash the cells before re-infusion. The technique can be used when there is a predictable amount of post-operative blood loss, e.g. when knee surgery is performed under tourniquet. The blood loss must also be relatively 'clean', i.e. this technique should not be used in the presence of obvious or suspected infection. The volume of blood loss needs to be between 500 and 1000ml to make the procedure worthwhile and this blood must be reinfused within 6 hours of the start of collection. Post operative cell salvage has been most applicable to orthopaedic procedures.

The need for allogeneic blood transfusion can often be eliminated in cases where post-operative cell salvage has been used. However there are contraindications, usually associated with contamination of the surgical field. Also a closed circuit must be maintained to ensure sterility otherwise the blood is not suitable for reinfusion.

Learnbloodtransfusion, available throughout the UK and the Republic of Ireland, includes a Learn Cell Salvage module. This module is designed to offer any learner the opportunity to gain a broad understanding of a range of blood conservation techniques.

This e-learning course is available at: www.learnbloodtransfusion.org.uk

References:

Norfolk D (Ed). (2013) Handbook of Transfusion Medicine, 5th edition. TSO. Ch 6.
http://www.transfusionguidelines.org.uk/transfusion-handbook

UK Cell Salvage Action Group:
http://www.transfusionguidelines.org.uk/transfusion-practice/uk-cell-salvage-action-group

5.3 Surgical Strategies to Minimise Blood Loss

Sophisticated techniques have been developed to help reduce blood loss in surgical procedures. The application of mechanical or other surgical devices have become effective tools for surgeons to help them perform major surgical procedures with minimal blood loss.

Such devices include:

Microwave Ablation
This consists of a microwave generator, which emits an electromagnetic wave through the non-insulated portion of an attached antenna. Electromagnetic microwaves then agitate water in the surrounding tissue, producing friction and heat which leads to cellular death by coagulation necrosis. Extensive experience has been gained in using microwave ablation to destroy tumours of the uterus, breast, skeletal muscle, liver and prostate.

Ultrasonic Surgical Aspirator
This surgical instrument emits ultrasonic sound waves to break up tissue into micro fragments. A small vacuum quickly removes this tissue from the surgical area. The aspirator selectively dissects soft tissues

leaving nerves and blood vessels relatively unaffected. It is used to remove tumours, including those in the brain because of the minimal trauma to the surrounding tissues.

Jet Cutter
The jet cutter works on a similar principle to the Ultrasonic Surgical Aspirator except, that it jets a beam of hypertonic sodium chloride solution which allows simultaneous selective tissue division to occur.

- **Ultracision shears** – convert electric energy to mechanical energy and then finally thermal energy. The shears offer a combination of effects, which enable the precise cutting, safe joining together and coagulation of vessels. Shears have been widely used in laparoscopic surgery
- **Ligature device** – an instrument and technique that reduces the need for microclips in surgery. The ligature device makes it possible to pass a suture under a blood vessel, or other diffuse areas of bleeding, with a single movement. This technique may be applied during complex laparoscopic procedures.

Laser Devices
The laser radiation wavelength allows intensification of cutting and coagulation properties that are useful in both contact and non-contact surgical procedures. The laser radiation is delivered through an optical fibre and due to the photo thermal effect photocoagulation can be achieved. Areas of application for its use are general surgery, gynaecology, urology, oncology and neurosurgery.

Radiofrequency Tissue Coagulation
Radio frequency is used to create heat in a specific place, at a specific temperature for a specific time and ultimately results in destroying unwanted tissue. Liver, pancreatic, gastric and colon surgery are some areas of its application.

Argon Beam Coagulator
The argon beam coagulator (ABC) quickly coagulates bleeding tissues. An ABC is a non-contact device that conducts a radio-frequency current to tissue along a jet of inert, non-flammable argon gas. A grounding pad placed under the patient allows the current to flow from the tip of the probe to the tissue. Argon gas has a lower ionisation potential than air and consequently directs the flow of current. The argon gas may also blow away blood and other liquids on the tissue surface, enhancing visualisation of the bleeding site as well as eliminating electric current dissipation in the blood. The ABC is thought to be the best means of endoscopically controlling diffuse gastric or other haemorrhage.

Fibrin Sealant
There are two types of tissue sealant; biological and non biological.
The most prominent of these sealants is Fibrin, which is biological in origin and consists of components of the natural clotting cascade. Fibrin sealants can be autologous or manufactured. When the two separate parts of the fibrin sealant are mixed, coagulation occurs. There are two different fibrin matrices:

- White non-transparent, which produce coarse clots. These can be used during tissue regeneration
- Transparent, which produce fine clots. Fine clots are relatively brittle and therefore not a good matrix for cellular growth.

Fibrin sealants stimulate vascular endothelial cells to form new blood capillaries, which is essential for successful tissue regeneration.
It is important to carefully select the correct type of tissue sealant, based upon fibrin clotting times and surgical procedure being performed.

Please note, the above information was sourced directly from the manufacturers. Please contact a member of the Patient Blood Management Team if you require contact information.

5.4 Anaesthetic Methods to Minimise Blood Loss

The anaesthetist's role in blood transfusion begins pre-operatively and continues through the post-operative period (Thomas et al 2004). Minimising intra-operative blood loss involves using many different approaches, all of which have application for particular types of surgery. There is however a need for careful co-operation between haematologist, surgeon and anaesthetist to ensure that this important goal is achieved (Davies 2002).

Anaesthetic methods to minimise blood loss include:

- Use of epidural and spinal anaesthesia for various types of surgery, as this can offer advantages over general anaesthesia by decreasing blood loss and transfusion requirements
- Hypotensive anaesthesia - to reduce bleeding, improve clarity of the operative field, reduce transfusion rate, improve surgical success and reduce operation time. Contra-indications to this include cardio-

vascular, cerebro-vascular, renal, hepatic and respiratory disease; hypovolaemia, profound anaemia and pregnancy. Hypotensive anaesthesia requires careful patient monitoring

- Maintenance of normothermia – a temperature <35.5C will impair haemostasis. Avoiding hypothermia can reduce blood loss and consequently the need for transfusion. It is achieved by reducing heat loss and increasing heat input by maintaining a high ambient temperature pre-operatively and in theatre; keeping the patient covered; having as short a perioperative period as possible and using minimally invasive surgery where appropriate
- Monitoring haemoglobin levels and coagulation using near patient testing equipment, where possible, to guide transfusion of blood components
- Appropriate fluid administration, as dilution will affect coagulation
- Careful patient positioning, e.g. operation site elevated, avoidance of obstruction to venous drainage, avoidance of coughing and straining.

References and Further Information:

British Committee for Standards in Haematology (2015). A practical guideline for the haematological management of major haemorrhage:
http://www.bcshguidelines.com/4_HAEMATOLOGY_GUIDELINES.html?dtype=Transfusion&dpage=0&sspage=0&ipage=0#gl

Davies M. J (2002) Minimising intra-operative blood loss Trans Apher Sci 27(1) 55-7

Royal College of Anaesthetists
http://www.rcoa.ac.uk/

The Association of Anaesthetists of Great Britain and Ireland (2008) Blood Transfusion and the Anaesthetist Red Cell Transfusion 2.
www.aagbi.org/sites/default/files/red_cell_08.pdf

The Association of Anaesthetists of Great Britain and Ireland (2005) Blood Transfusion and the Anaesthetist Blood Component Therapy.
www.aagbi.org/sites/default/files/bloodtransfusion06.pdf

Thomas D, Thompson J, Ridler B (Eds) (2005) A Manual for Blood Conservation, Tfm publishing
ISBN 1 903378 24 9

5.5 Pharmacological Agents

Anticoagulants
These drugs are used primarily for the prevention of thromboembolism in a variety of clinical conditions and their effect on the haemostatic system is monitored by laboratory tests.

Oral Anticoagulants
Oral anticoagulants antagonise the effect of Vitamin K.
Warfarin is the most common drug of choice.
The main adverse effect is haemorrhage – checking the International Normalised Ratio (INR) regularly, and altering / omitting doses when indicated is essential. Patients at risk of haemorrhage may require Vitamin K (phytomenadione) either orally or by IV injection. Occasionally, if associated with major bleeding, prothrombin complex concentrate (factors II, VII, IX and X) may be needed or FFP (only if no concentrate is available).

Newer Oral Anticoagulants
These include:

- direct oral thrombin inhibitors, such as dabigatran
- direct oral Factor Xa inhibitors, such as rivaroxaban and apixaban.

The drugs do not need laboratory monitoring and the tests to measure dosage may vary depending on the anticoagulant.
Currently there is no specific antidote. The half life of these drugs is relatively short although this maybe prolonged if the patient has reduced renal function. For patients at risk of bleeding or undergoing surgery, treatment should be stopped at least 24 hours before procedure.
The main side effect is the risk of haemorrhage.

Parenteral Anticoagulants

Heparin – initiates anticoagulation rapidly but has a short duration of action. It is often referred to as standard or unfractionated heparin to distinguish it from the low molecular weight heparins. For patients at risk of bleeding, heparin may be more suitable than low molecular weight heparin because its effect can be terminated rapidly by stopping its administration.
Potential side effects may include haemorrhage, skin necrosis, thrombocytopaenia, hyperkalaemia and hypersensitivity reactions.

Low Molecular Weight Heparins have a longer duration of action than unfractionated heparin, often only requiring once daily subcutaneous injection e.g. bemiparin, certoparin, dalteparin, enoxaparin, reviparin, tinzaparin.
Potential side effects – see heparin.

Further Information:

British Committee for Standards in Haematology (BCSH) Guidelines:

- Guidelines on oral anticoagulation with warfarin – fourth edition (2011) British Journal of Haematology 154 (3), 311-324
- Safety indicators for inpatient and outpatient oral anticoagulant care (2007) British Journal of Haematol. 136, 26-29
- Guidelines on the use and monitoring of heparin (2006) British Journal of Haematol. 133, 19-34
- Guideline on the management of bleeding in patients on antithrombotic agents (2012) British Journal of Haematol. 160, 35-46
- Effects on routine coagulation screens and assessment of anticoagulant intensity in patients taking oral dabigatran or rivaroxaban (2012) British Journal of Haematol. (2012) 159, 427-429

Heparin Induced Thrombocytopenia (HIT)
Extensive studies show that despite its invaluable benefits, there is a life threatening complication of heparin therapy - Heparin Induced Thrombocytopenia. HIT occurs in approximately 0.5 - 2% of patients treated with unfractionated heparin and in less than 0.2% of those treated with low molecular weight heparin. It differs from the mild thrombocytopenia which reverses spontaneously (HIT type I) and is often associated with heparin therapy and so is known as HIT type II.
First indications are a sudden drop in platelet count, signs of skin necrosis or thrombosis and must be acted upon immediately.
Symptoms can develop between 5 and 15 days following commencement of heparin therapy, however patients who have had previous exposure to heparin therapy can develop HIT over a number of hours (rapid onset).
If any of these signs are noted then intervention should be immediate, heparin therapy should be ceased and replaced by another antithrombotic therapy or anticoagulant drug.
The diagnosis of HIT type II must be confirmed by platelet function tests or the measurement of heparin dependant antibodies.

Further Information:
Amiral J, Jones G and Vissac A M (2007) Heparin-induced thrombocytopenia: a clinical paradox. The Biomedical Scientist. June. 440-444

British Committee for Standards in Haematology (2012) Guidelines on the diagnosis and management of heparin-induced thrombocytopenia: second edition. British Journal of Haematology. 159, 528-540
http://www.bcshguidelines.com/4_HAEMATOLOGY_GUIDELINES.html

Antifibrinolytics
Antifibrinolytics are a group of drugs that reduce the breakdown of blood clots. If given before surgery they help reduce post-surgical bleeding. These drugs need to be given prior to the first skin incision to work effectively.
There are two main groups of antifibrinolytic drugs: naturally derived e.g. aprotinin and synthetic e.g. tranexamic acid.

Aprotinin reduces fibrinolysis by inhibiting preteolytic enzymes. It can result in severe allergic reactions in up to 1:200 patients on first exposure. It is only recommended for use in patients with a particularly high risk of bleeding whom the benefits are believed to exceed the risks.

Tranexamic Acid is a synthetic antifibrinolytic. It competitively blocks a lysine binding site of plasminogen and therefore inhibits fibrinolysis. It has been shown to reduce intra and post operative blood loss in a variety of types of surgery.
It is necessary to give the first dose of Tranexamic Acid before the first skin incision. The recommended dose is extremely variable between publications. However, a dose of 10mg/kg followed by 1mg/kg/h has recently been recommended for high risk (bleeding) surgery (BCSH,2015).
As with aprotinin, there are concerns that tranexamic acid could lead to a hypercoagulable state and increase the risk of deep vein thrombosis and pulmonary embolism although if used within the suggested time frames this has not been proven.
The CRASH-2 study (2010) looked at tranexamic acid in trauma patients. This study recommended that tranexamic acid should be given within 3 hours of the event followed by a second dose over 8 hours. However, if given late after injury, tranexamic acid is less effective and may be harmful.
In light of the CRASH-2 trial results it is recommended that Tranexamic acid should be included in major traumatic haemorrhage protocols and may safely be used in most surgical blood conversation programmes.

References and Further Information:

British Committee for Standards in Haematology (2015). A practical guideline for the haematological management of major haemorrhage:
http://www.bcshguidelines.com/4_HAEMATOLOGY_GUIDELINES.html?dtype=Transfusion&dpage=0&sspage=0&ipage=0#gl

CRASH-2 Trial Collaborators (2011) The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. The Lancet, 2011 DOI:10.1016/S0140-6736(11)60278-X.

CRASH-2 Trial Collaborators (2010) Effects of tranexamic acid on death, vascular occlusive events and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. The Lancet, 376(9734), 23-32

NICE (2015) Blood Transfusion
http://www.nice.org.uk/guidance/ng24/

Antiplatelet Drugs
Antiplatelet drugs decrease platelet aggregation and may inhibit thrombus formation in the arterial circulation where anticoagulants have little effect. Examples include abciximab, aspirin, clopidogrel, diclofenac, dipyridamole, eptifibatide, and tirofiban.
If safe to do so, it is usually prudent to advise patients to stop taking these medications prior to surgery. It must be borne in mind that these drugs maintain their anti-platelet effect for varying periods of time after the last dose. This may range from 2 to 7 days; thus the patient will need to be advised accordingly.

Further information on these drugs may be found in the British National Formulary (BNF).

Posterior pituitary hormones
Desmopressin is used in the management of mild to moderate haemophilia (also von Willebrand).
Vasopressin infusion is used to control variceal bleeding in portal hypotension, prior to more definitive treatment and with variable results.
Terlipressin, a derivative of vasopressin, is used similarly.

5.6 Pharmacological Alternatives to Transfusion

The use of pharmacological alternatives to transfusion should be explored by Hospital Transfusion Teams. For example, patients with vitamin B deficiency will respond well to the use of Vitamin B while the use of some of the drugs listed below may help avoid the need to use blood products.
Pharmaceutical and biological agents occasionally replace transfusion therapy, but are more commonly used as adjuncts in the treatment of patients with haemostatic disorders. A wide range of agents are now available.

DDAVP (Desmopressin) is a synthetic version of a naturally occurring hormone - antidiuretic hormone (ADH) or vasopressin. Desmopressin causes a dose-dependent increase in plasma factor VIII and von Willebrand factor from endothelial cells. This medication may also cause constriction of bleeding vessels so as to limit blood loss.

Vitamin preparations e.g. Vitamin K (Phytonadione) is a synthetic product identical to naturally occurring Vitamin K. It is required for the production of certain blood clotting factors (factors II, VII, IX and X) in the liver. Causes of vitamin K deficiency include inadequate dietary intake, poor absorption, and drug

interactions e.g. antibiotics, stroke medications. Physicians report that vitamin K can be a useful adjunct in the management of haemorrhage.

Haematinics include substances such as iron and folic acid, which are necessary for haemoglobin and red cell production. A frequent finding in audits of red blood cell usage in hospitals is that patients are transfused because of a low haemoglobin resulting from haematinic deficiency. Oral iron is the preferred first line therapy for most patients but parenteral iron therapy may be given if gastric toxicity or malabsorption is a problem. Post-operatively, a patient who has bled down to a haemoglobin level of 80g/L may often be safely managed by treatment with iron and folic acid, rather than by exposure to the risks of transfusion. However, each patient must be individually assessed.

rFVIIa is the recombinant form of human factor VIIa. It is a haemostatic agent with proven benefit to reduce bleeding in haemophiliacs with inhibitors, but it may also be effective in patients with thrombocytopenia and thrombopathy. Its 'off-licence' use in life-threatening haemorrhage in post-surgical and trauma patients currently remains under review and debate and is not currently recommended (BCSH,2015).

Prothrombin Complex Concentrate (PCC)
Prothrombin Complex Concentrate (PCC) is a combination of blood clotting factors II, VII, IX and X with Protein C and Protein S. It is a human derived pooled plasma product which is virally inactivated.

Licensed Use	Contraindications
Treatment and perioperative prophylaxis of bleeding in: 1. acquired deficiency of prothrombin complex coagulation factors when rapid correction of the deficiency is required. 2. congenital deficiency of any of the vitamin K dependant coagulation factors when purified specific coagulation factors are not available.	Known hypersensitivity to any of the product components. Known history of heparin induced thrombocytopenia. Use caution if administering to patients with a history of coronary artery disease, liver disease or at risk of thrombosis.

Associated laboratory tests
Over-coagulation can occur from excessive Warfarin. Warfarin achieves its anticoagulation by inhibiting the vitamin K effect on factor II, factor VII, factor IX and factor X, causing a functional deficiency of these factors and of anticoagulant proteins C and S. Anticoagulation is indicated by prolonged prothrombin time (PT) standardised by the international normalised ratio (INR). The dose of PCC will depend on the INR before treatment and the targeted INR. The advice of a Consultant Haematologist should be sought before using PCC.

Guidelines
BCSH Guidelines for the use of FFP, Cryoprecipitate and Cryosupernatant (2004) recommend that FFP should never be used for the reversal of Warfarin where there is no evidence of severe bleeding. PCC is recommended as the preferred option.

BCSH Guidelines on oral anticoagulation with warfarin (4th edition, 2011) states that rapid correction is most effectively achieved by the administration of PCC and recommends that all hospitals managing patients on warfarin should stock a licensed four-factor PCC.

References and Further Information:

British Committee for Standards in Haematology (2015). A practical guideline for the haematological management of major haemorrhage:
http://www.bcshguidelines.com/4_HAEMATOLOGY_GUIDELINES.html?dtype=Transfusion&dpage=0&sspage=0&ipage=0#gl

Lankiewitz MW et al (2006) Urgent reversal of Warfarin with prothrombin complex concentrate. Journal of Thrombosis and Haemostasis 4 (5) 967-970

Makris et al (1997) Emergency Oral Anticoagulant Reversal. Journal of Thrombosis and Haemostasis. 77. 477-480

Poster by Dolan G (2005) Consensus protocol for the use of concentrated vitamin K dependant coagulation factors in the reversal of coumarin – induced (i.e. Warfarin) anticoagulation. Presented at 25th International Symposium on Intensive Care and Emergency Medicine 2005.

Reiss HB et al (2007) Prothrombin Complex Concentrate (Octaplex) in patients requiring immediate reversal of oral anticoagulation. Thrombosis Research. 121 (1) 9-16

Haematopoietic growth factors produced by recombinant technology are being increasingly used in clinical medicine, and in many cases their administration has either complimented or replaced transfusion therapy.

The following haematopoietic agents are used to stimulate blood cell growth and development:

- **For Red Blood Cells: Recombinant Erythropoietin** (r-Hu-EPO) is a biosynthetic form of a natural human hormone responsible for stimulation of red blood cell production. It is manufactured using recombinant DNA technology, and has the same pharmacological effects as endogenous human erythropoietin, stimulating the bone marrow to produce red blood cells. EPO is among the non-haemostatic agents that may be effective in reducing blood requirements in medical and surgical patients. It can also be used to accelerate haematopoietic recovery in cancer patients undergoing chemotherapy, or to treat anaemia in patients with chronic renal failure.

Iron and other haematinics can be administered concurrently to support erythropoietin-stimulated red blood cell production and reduce the need for blood transfusions. This includes pre-operative surgical patients and medical patients, particularly the elderly.
EPO may also be used for Jehovah's Witness patients, many of whom will accept recombinant human erythropoietin as an alternative to blood transfusion. In paediatric patients, for instance those requiring spinal surgery, use of erythropoietin may be more desirable than blood transfusion.

In the majority of studies, erythropoietin has still proved to be a more expensive option than allogeneic transfusion if the straightforward costs of erythropoietin and units of RBCs are compared. In health economic terms, however, the costs of managing the complications of transfusion, the additional drugs and therapies that may be necessary, long-term follow-up and the potential for litigation, may make transfusion more costly than erythropoietin therapy.

- **For White Blood Cells: Recombinant Granulocyte Colony Stimulating Factor** (r-Hu-G-CSF) is a biosynthetic form of a natural human hormone that stimulates production of neutrophils (a specific type of infection-fighting white blood cell) in the bone marrow. It is manufactured using recombinant DNA technology, and has the same biological effects as endogenous human granulocyte colony stimulating factor.

- **For Platelets: Recombinant Interleukin-11** (r-Hu-IL-11) is a genetically produced form of a naturally occurring human hormone that stimulates the body's platelet production. Interleukin-11 is important in managing patients who receive drug therapy that tends to suppress the development of platelets, such as chemotherapy, but is not actually used in routine practice.

Further Information:

British National Formulary:
https://www.evidence.nhs.uk/formulary/bnf/current

Klein HG and Anstee DJ (2005) Mollinson's Blood Transfusion in Clinical Medicine 11th Edition, Blackwell Publishing, ISBN 0632064544

Network for Advancement of Transfusion Alternatives:
www.nataonline.com

NICE (2015) Blood Transfusion
http://www.nice.org.uk/guidance/ng24/

Norfolk D (Ed) (2013) Handbook of Transfusion Medicine 5th Edition, The Stationary Office
ISBN 9780117068469
http://www.transfusionguidelines.org.uk/transfusion-handbook

Thomas D and Ridler B (2005) A Manual for Blood Conservation, Tfm Publishing Ltd
ISBN 1903378249

6. Adverse Effects of Transfusion

There are a large number of possible adverse effects that can be associated with a transfusion and for the purposes of this document these have been divided up into:

- Incorrect blood component transfused
- Inappropriate, unnecessary and under/delayed transfusion
- Immune complications of transfusion
- Transfusion transmitted infections
- Fluid overload
- Iron overload

The Serious Hazards of Transfusion (SHOT) scheme provides an analysis of serious transfusion complications in the UK. Incidents are classified under a series of headings to aid reporting and enable trends to be highlighted.
For further information and additional categories see SHOT website: http://www.shotuk.org

- **Incorrect Blood Component Transfused (IBCT)**

IBCT – Wrong Blood Transfused: Where a patient was transfused with a blood component:

a) Which was intended for another patient
b) As a consequence of a laboratory error which resulted in transfusion with an incorrect unit
c) Due to a "Wrong blood in Tube" incident

IBCT – Specific Requirements Not Met (SRNM): transfusion with a component that did not meet the patient's specific requirements.

All incidents in this category are preventable.

- **Avoidable Transfusion, Delayed Transfusion or Under Transfusion (ADU) – Formerly I and U**

a) Where the decision leading to transfusion is flawed
b) Where a transfusion of a blood component was indicated but was not undertaken or significantly delayed
c) When O Negative units were transfused despite group specific or crossmatched units being available.

- **Immune Complications of Transfusion**

Classically, an immune reaction associated with a transfusion involves the antibody that is already present in the patient's circulation reacting with the corresponding antigen being transfused (major reactions); although passively transfused antibodies in donor plasma may also cause problems (minor reactions).
Immune related reactions vary greatly from mild urticaria (an allergic reaction) that rarely needs treatment, febrile reactions involving shivering followed by fever (e.g. caused by antibodies to white cells) to haemolytic reactions resulting in the destruction of red cells. In addition, each type of hazard can vary in its clinical effects between different patients.

SHOT categorises immune complications into the following:

Acute Non-haemolytic Transfusion Reaction (ATR)
Reactions occurring at any time up to 24 hours following a transfusion of blood or components, excluding IBCT, Haemolytic Transfusion Reaction, Transfusion Related Acute Lung Injury, Transfusion Associated Circulatory Overload, Transfusion Associated Dyspnoea and those due to bacterial contamination of the component. The signs and symptoms of ATRs are not unique and may be related to the patients underlying condition. Nevertheless it is worthwhile recording the clinical features, management and investigation of cases when ATR is considered possible, in order to promote best practice.

British Committee for Standards in Haematology (BCSH) Classification:
Febrile – Mild (1) Temperature rise of up to 2℃ to Severe (3) Temperature rise of 2℃ or more and/or rigors and other inflammatory symptoms.
Allergic – Mild (1) Transient flushing, urticaria or rash to Severe (3) Bronchospasm, stridor, angioedema or circulatory problems or anaphylaxis.
Allergic and Febrile: Mild (1) to Severe (3) combined features of both types of reaction.
Hypotensive: Moderate (2) isolated fall in systolic or diastolic pressure to Severe (3) Shock e.g. acidaemia, impairment of vital organ function (without allergic or inflammatory symptoms).

Haemolytic Transfusion Reaction: Acute and Delayed (HTR)
Acute haemolytic transfusion reaction (AHTR): Fever and other signs of haemolysis within 24 hours of transfusion. Confirmed by one or more of the following: a fall in haemoglobin (Hb), rise in lactate dehydrogenase (LDH), positive Direct Antiglobulin Test (DAT) and positive cross-match.
Delayed haemolytic transfusion reaction (DHTR): Fever and other signs of haemolysis more than 24 hours after transfusion. Confirmed by one or more of a fall in Hb or a failure in increment, a rise in bilirubin, positive DAT and positive cross-match not detectable pre-transfusion. Simple serological reactions (development of antibody without positive DAT or evidence of haemolysis) are excluded.

Alloimmunisation
2010 was the first year SHOT collected data on alloimmunisation. It occurs when, after transfusion, there is demonstration of clinically significant antibodies against red cells (RBCs) that were previously absent and when there are no signs of haemolysis. It is categorised as Delayed Serological Transfusion Reaction (DSTR). Development of an antibody with a positive DAT or haemolysis should be reported in the HTR category.

Transfusion-associated Graft-versus-host Disease (TA-GvHD)
Generally a fatal immunological complication characterised by the development of fever, rash, liver-dysfunction, diarrhoea, pancytopenia and bone marrow hypoplasia occurring less than 30 days following transfusion. The diagnosis is usually supported by skin/bone marrow biopsy appearances and/or the identification of donor-derived cells, chromosomes or deoxyribonucleic acid (DNA) in the patients' blood and/or affected tissues.

Post-transfusion Purpura (PTP)
Thrombocytopenia arising 5 - 12 days following transfusion of red cells associated with the presence in the patient of antibodies directed against the Human Platelet Antigen (HPA) systems.

Transfusion-related Acute Lung Injury (TRALI)
Acute dyspnoea with hypoxia and bilateral pulmonary infiltrates during or within 6 hours of transfusion, not due to circulatory overload or other likely cause.

Transfusion Associated Dyspnoea (TAD)
It is characterised by respiratory distress within 24 hours of transfusion that does not meet the criteria of TRALI, TACO or allergic reaction. Respiratory distress could not be explained by the patient's underlying condition or any other known cause. This allows classification of all pulmonary reactions without exceptions or inappropriate assignment.

Previously Uncategorised Complication of Transfusion (PUCT)
Physiological reaction or adverse effect in temporal association with transfusion which cannot be attributed to already defined side effects and with no risk factor other than transfusion.

Drugs Commonly Used When a Blood Transfusion Reaction is Suspected

- **Antibiotics**

Bacterial contamination of blood components is an uncommon but potentially fatal adverse effect of blood transfusion. It may be difficult initially to determine the exact cause, so therefore broad-spectrum intravenous (IV) antibiotics should be initiated if bacterial contamination is suspected (before culture results are known). Hospital pharmacies should advise on local protocols.

- **Adrenaline –** Inotrope

Used in allergic emergencies; emergency treatment of acute anaphylaxis; angioedema; cardiopulmonary resuscitation. Often used in combination with chlorpheniramine and hydrocortisone.

- **Chlorpheniramine** – Antihistamine

Given for symptomatic relief of allergy; emergency treatment of anaphylactic reactions.

- **Furosemide (Frusemide)** – Loop diuretic

Given to treat oedema and used if fluid overloaded. Also used in the management of an acute transfusion reaction to maintain urine output.

- **Hydrocortisone** – Glucocorticoid

Treatment for shock; hypersensitivity reactions e.g. anaphylactic shock and angioedema. Often used in combination with adrenaline and chlorpheniramine.

- **Paracetamol –** antipyretic

An agent that reduces fever.

- **Salbutamol** – beta antagonist

Treats conditions associated with reversible airways obstruction e.g. severe allergic reaction. Recommended method of administration is nebuliser.

Further Information:

Norfolk D (2013) Handbook of Transfusion Medicine 5th Edition, The Stationary Office
http://www.transfusionguidelines.org.uk/transfusion-handbook

Minimum Standards for Investigation of Transfusion Related Adverse Reactions
A document has been developed by SHOT, in the absence of a definitive guideline and is intended to provide a checklist of investigations to support the differential diagnosis and assessment of transfusion related adverse reactions. The standards are endorsed by the Transfusion Taskforce of the British Committee for Standards in Haematology and it will be expected that, when reactions are reported to SHOT and to MHRA, the investigations listed in this document will have been carried out, as a minimum.
All severe transfusion reactions must be reported immediately to the hospital transfusion laboratory and the implicated blood pack returned to them.
The full document will be available on the SHOT website: http://www.shotuk.org

MHRA and SABRE
There is now a legal requirement to report Serious Adverse Blood Reactions and Events (SABRE) that occur in hospitals and laboratories to the Medicines and Healthcare Regulatory Agency (MHRA) via their website http://www.mhra.gov.uk. This was introduced on 8th November 2005 under the Blood Safety and Quality Regulations 2005.

All staff involved in the transfusion chain need to be aware of these requirements and report serious transfusion reactions and events immediately to the Hospital Transfusion Team.
This SABRE system does not replace existing reporting procedures for reporting to local risk management systems, nor does it affect any arrangements for reporting to other organisations e.g. the Health and Safety Executive etc.

In SABRE, a serious adverse reaction is defined as 'an unintended response in a donor or in a patient that is associated with the collection or transfusion of blood or blood components that is fatal, life-threatening, disabling or incapacitating or which results in or prolongs hospitalisation or morbidity'.
These are:

- Immunological haemolysis due to ABO incompatibility
- Immunological haemolysis due to other allo-antibody
- Non-immunological haemolysis
- Transfusion-transmitted bacterial infection
- Anaphylaxis / hypersensitivity
- Transfusion related acute lung injury (TRALI)
- Transfusion-transmitted viral infection (HBV)
- Transfusion-transmitted viral infection (HCV)
- Transfusion-transmitted viral infection (HIV-1/2)
- Transfusion-transmitted viral infection, other (specify)
- Transfusion-transmitted parasitical infection (Malaria)
- Transfusion-transmitted parasitical infection, other (specify)
- Post-transfusion purpura
- Transfusion associated graft-versus-host disease
- Other serious reaction(s) – specify (e.g. transfusion associated circulatory overload (TACO), transfusion associated dyspnoea (TAD), febrile non haemolytic transfusion reactions (FNHTR) and uncharacterised unintended responses).

A serious adverse event is defined as 'any untoward occurrence associated with the collection, testing, processing, storage and distribution, of blood or blood components that might lead to death or life-threatening, disabling or incapacitating conditions for patients or which results in or prolongs, hospitalisation or morbidity'.

An “adverse incident involving failures or problems with medical devices (e.g. blood bags, syringes, needles and irradiators etc) should also be reported to the MHRA Adverse Incident Centre – preferably using the appropriate online system”.

- **Transfusion-Transmitted Infection (TTI)**

If, following investigation, the recipient had evidence of infection following transfusion and there was no evidence prior to transfusion or evidence of an alternative source of infection. Plus, either at least one component received by the infected recipient was donated by a donor who had evidence of the same transmissible infection or at least one unit received by the infected recipient was shown to contain the agent of infection.

It is important for the blood service to be notified immediately about suspected implicated transfusions so that investigations can be conducted. This is essential to prevent further transmissions by other components and/or by chronically infected donors and to reveal any systematic errors or deficiencies in the blood service testing. Such investigations may involve microbiological testing of many donors and may take several months to complete.

A surveillance system to collect standardised information about infections suspected to have been transmitted by transfusion was introduced in October 1995 in the UK (excluding Scotland) and the Republic of Ireland as a collaboration between the Health Protection Agency Centre for Infections and the transfusion services. Blood centres in Scotland report all incidents to the Microbiology Reference Unit of the Scottish National Blood Transfusion service and the details and conclusion of each case are then provided to the SHOT system.

Current blood donation testing strategies minimise the risk of viral transfusion transmitted infections in the UK but on very rare occasions infectious donations are undetected and enter the blood supply. This is either as a result of falsely negative test results (as test sensitivities are less than 100%), blood donations made during the infectious ‘window period’ following infection when tests in use are unable to detect the infection or blood donations erroneously issued as negative due to sampling/processing error. The latest figures showing frequency of infections in blood donors is available from Public Health England at:
https://www.gov.uk/government/publications/safe-supplies-annual-review

Bacterial Infection/Contamination
After the introduction of diversion of the first 20 - 30 ml of a donation by NHS Blood and Transplant (NHSBT) and improved donor arm disinfection, bacterial contamination of platelets and red cells continues to occur, albeit at a low level and could cause major morbidity in transfusion recipients.
It is important that staff starting the transfusion visually check all components prior to transfusion. However, bacterial contamination is possible even in the absence of visible features and staff should remain vigilant for any adverse reactions post transfusion.

In order to comply with the requirements of the new Blood Safety and Quality Regulations there has been a need to improve adverse event and reaction reporting and associated documentation both in hospitals and from blood establishments. To assist with this process documents and forms are now available from the Hospitals & Science website for use in hospital blood transfusion laboratories. These include a “Summary of actions for hospital staff” and a form to request “Investigation of serious adverse reaction to blood and component transfusion”. See: http://hospital.blood.co.uk/diagnostic-services/reporting-adverse-events/. In addition all duty consultants and Patient Clinical Team consultants within NHSBT are trained to deal with all adverse events and reactions arising within hospitals or blood establishments.

The process to screen platelets for bacterial contamination is now operational. Any initial reactives (IRs) go for confirmatory culture, contaminating organisms have been identified in a small number of these IRs demonstrating the benefits of testing in producing safer components for patients. If an IR unit has been transfused the hospital will be faxed a simple form and an information sheet. This form, which will require completion and faxing back, records whether the patient has had any reaction to the component and the information sheet provides more detail on hospital actions and an indication of the organisms which may be expected should the reactive unit prove to be contaminated. The confirmatory culture of IR units will take at least two weeks and hence will not be available to inform the immediate medical care of the patient. Any transfused unit that causes a reaction should be reported to SHOT/SABRE.

Further Information:

Information for Hospital Transfusion Teams on the Introduction of bacterial screening of platelet components: http://hospital.blood.co.uk/media/1918/2f291133-4143-42b6-8705-11823fdb6f8d.pdf

- **Transfusion Associated Circulatory Overload (TACO)**

TACO includes any four of the following occurring within 6 hours of transfusion: acute respiratory distress, tachycardia, increased blood pressure, acute or worsening pulmonary oedema, evidence of positive fluid balance.
When too much fluid is transfused or the transfusion is too rapid, acute left ventricular failure may occur with dyspnoea, tachypnoea, non-productive cough, raised jugular venous pressure, basal lung crackles, hypertension and tachycardia. The transfusion should be stopped and standard medical treatment including diuretic and oxygen given.
In patients with signs/history of cardiac failure, each unit of red cells should be given slowly (maximum 4 hours). Consider giving one unit only in a 12-hour period. The patient may require diuretic therapy e.g. intravenous furosemide and should be closely observed. It may be possible for the transfusion to be completed at a slower rate as clinically indicated. Diuretics should not be prescribed routinely for all patients. The decision to administer diuretics should be based on clinical indications.

Blood Component Volumes:

Blood Component	Volume (mls)
Whole blood	405-495mls
Red cells in additive solution	220–340mls
Platelets pooled	Up to 300mls
Platelets apheresis	According to local product specification Average 215mls (53-55mls paediatric size)
Standard FFP	According to local product specification Average 271mls
MB FFP	According to local product specification Average 239mls (also 60mls paediatric size)
MB Cryoprecipitate	38mls (single unit)
Cryoprecipitate	40 mls(single unit) 100-250mls (5 units pooled)
Granulocytes	According to local product specification Average 312mls

Further details can be found at: :
http://hospital.blood.co.uk/media/27048/spn223-v6-2.pdf

- **Iron Overload (Haemosiderosis)**

The average Western diet contains 10-15mg of iron from which only approximately 5-10% is normally absorbed. Approximately 1mg of iron is excreted per day and the average total body iron store is approximately 4g.
Each unit of red cells contains approximately 250mg of iron. Transfusion-dependent patients receiving red cells over a long period of time can become overloaded with iron and the body has no way of excreting this excess iron.
Accumulation of iron in the body causes toxic effects after 10-50 units have been transfused. Signs and symptoms of iron overload do not generally occur until iron stores are in the range of 20-30g i.e. when approximately 100 units of red cells have been transfused.

The main organs affected by iron overload are shown in the table below:

Organ	Effects
Skin	Abnormal pigmentation – slate grey or bronze discoloration
Endocrine glands	Diabetes mellitus Developmental delay in children – growth retardation, hypogonadism (delayed or absent sexual maturation)
Liver	Hepatomegaly, cirrhosis, chronic hepatitis, fibrosis, hepatocellular carcinoma
Heart	Cardiomyopathy Heart failure Cardiac arrhythmias

Note: patients who have massive iron overload are at high risk of death due to cardiac complications.

Iron chelation therapy; Parenteral desferrioxamine, is the current standard treatment for the removal of excess iron. Subcutaneous injections of desferrioxamine are given over 8–12 hours, 3–7 times a week. The dose should reflect the degree of iron overload. For children starting therapy (and who have low iron overload), the dose should not exceed 30mg/kg. For established overload, the dose is usually between 20 and 50 mg/kg daily.
Side-effects include: hypotension (especially when given too rapidly by intravenous injection), disturbances of hearing and vision (including lens opacity and retinopathy), injection site reactions, gastro-intestinal disturbances, pyrexia, headache, arthralgia and myalgia, anaphylaxis, very rarely acute respiratory distress syndrome, neurological disturbances (including dizziness, convulsions, neuropathy and parasthesia), Yersinia and Mucormycosis infections, rash, renal impairment, hepatic impairment, leg cramps, bone pain, growth retardation and blood dyscrasias.

Iron excretion induced by desferrioxamine is enhanced by administration of ascorbic acid (vitamin C) in a dose of 200mg daily (100mg in infants). It should be administered separately from meals since it also enhances iron absorption. Ascorbic acid should not be given to patients with cardiac dysfunction as it may worsen iron toxicity, particularly to the heart. In patients with normal cardiac function ascorbic acid should not be introduced until 1 month after starting desferrioxamine as there may be excessive tissue iron.

Deferasirox is an oral iron chelator, it is licensed for the treatment of chronic iron overload in adults and children over 6years with thalassaemia major who receive frequent blood transfusions (more than 7ml/kg/month of packed red blood cells). It is also licensed for chronic iron overload when desferrioxamine is contra-indicated or inadequate in patients with thalassaemia major who receive infrequent blood transfusions (less than 7ml/kg/month of packed red blood cells), in patients with other anaemia's and in children aged 2-5 years.

The *Scottish Medicines Consortium* has advised (January 2007) that deferasirox is accepted for restricted use within NHS Scotland for the treatment of chronic iron overload associated with the treatment of rare acquired or inherited anaemia's requiring recurrent blood transfusions. It is not recommended for patients with myelodysplastic syndromes.
Side effects include: gastro-intestinal disturbances (including ulceration and fatal haemorrhage), headache, proteinuria, pruritus, rash, less commonly hepatitis, cholelithiasis, oedema, fatigue, anxiety, sleep disorder, dizziness, pyrexia, pharyngitis, glucosuria, renal tubulopathy, disturbances of hearing and vision (including lens opacity and maculopathy), skin pigmentation, hepatic failure, acute renal failure, blood disorders (including agranulocytosis, neutropenia, pancytopenia and thrombocytopenia), hypersensitivity reactions (including anaphylaxis and angioedema) and alopecia.

Deseriprone is an iron chelator, it is licensed for the treatment of iron overload in patients with thalassaemia major in whom desferrioxamine is contra-indicated or is inadequate. Blood dyscrasias, particularly agranulocytosis, have been reported with deferiprone.
Side effects include: gastro-intestinal disturbances (reducing dose and increasing gradually may improve tolerance), increased appetite, headache, red-brown urine discolouration, neutropenia, agranulocytosis, zinc deficiency and arthropathy.

Further Information:

British National Formulary:
https://www.evidence.nhs.uk/formulary/bnf/current

Public Health England:
https://www.gov.uk/government/publications/safe-supplies-annual-review

Learoyd P (2003), An Introduction to Blood Group Serology and Transfusion, NBS 3rd Edition

Murphy MF and Pamphilon DH (Eds) (2005) Practical Transfusion Medicine, Blackwell Science Ltd

Norfolk D (2013) Handbook of Transfusion Medicine, 5th Edition, The Stationery Office
ISBN 9780117068469
http://www.transfusionguidelines.org.uk/transfusion-handbook

Serious Hazards of Transfusion website:
www.shotuk.org

TA-GvHD Information Document from the NHS Blood and Transplant:
http://hospital.blood.co.uk/media/2129/4b4c5eba-2721-420b-813b-007f0947110f.pdf

7. Emergency and Massive Transfusion

- **Conservation and Emergency Use of O Negative Red Cells**

Group O RhD negative (O negative) red cells are a valuable commodity as they can usually be given to patients of any ABO blood group; hence O negative donors are called 'Universal Donors'. Hospital transfusion laboratories keep extra stocks of O negative red cells for use in life-threatening emergencies when there may be insufficient time to wait for group compatible i.e. patient's own ABO blood group, or cross-matched red cells. This emergency O negative blood is suitable for most patients, but not all. A small number of patients have red cell antibodies due to previously having been exposed to 'foreign' red cells by pregnancy or transfusion. Antibodies such as Kidd (Jka) or Duffy (Fya) can cause such patients to have a reaction if transfused with uncross-matched O negative red cells. Therefore, if the patient can wait for cross-matched red cells this is the safest option. Some hospitals stock and use more units of O negative blood than NHS Blood and Transplant can easily supply them with. Hospitals using large amounts of O negative can cause a 'supply and demand' shortfall. The Blood Stocks Management Scheme survey of the 'Distribution of ABO and RhD blood groups within hospital populations' August 2009 showed a national mean percentage of patients who are O RhD Neg in hospitals is 7.81%, with some regional variation. The 2010 NCA Re-Audit of the use of O RhD Negative red cells recommended a stockholding level of less than 10.5%. The NHSBT Patient Blood Management Team is working with some Hospitals, by sharing ideas and good practice from regional and national colleagues, to reduce their O negative issues to less than 10.5%.

Further Information

O RhD Neg Red Cell Resources including;
1. NBTC recommendations on the appropriate use of Group O RhD negative red cells (April 2009)
2. NCA Re-audit of the use of Group O RhD negative red cells 2010
3. Red cells for emergency use – Best practice from BSMS Regional Roadshows (2014)
are available at:
http://hospital.blood.co.uk/patient-services/patient-blood-management/o-d-negative-red-cell-toolkit/

NHS Blood and Transplant Hospitals & Science website
http://hospital.blood.co.uk/

- **Management of Massive Blood Loss**

Recognition of massive blood loss
The following definitions of major haemorrhage/massive blood loss are widely accepted:
1. The loss of one blood volume within a 24 hour period (Mollison et al, 1997) or
2. 50% blood volume loss within 3 hours or
3. at a rate of loss of 150ml per minute (Fakhry & Sheldon, 1994).

However these are retrospective measures and therefore difficult to apply during an acute situation. With this in mind the BCSH guidelines 2015 (Hunt et al) suggest the following:
"…major haemorrhage is bleeding which leads to a heart rate more than 110 beats/min and /or systolic blood pressure less than 90 mmHg. Hospitals must have locally agreed triggers."
The BCSH recommend that:
"Medical, nursing and midwifery staff involved in frontline care must be trained to recognise major blood loss early, know when to activate/trigger the local major hamorrhage protocol and take prompt and appropriate action" (BCSH, 2015).

Organisational principles
In October 2010 the National Patient Safety Agency issued an alert RRR017 requiring that from April 2011 Hospital Transfusion Committees (HTCs) develop a local protocol for management of massive transfusion within their Trust. They must also ensure that staff (clinical, laboratory and support staff) know where to find the massive blood loss protocol in all relevant clinical and laboratory areas and are familiar with it, supported by training and regular drills. This recommendation has been reiterated by the BCSH and in addition recommend that adaptations, to protocols, are made for specific clinical areas (BCSH, 2015).

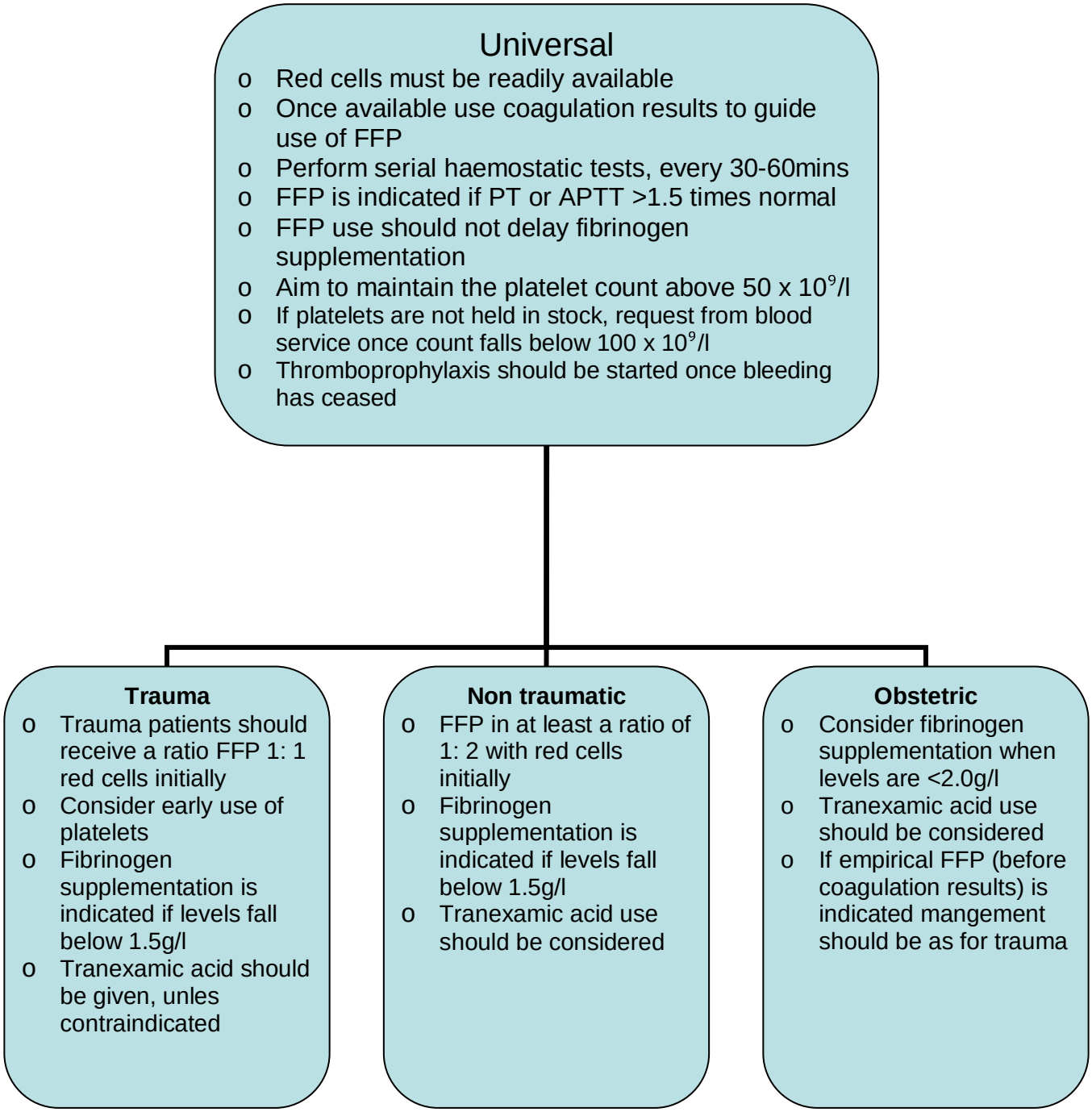
Team work and good communication is essential for the optimal management of these patients, including transfusion of blood components. A team leader needs to be quickly identified to coordinate management of the patient they inturn, should allocate responsibility for communication with the transfusion laboratory (and other areas/support staff) to a specific member of the clinical team. Clear communication and record keeping is also essential within the laboratory particularly, as they may be required to respond to more than one major haemorrhage event at a time.

Clinical principles

There are three elements in the management of a patient with major haemorrhage:

1. assessment and resuscitation (advanced life support principles)
2. control of bleeding (e.g. surgical, radiological, endoscopic)
3. haemostatic (including transfusion)

The table below summarises the BCSH (2015) recommendations for adults:



References and Further Information:

Adult guidelines for Massive Blood Loss – a flowchart example from the East of England RTC
http://www.transfusionguidelines.org.uk/uk-transfusion-committees/regional-transfusion-committees/east-of-england/policies

British Committee for Standards in Haematology (2015). A practical guideline for the haematological management of major haemorrhage:
http://www.bcshguidelines.com/4_HAEMATOLOGY_GUIDELINES.html?dtype=Transfusion&dpage=0&sspage=0&ipage=0#gl

Fakhry SM, Sheldon GF (1994) Massive transfusion in the surgical patient, Massive Transfusion (ed. by Jeffries LC & Brecher ME) American Association of Blood Banks, Bethesda

Mollison PL, Engelfreit CP, Contreras M (1997) Transfusion in Oligaemia, Blood Transfusion in Clinical Medicine, p. 47. Blackwell Science, Oxford

NPSA Alert (2010) The Transfusion of Blood and Blood Components in an Emergency, NPSA/2010/RRR017
http://www.nrls.npsa.nhs.uk/resources/type/alerts/?entryid45=83659

NW RTC Massive Haemorrhage Toolkit
http://www.transfusionguidelines.org.uk/uk-transfusion-committees/regional-transfusion-committees/north-west/policies/massive-haemorrhage-toolkit

Paediatric Guidelines for Massive Blood Loss in Children – an example of a flow chart from the East of England RTC
http://www.transfusionguidelines.org.uk/uk-transfusion-committees/regional-transfusion-committees/east-of-england/policies

Spahn DR, Cerny V et al (2007) Management of bleeding following major trauma: a European Guideline Critical Care 11(1):R17

The Association of Anaesthetists of Great Britain and Ireland, Management of Massive Haemorrhage
http://www.aagbi.org/sites/default/files/massive_haemorrhage_2010_0.pdf

8. Transfusion Therapy for Specific Groups

8.1 Paediatric Transfusion

Transfusion in paediatric practice shares much of the same knowledge required for adult transfusion practice, however in addition, paediatric transfusion practice requires specialist knowledge.

In terms of transfusion, children are a vulnerable group for a number of reasons:

- They have immature immune and metabolic processes and are still undergoing rapid neurodevelopment. This is particularly the case with neonates who are especially vulnerable to the potential infective and toxic effects of transfusion
- The acute side effects of transfusion may be greater for small children than for adults, as a single unit of transfused blood with the potential to cause harm, may represent a much greater proportion of their blood volume than that in an adult
- Due to the long-term recovery of most of this group, consideration of the long-term effects of transfusion is important
- In general paediatric wards, the transfusion of blood and blood components is not common and this may lead to a reduced awareness of transfusion related hazards.

In addition, other issues which impact on paediatric transfusion practice particularly in the neonatal setting include:

- Special and complex blood component requirements
- Special administration techniques
- Complex prescription calculations
- Issues relating to patient identification e.g. patients are less able to identify themselves and neonates are sometimes un-named and unlabelled.

The Serious Hazards of Transfusion Scheme (SHOT) 2012 Report and Paediatric Transfusion

The 2012 SHOT report identified that there was a disproportionately high incidence of transfusion adverse events in children compared to adults. In 2012, paediatric reports accounted for 6.7% (110) of all adverse incidents reported, 7.3% if near misses and right blood, right patient are included. Of these, 29% were in infants less than one year in age. Within this group 65.6% were neonates less than 28 days old. A study in the North of England carried out in 2004 found that only 1.7% of red cells are transfused to infants under 12 months and 2.5% transfused to children aged 1 to 17 years inclusive.

SHOT also reports a higher percentage of reports in the category ‘Incorrect Blood Component Transfused’ for paediatrics (14%) compared with total reports in this category (5%). The number of Acute Transfusion Reaction (ATR) reports in children has been showing a year on year increase. This year 46.4% of reports were attributed to red blood cells, 39.3% to platelets, 7.14% to plasma, and 7.14% to mixed components.

Recommendations from SHOT to help prevent adverse incidents in paediatric transfusion practice include:

- Specific education of laboratory and clinical staff in paediatric transfusion practice is crucial
- There is a need for local consideration of the design of prescription charts to facilitate the correct prescription of blood component volumes and rates for children. Prescription of red cells should be written as millilitres (mls) rather than units
- The wearing and checking of patient identification e.g. wristbands is essential in the paediatric age group
- BCSH guidelines on blood administration are as applicable to children as they are to adults and should be followed
- Children receiving components should be closely monitored for acute adverse reactions, as in adult practice, with appropriate baseline recordings and an early check 15 minutes after commencing each unit
- Communication mechanisms must be in place for both clinicians and laboratories where patients are cared for between more than one hospital
- Laboratory staff competency on the issues surrounding neonatal and infant pre-transfusion compatibility testing should be targeted during training.

National Comparative Audit of the Use of Red Cells in Neonates and Children (2010): Some Key Findings and Recommendations.

141 hospital sites contributed to the audit providing data from 2524 patients with a total of 4020 transfusion episodes.

- Of these, 85% of hospitals had a policy for neonatal red cell transfusion but only 68% had a policy for children. Transfusion practice in these groups of patients is similar but there are important differences which could affect patient safety
- 40% of hospitals had guidance on minimising excessive/unnecessary blood testing. A common reason for transfusing neonates is excessive or unnecessary blood sampling, resulting in a drop in haemoglobin levels
- 48% of all patients transfused outside neonatal units had a haematological/malignant diagnosis (leukaemia/cancer, haemoglobinopathy) as their main underlying reason for their admission. It is important that care is tailored as specifically as possible for these patients
- In a third of all transfusions on wards (other than the neonatal unit) - the volume of red cells to be transfused was prescribed in 'units' rather than 'mls'. It was most frequent in children >12months (median age of 12 years), but was seen at all ages and in all locations
- Anaemia, with or without symptoms, was reported as the main reason for transfusion for just over half of the transfusions outside neonatal units. 13% of transfusions were given for patients with bleeding.

Recommendations:

- Every Trust / Hospital which transfuses children should have guidelines/policies for use of red cell transfusions to all children and not just neonatal groups.
- Trusts / Hospitals should provide guidance for minimising excessive/unnecessary blood testing.
- Blood prescribed to infants and younger children should be prescribed in mls rather than units.

It is essential that both children and parents understand the need for transfusion, the risks, benefits and alternatives to transfusion that might be available. Patient information leaflets for both children and parents are available from NHS Blood and Transplant:
http://hospital.blood.co.uk/patient-services/patient-blood-management/patient-information-leaflets/

There is limited evidence to support specific indications for transfusion in paediatric practice. The British Committee for Standards in Haematology (BCSH) Transfusion Guidelines for neonates and children provide a good mix of evidence based and expert consensus guidance.

Further Information:

British Committee for Standards in Haematology (2004). Transfusion Guidelines for neonates and older children British Journal of Haematology 124, 433-453 and Erratum 2005
http://www.bcshguidelines.com/4_HAEMATOLOGY_GUIDELINES.html

Hillyer CD, Strauss RG, Luban NLC (2004) Handbook of Paediatric Transfusion Medicine, (American)
New HV (2006) Paediatric transfusion, Vox Sanguinis 90, 1-9

NPSA: Prevention of over infusion of intravenous fluid* and medicines in neonates.
http://www.nrls.npsa.nhs.uk/alerts/?entryid45=75519&q=0%c2%acneonates%c2%ac

SHOT (2012) Serious Hazards of Transfusion for Children See:
http://www.shotuk.org/home/

Wallace JP, Wells AW and Chapman CE (2006) Changing indications for red cell transfusion from 2000 to 2004 in the North of England. Transfusion Medicine 16, 411-417

- **Exchange Transfusion**

Exchange transfusion can be used to manage severe anaemia at birth and to treat hyperbilirubinaemia, usually caused by Haemolytic Disease of the Newborn (HDN). It involves the slow removal of the baby's blood and its replacement with equal amounts of a donor blood. (It is also used in adults to treat patients with sickle cell disease who have acute chest syndrome, intractable priapism, to prevent recurrence of stroke, for red cell aplasia (due to parvovirus infection) and to treat splenic or hepatic sequestration).

- **Intra-uterine Transfusion (IUT)**

An intrauterine transfusion provides red cells to a Rh-positive fetus when fetal red cells are being destroyed by antibodies e.g. Rh, Kell. A blood transfusion is given to replace fetal red blood cells that are being destroyed by the sensitised mothers' immune system. This treatment is expected to keep the fetus healthy until they are mature enough to be delivered. Platelets can also be given by IUT for immune platelet problems. Special components are needed for both of these procedures due to the very small size of the recipient. All components for IUT are irradiated and usually CMV sero negative.

- **Paedipacks**

Blood centres provide neonates with components of lower volume by dividing standard components into 6 aliquots known as paedipacks. This reduces wastage and provides the potential to limit donor exposure. Each aliquot will be uniquely identified to help ensure traceability.

- **Plasma**

Anyone born on or after 1st January 1996 should receive MB FFP or SD FFP which has been sourced from outside the UK (in order to reduce the risk of exposure to vCJD).

- **Donors**

Components for transfusion in utero or to children under 1 year of age are prepared from blood donated by donors who have given at least one previous donation within the past 2 years, which was negative for all mandatory markers.

8.2 Obstetric Transfusion

- **Obstetric Anaemia**

The diagnosis and effective treatment of chronic anaemia in pregnancy is an important way of reducing the need for future transfusions. The decision to transfuse should not be based on haemoglobin levels alone, but also on the patient's clinical need.

- **Haemolytic Disease of the Newborn (HDN)**

One of the most important aspects of transfusion medicine in relation to obstetrics is the prevention, recognition and treatment of haemolytic disease of the newborn (HDN). HDN is a disease that begins in intrauterine life. The lifespan of the infants' red cells is shortened by the action of specific antibodies derived from the mother by placental transfer.

The antibodies most commonly implicated in HDN are Rh group (D, c, C, E, e, Ce and Cw), Kell, Duffy and Kidd groups. Anti-D is the most common cause of severe HDN and is highly immunogenic and of high incidence (15% of women are RhD negative).

The National Institute for Health and Clinical Excellence (NICE) and BCSH have issued guidance stating that anti-D should be given to all RhD negative women without anti-D antibodies.

The Kleihauer test is a simple inexpensive test used to detect whether there has been a fetomaternal bleed and the size of that bleed.

- **Anti-D**

The use of anti-D immunoglobulin since 1968 has prevented an enormous amount of fetal and neonatal morbidity and mortality. Scrupulous attention to ensuring that RhD negative women of childbearing potential receive sufficient prophylaxis is essential. Anti-D must be given in a sufficient dose and is not effective in women who are already immunised to the D antigen.

Anti-D immunoglobulin is available from a number of manufacturers in dose sizes ranging from 250iu, 500iu, 1250iu, 1500iu to 2500iu, and may be given in a number of ways.

Anti-D prophylaxis may be given in response to sensitising events during pregnancy, such as trauma, extra cephalic version, amniocentesis, PV bleeding or surgical miscarriage.

- For pregnancies under 12 weeks gestation, 250iu is indicated if:
    - there is surgical intervention
    - termination of pregnancy
    - ectopic or molar pregnancy
    - unusual heavy bleeding
    - unusual severe pain
    - unsure of gestation.

In all other cases there is usually no need to administer anti-D, as the blood volume of the fetus is considered too small to be significant.

- For pregnancies over 12 weeks and up to 20 weeks gestation, a dose of at least 250iu anti-D is recommended but no Kleihauer test required
- For pregnancies over 20 weeks, and for women who deliver a RhD positive baby:

- a dose of at least 500iu anti-D is recommended
- Kleihauer test is required to ensure that there has not been a larger than expected bleed of foetal cells into maternal circulation. More anti-D than the basic dose may be required depending on these results.

In addition, NICE guidance advises Routine Antenatal Anti-D Prophylaxis (RAADP), where anti-D is administered during the third trimester in an attempt to cover silent bleeds that may otherwise go undetected. Even if a woman has received RAADP, further doses of anti-D should still be administered in response to sensitising events during the pregnancy.
RAADP is administered according to two different regimes, either at least 500iu given at 28 and at 34 weeks gestation, or as a single dose of 1500iu given at around 28 weeks.

Anti-D administration is also indicated following transfusion of RhD positive blood components containing cellular material to RhD negative women of childbearing potential.

There have been a significant number of errors of administration associated with anti-D immunoglobulin documented in successive SHOT reports, the majority apparently due to failure to follow policies, protocols and national guidance.
The following categories are reportable to SHOT:

- Omission or late administration of anti-D
- Inappropriate administration of anti-D
  - to RhD positive women
  - to mothers of RhD negative babies
  - to a different patient than intended
  - to a woman who already has immune anti-D
- Administration of an incorrect dose of anti-D, according to protocol
- Administration of an expired dose of anti-D or a dose out of temperature control.

There has been a steady increase in anti-D errors reported to SHOT since 2006 (77 in 2006, 241 in 2010, 313 in 2012). The latest report indicated that almost two thirds of errors related to clinical staff and one third to laboratory staff.
2012 SHOT recommendations included recommending that a flowchart or checklist reflecting national guidance is used to aid decision making and ensure that the appropriate dose of anti-D is issued and administered.
The 2010 SHOT report advised that if there is any doubt about the patients RhD status, which cannot be quickly resolved, then prophylactic anti-D should be administered rather than placing the patient at risk by withholding it.

Patient Information Leaflets
Patient information leaflets are available free from NHS Blood and Transplant.
'Blood group and red cell antibodies in pregnancy' aims to give information about the significance of blood groups and red cell antibodies in pregnancy. The leaflet also contains information about the treatment that prevents the formation of antibodies that can cause haemolytic disease of babies.
'Protecting women and babies with anti-D immunoglobulin' provides additional information.

Further Information:

BCSH guideline for the use of anti-D immunoglobin for the prevention of haemolytic disease of the fetus and newborn and the Amendment (2014) at:
http://www.bcshguidelines.com/4_HAEMATOLOGY_GUIDELINES.html?dtype=Transfusion&dpage=0&sspage=0&ipage=0#gl

Guideline for blood grouping and antibody testing in pregnancy BCSH approved document (2006)
http://www.bcshguidelines.com/4_HAEMATOLOGY_GUIDELINES.html?dtype=Transfusion&dpage=0&sspage=0&ipage=0#gl

Guidelines on the estimation of fetomaternal haemorrhage (BCSH 2009 update and summary)
http://www.bcshguidelines.com/4_HAEMATOLOGY_GUIDELINES.html?dtype=Transfusion&dpage=0&sspage=0&ipage=0#gl

Guidelines for the use of prophylactic anti-D immunoglobulin, BCSH approved document (2006):
http://www.bcshguidelines.com/4_HAEMATOLOGY_GUIDELINES.html?dtype=Transfusion&dpage=0&sspage=0&ipage=0#gl

National Institute for Health and Care Excellence (NICE) guidelines for therapeutic and routine antenatal anti-D prophylaxis (RAADP)
http://www.nice.org.uk/TA156

Royal College of Obstetricians guidelines:

http://www.rcog.org.uk/womens-health/clinical-guidance/blood-transfusions-obstetrics-green-top-47
http://www.rcog.org.uk/womens-health/clinical-guidance/use-anti-d-immunoglobulin-rh-prophylaxis-green-top-22

Neonatal Alloimmune Thrombocytopenia (NAIT)

Neonatal alloimmune thrombocytopenia (NAIT) is estimated to occur in approximately 1 in 1100 pregnancies and is the most common cause of severe neonatal thrombocytopenia. Movement of maternal alloantibodies, directed against foetal platelet antigens, across the placenta are the most frequent cause of NAIT in otherwise well neonates delivered at term. These alloantibodies cause thrombocytopenia, which may result in intracranial haemorrhage. Most cases arise unexpectedly and prompt diagnosis and treatment are essential to reduce the chances of death and disability caused by the haemorrhage. A diagnosis may be made coincidentally by the finding of a low platelet count arising from a routine full blood count test and the condition should be suspected in any baby presenting with thrombocytopenia or haemorrhage in the absence of systemic disease.

NHS Blood and Transplant provides platelets negative for human platelet antigens for the immediate treatment of neonates with thrombocytopenia suspected of having or known to have alloimmunity.

An information sheet will be provided for women with pregnancies affected by NAIT by the NHS Blood and Transplant Platelet Immunology Reference laboratory and a HPA antibody card will be issued for patients with HPA antibodies in case they should require further transfusions.

Further Information:

Norfolk D (Ed) (2013) Handbook of Transfusion Medicine 5th Edition. Neonatal Alloimmune Thrombocytopenia p119
http://www.transfusionguidelines.org.uk/transfusion-handbook

Rayment R, Birchall J, Yarranton H, Hewertson J, Allen D, Murphy MF, Roberts DJ (2003) Neonatal alloimmune thrombocytopenia. BMJ 327 p331-332

Obstetric Haemorrhage

Obstetric bleeding may be unpredictable and massive. Every obstetric unit should have a current protocol for major obstetric haemorrhage and all staff should be trained to follow it. The blood flow to the placenta is 70ml/minute at term, so bleeding is likely to be rapid. It is also often unexpected and difficult to control. Disseminated intravascular coagulation (DIC) is common in obstetric haemorrhage due to placental abruption, amniotic fluid embolism and intrauterine death (McClelland, 2006).

Cell Salvage in Obstetrics

The National Institute for Health and Clinical Excellence (NICE) has issued full guidance to the NHS in England, Wales, Scotland and Northern Ireland on intra-operative blood cell salvage in obstetrics. Please see the earlier chapter on cell salvage.

Further Information:

Bick R L et al (Ed.) (2006) Haematological complications in Obstetrics, Pregnancy, and Gynaecology Cambridge University Press ISBN-13: 9780521839532 ISBN-10: 052183953X

British Committee for Standards in Haematology (BCSH) guidelines:
http://www.bcshguidelines.com/4_HAEMATOLOGY_GUIDELINES.html?dtype=Transfusion&dpage=0&sspage=0&ipage=0#gl
(2006) Guideline for blood grouping and antibody testing in pregnancy
(2003) Guidelines for the use of prophylactic anti-D immunoglobulin
(1999) The estimation of fetomaternal haemorrhage. Transfusion Medicine. 9 (1) 87-92

Murphy MF, Pamphilon DH (Eds) (2005) Practical Transfusion Medicine, Blackwell Science Ltd ISBN 140511844X

NICE (2005) Guidelines Intraoperative blood cell salvage in Obstetrics
ISBN 1-84629-104-6 IP Guidance Number: IPG144
http://www.nice.org.uk/guidance/IPG144

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9. Examples of Haematological Disorders (Resulting in Anaemia/Thrombocytopaenia)

Anaemias	**Aplastic anaemia**	A gross reduction or absence of haemopoietic precursors in all 3 cell lineages in bone marrow resulting in pancytopaenia (a shortage of all types of blood cells). A rare condition of unknown cause in most cases. More severe cases will need supportive treatment with red cell and platelet transfusions
	Haemolytic anaemia	Haemolytic means having the power to destroy red blood cells. There are many different causes of haemolytic anaemia, for example: - Haemolytic transfusion reactions - Haemolytic disease of the newborn - Allografts, especially marrow transplantation - Infections e.g. malaria - Drug associated e.g. certain drugs may interact with red blood cell membrane generating antigens that stimulate antibody production e.g. penicillin's or cephalosporin's – note: penicillin-induced immune haemolytic anaemia's only occur with massive doses of the antibiotic - Autoimmune haemolytic anaemia (AIHA) – due to the production of antibodies by the body against its own red cells. They are characterised by a positive direct antiglobulin test (DAT) and can be either: - Warm AIHA – antibody reacts better with red cells at 37℃ - Cold AIHA – antibody reacts better with red cells at 4℃
	Iron deficiency anaemia	The average Western diet contains 10 – 15mg of iron from which only 5 – 10% is normally absorbed. Causes of iron deficiency anaemia include: - Chronic blood loss e.g. uterine - menorrhagia - GI tract e.g. oesophagitis, oesophageal varicies, peptic ulcer, inflammatory bowel disease, carcinoma - Malabsorbtion e.g. Coeliac disease, gastrectomy - Pregnancy - Dietary e.g. vegans, elderly
	Pernicious anaemia	A chronic anaemia caused by a lack of intrinsic factor, a protein produced by the stomach that is necessary for the absorption of vitamin B12
Coagulation disorders	**Haemophilia A (Classic Haemophilia)**	Haemophilia is a congenital bleeding disorder characterised by impaired coagulation of the blood, and a strong tendency to bleed. Haemophilia A – a deficiency of clotting factor VIII Haemophilia B – a deficiency of clotting factor IX Mild, moderate and severe forms of haemophilia exist
	Haemophilia B (Christmas disease)	
	Von Willebrand's disease (VWB)	Von Willebrand was a Finnish physician 1870 – 1949. Von Willebrand's disease is an inherited bleeding disorder due to defective production of von Willebrand factor (vWF)
Leukaemia	**ALL**	Acute Lymphoblastic Leukaemia is a malignant tumour of the haemopoietic precursor cells of the lymphoid lineage. Commonest malignancy in childhood. Rare in adults
	AML	Acute Myeloid Leukaemia is a malignant tumour of the haemopoietic precursor cells of the non-lymphoid lineage. Increasing frequency with age (median 60years)
	CLL	Chronic Lymphocytic-Leukaemia is the most common leukaemia. The disease is characterised by abnormal lymphocytes that fill the bone marrow, reducing the number of normal cells produced. Lymph nodes can be enlarged in the neck, armpits, groin, spleen and liver
	CML	Chronic Myeloid Leukaemia is a rare cancer that causes the body to make too many white cells. It may occur at any age but is more common in middle-aged and older people
	Hairy Cell	Rare low grade B-cell lymphoproliferative disorder. The blood film reveals a variable number of unusual large lymphocytes with an irregular cytoplasmic outline ('hairy' cells) in the peripheral blood, bone marrow, liver and other organs. Mainly affects middle aged men
Leucocytosis		An increase in the number of leucocytes in the blood

Leucopenia		A reduction in the number of leucocytes in the blood
Lymphomas	**Hodgkin's**	T. Hodgkin was a British physician, 1798 – 1866. Hodgkin's Lymphoma is a malignant lymphoma where there is replacement of normal lymphoid structure by collections of abnormal cells. Hodgkin's disease is characterised by the presence of Reed Sternberg (RS) cells
	Non Hodgkin's (NHL)	A malignant lymphoma – there is replacement of normal lymphoid structure by collections of abnormal cells. Non-Hodgkin's lymphoma is characterised by diffuse or nodular collections of abnormal lymphocytes (or rarely histocytes). There are many different types of NHL
	Burkitt's	DP Burkitt was an Irish surgeon 1911 - 1993. Burkitt's Lymphoma is a B-lymphoblastic lymphoma, frequently of the jaw, occurring almost exclusively in children. Largely confined to tropical Africa. Burkitt's is a type of Non-Hodgkin's Lymphoma
Multiple myeloma		A B-cell lymphoid malignancy of the plasma cells which secrete paraprotein. These cells invade the bone marrow and suppress its functioning. 98% of cases occur over the age of 40 years with a peak in the seventh decade
Myelodysplastic syndromes	**Myelodysplasia**	Myelodysplasia (MDS) describes a range of acquired clonal disorders of the bone marrow, characterised by qualitative and quantitative abnormalities of all three myeloid cell lines. May occasionally progress to AML. Incidence increases with age
Myelo-proliferative disorders	**Myelofibrosis**	A clonal neoplastic disorder of all haemopoietic cell lines with associated marrow fibrosis. Severe symptomatic anaemia may require supportive treatment with blood transfusions. Its cause is unknown. Occurs mainly in older people
	Polycythaemia	An abnormal increase of red blood cells in the blood. This may require venesection to maintain a normal blood count
	Thrombo-cythaemia (essential)	Abnormal proliferation of megakaryocytes leading to an increased number of platelets in the blood
Polycythaemia		An increase in the packed red cell volume in the blood
Sickle cell		A hereditary haemolytic anaemia. Mainly affects people of African ancestry. Found in high frequency where malaria is endemic as offers some protection. Red blood cells containing HbS deform (sickle) under conditions of reduced oxygenation, leading to microcirculation vascular occlusion and sickle cell crisis
Thalassaemia		A chronic haemolytic disease. Widespread throughout Africa, the Mediterranean, Middle East, India and Asia. Found in high frequency where malaria is endemic and thalassaemia trait probably offers some protection. Severity depends on the type of mutation or deletion of the alpha or beta globin gene. Beta-thalassaemia major (also known as Cooley's anaemia) becomes apparent 3-6 months after birth with severe anaemia. Patients are transfusion dependent. Repeated transfusion results in iron overload requiring chelation therapy

Thrombo-cytopenia		A reduction in the number of platelets in the blood. Characterised by spontaneous skin purpura, haemorrhage and prolonged bleeding after trauma. Main causes are: - Failure of platelet production due to e.g. drugs, chemicals, viral infections - Part of general bone marrow failure e.g. due to chemo/radiotherapy, haematological disorders - Increased consumption of platelets – e.g. immune / idiopathic / drug-induced / disseminated intravascular coagulation (DIC) / thrombotic thrombocytopenic purpura (TTP) - Abnormal distribution of platelets e.g. splenomegaly - Dilutional loss – massive transfusion of stored blood to bleeding patients - Platelet transfusions are beneficial in patients with acute life-threatening bleeding. Their benefit will only last a few hours
Thrombotic Thrombo-cytopenic Purpura	**TTP**	Rare blood condition, causing blood clots to form in small blood vessels throughout the body. Can cause serious problems if blood flow is restricted to the brain, kidneys or heart. Plasma exchange is often required