North West Anglia
NHS Foundation Trust

Guidelines on the use of OCTAPLEX® (Prothrombin complex concentrate/PCC) for rapid reversal of warfarin in association with life threatening bleeding

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Target Audience	All staff involved in prescribing or administering Octaplex for the rapid reversal of warfarin therapy

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DOCUMENT VERSION CONTROL SCHEDULE					
Year and Version Number	**Author**	**Date Published on Document Library**	**Revisions from previous issue**	**Ratifying Committee**	**Date of Ratification**
2007 Version 1	Kanchan Rege	September 2007	Original Version on introduction of use of Octaplex in the trust	Clinical Management Board	September 2007
2011 Version 2	Kanchan Rege	January 2011	Planned review. Changes made to reflect move to PCH.	Hospital Transfusion Committee	January 2011
2014 Version 3	Kanchan Rege	June 2014	Planned review. Inclusion of flowchart for emergency reversal of warfarin (appendix 2)	Quality Governance Operational Committee	12/05/2014
2014 Version 4	Kanchan Rege	17/12/2014	Inclusion of instructions for new mix 2 vial	Quality Governance Operational Committee	16/12/2014
2017 Version 5	Kaye Bowen Andy King Venables	04/01/18	Planned review. Changes made to reflect use of Octaplex at Hinchingbrooke Hospital. Reformatted into NWA template.	Quality Governance Operational Committee	03/01/2018
2021 Version 6	Hospital Transfusion Team	12/7/2021	Amendment made -In life threatening bleeds, when a request for Octaplex without an INR result is made, a single dose of 1000 IU will be issued with the understanding that a coagulation sample will be sent to the laboratory without delay. Once the INR is known, the remainder of the required dose must then be requested. Removal of flowchart for emergency reversal of warfarin (formerly appendix 2) Change to reconstitution device	Quality Governance Operational Committee	8/7/2021

Summary of key points in this document

- Provides guidance for clinicians on rapid reversal of warfarin therapy in cases of life threatening bleeding.

- Outlines the indications and contraindications for the use of Octaplex (Prothrombin Complex Concentrate).

Contents

1. Introduction

Octaplex® is licensed in the UK for treatment of bleeding disorders including reversal of oral anticoagulation with vitamin K antagonists (eg Warfarin).

It contains freeze dried human derived Factors II, VII, IX, X and Proteins S and C.

It provides very effective, rapid reversal of warfarin.

Octaplex® is potentially thrombogenic and may provoke arterial or venous thrombosis. Its use should therefore be restricted to life threatening situations when the thrombotic risks are relatively less than the risk of continued bleeding.

Although the risk of bleeding on warfarin increases when the international normalised ratio (INR) >4.5 most bleeds (including intracranial bleeds) occur with the INR in the therapeutic range.

2. Purpose

These guidelines have been produced to ensure that Octaplex® is used appropriately when clinically indicated, in cases of life threatening bleeding.

3. Scope

These guidelines should be referred to by all staff responsible for requesting, prescribing and administering Octaplex®, and are based on British Committee for Standards in Haematology guidelines.

4. Definitions

Octaplex® PCC – Octaplex Prothrombin Complex Concentrate contains freeze dried human derived Factors II, VII, IX, X and Proteins S and C.

iu – International unit.

SHOT – Serious Hazards of Transfusion a UK wide reporting system for adverse transfusion events and ‘near misses’.

SABRE – Serious Adverse Blood Reactions and Events. This system allows reporters to electronically submit reports of serious adverse events or serious adverse reactions directly to the Medicines and Healthcare Products Regulatory Agency (MHRA).

5. Process

The request, prescription and administration of Octaplex® PCC

6. Indications for use

Life threatening haemorrhage.

Intracranial haemorrhage (this carries a 50% mortality in patients on warfarin).

Treatment of bleeding and prophylaxis of bleeding in patients being treated with Vitamin K antagonists, where rapid correction is clinically indicated (where vitamin K alone or delaying intervention is not clinically reasonable)

Octaplex® can be considered for 'off licence' use for continued bleeding in patients on Direct Oral Anti-Coagulation therapies (DOAC) - consult DOAC guidelines and a Consultant Haematologist for further advice and authorisation.

Octaplex® may not be suitable for treatment of Jehovah's Witnesses as it is prepared from human plasma. This will be down to the individual patient's wishes.

It is not indicated for minor Bleeding (WHO bleeding scale grade 1- see Appendix 1) or for preparation for elective surgery.

Patients on Warfarin with a strong suspicion of intracerebral haematoma after a clear head injury should have their INR reversed with PCC immediately, and **before** the CT and INR results are available. (BSH 2011).

In genuine emergency situations (life threatening bleeding) when a request for Octaplex® **without** an INR result is made, a **single dose of 1000 IU** will be issued with the understanding that a coagulation sample will be sent to the laboratory without delay**. Once the INR is known, the remainder of the required dose must then be requested from the transfusion laboratory.**

PCC's are able to completely reverse the warfarin-induced anticoagulation within 10 min but the infused clotting factors have a finite half-life, the shortest of which is FVII at 6 h. In view of this**, 5 mg intravenous vitamin K should be given with the PCC** (BSH 2011)

7. Dose

Wt (kg)	INR 2-2.5	INR 2.5-3	INR 3-3.5	INR >3.5
50	1500iu	2000iu	2500iu	2500iu
60	2000iu	2000iu	2500iu	3000iu
70	2500iu	2500iu	3000iu	3000iu
80	2500iu	3000iu	3000iu	3000iu
90	2500iu	3000iu	3000iu	3000iu
100	3000iu	3000iu	3000iu	3000iu

Maximum single dose is 3000iu

Once a vial is reconstituted please use the complete vial. **DO NOT discard part used vials**

8. Contraindications

- Known hypersensitivity to plasma proteins.
- Disseminated Intravascular Coagulation.
- Recent arterial thrombosis.
- Previous history of heparin associated thrombocytopenia type II.
- Uncompensated liver disease.

9. Relative contraindications

- Patients with history of Ischaemic Heart Disease.
- Liver disease.
- Safety in pregnancy not established.

10. Risks

- Thrombosis (arterial and venous) and may provoke DIC.
- Anaphylaxis.
- Viral transmission.

11. Consequences of not administering the drug

The British Committee for Standards in Haematology recommend that all hospitals managing patients on warfarin should stock a licensed four-factor prothrombin complex concentrate (e.g.: Octaplex®).

As Fresh Frozen Plasma produces suboptimal anticoagulation reversal it should not be used for reversal of warfarin (NICE 2015)

12. Reconstitution

Octaplex® is stocked in the Transfusion Laboratory, and should be collected from the blood bank as soon as it is available after being requested.

Octaplex® is provided as a dried powder (available vial sizes are 500 IU and 1000IU per vial) along with sterile water. It will need to be reconstituted in the clinical area by the nurse or doctor responsible for the patient. Multiple boxes will be issued to provide the correct dose.

One box of Octaplex® contains:-

- Octaplex powder in a vial with a stopper and flip off cap.
- Solvent (water for injection) with a stopper and flip off cap.
- A needle free transfer set.
  Currently this is the Mix2Vial™, however during 2021 it is expected that this will change to the Nextaro® transfer device.
  Instructions for both devices are included as appendices to these guidelines
  Appendix 3 = Mix2Vial™
  Appendix 4 = Nextaro® transfer device

To reconstitute, follow the instructions provided in the pack

- Warm to room temperature by gently rolling the bottle in your hands
- Remove the flip off caps from the powder vial and the solvent vial and clean the rubber stoppers with an alcohol swab.
- Peel away the lid of the needle free device package. Do not remove the device from the package.
- Seat the **blue** end of the device on the **solvent** vial, using the blister pack as a holder. Place the solvent vial on an even surface and hold it firmly. Push down the mixing device until the spike penetrates the stopper and the device snaps into place. Do not twist while attaching.
- While holding the solvent vial, carefully remove the plastic package and discard it, being careful to leave the mixing device attached to the solvent. Take care not to touch the exposed end of the device.
- Place the powder vial on an even surface and hold it firmly. Turn the solvent vial with the attached mixing device upside down and insert the clear/white end of the mixing device into the powdered Octaplex® vial, pushing down until the spike penetrates the stopper and the device snaps into place. Do not twist while attaching.
- The solvent will automatically flow into the Octaplex powder vial. With both vials still attached, gently swirl the vial to make sure the Octaplex is thoroughly mixed. Octaplex® dissolves quickly at room temperature to a colourless/ slightly blue solution. If the powder fails to dissolve completely or a deposit is formed, do not use the preparation.
- Remove the empty solvent vial and blue part of the mixing device by turning it anti-clockwise, and dispose of it.
- Attach a 60 ml luer lock syringe to the Octaplex® vial. The syringe must be clearly labelled with the name and strength of the drug.
- The total number of vials required to give the final dose can be reconstituted at the same time.

13. Administration

Administer the reconstituted Octaplex® solution by the intravenous route using a syringe pump.

In the summary of product characteristics issued by the manufacturer, the recommended administration rate is 2 to 3mls/minute, but this relates to treatment in non-emergency situations when **immediate** reversal is unnecessary – this is not practical in cases of life threatening haemorrhage. There is evidence to show that faster administration rates of up to 10ml/minute have been used without any adverse reactions (Reiss et al 2007, Franken et al 2007). In life threatening situations, using an administration rate of 4 to 8ml/minute means that a dose of 3000 iu can be given over a total of 15 to 30 minutes.

There is a small risk of allergic reactions – if these occur the infusion should be stopped immediately and standard allergy/anaphylaxis therapy should be instituted. As a precautionary measure, the patients pulse rate should be measured before and during the infusion. If a marked increase in the pulse rate occurs the infusion speed must be reduced or the administration must be interrupted.

No blood must flow into the syringe due to the risk of formation of fibrin clots.

Once reconstituted, the solution should be used immediately.

14. Post Administration

Repeat PT/INR 30-60 minutes post administration and at 6 hours + 18 hours (the patient may need further therapy).

Monitor clinical response and for evidence of disseminated intravascular coagulation DIC/thrombosis.

Daily full blood counts (FBCs) and INRs/clotting screens are required for 2-3 days post infusion.

Some severely over anticoagulated patients may need further doses of vitamin K if there is a clinical need to maintain complete reversal.

Once the acute event has been treated and the patient is stable it may be appropriate to consider prophylactic heparin in some situations e.g.: mechanical heart valve.

Always record the efficacy of Octaplex in the patien’st notes.

15. Ratification

The policy will be approved by the Hospital Transfusion Committee & ratified by the Quality Governance Operational Committee.

16. Distribution

The guideline will be stored on the trust intranet. Staff will be made aware of the guideline during induction and clinical update sessions.

17. References

British Standards in Haematology, (2011), Guidelines on oral anticoagulation (warfarin): fourth edition – Available: http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2011.08753.x/pdf [Accessed 13/03/2020].

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Appendix 1 The modified World Health Organization (WHO) bleeding scale

Grade 1
- Mild/moderate petechiae, purpura.
- Mild/moderate oropharyngeal bleeding, epistaxis <30 minutes in duration

Grade 2
- Melaena, haematemesis, haemoptysis, fresh blood in stool, musculoskeletal bleeding or soft tissue bleeding ***not requiring red cell transfusion within 24 hours of onset and without haemodynamic instability***
- Profuse epistaxis or oropharyngeal bleeding *i.e.> 30 minutes in continuous duration*
- Symptomatic oral blood blisters *i.e. bleeding or causing discomfort*
- Extensive petechiae, purpura *i.e. numerous in number and/or positioned on either face or abdomen and/or spreading by comparison to previous assessment*
- Visible blood in urine
- Bleeding from invasive sites requiring 2 ≥ changes of dressings in a 24 hr period
- Unexpected vaginal bleeding saturating 2 ≥ pads with blood in a 24hr period
- Red cells in body cavity fluids obvious macroscopically
- Retinal haemorrhage with/without visual impairment

Grade 3
- Melaena, haematemesis, haemoptysis, haematuria -including intermittent gross bleeding without clots, abnormal vaginal bleeding, fresh blood in stool, epistaxis, and oropharyngeal bleeding, bleeding from invasive sites, musculoskeletal bleeding, or soft tissue bleeding ***requiring red cell transfusion specifically for support of bleeding within 24 hours of onset and without haemodynamic instability***
- Body cavity fluids reported as grossly bloody in laboratory, nursing, or medical notes
- CNS bleeding noted on CT (computerized tomography) without clinical consequences

Grade 4
- Debilitating bleeding including retinal bleeding with visual impairment*
- Non-fatal CNS bleeding with neurological signs and symptoms
- Bleeding associated with haemodynamic instability (hypotension, >30 mm Hg change in systolic or diastolic HP)
- Fatal bleeding from any source

**visual impairment is defined as a field deficit, and patients with suspected visual impairment require an opthalmologic consultation*

Appendix 2

Summary of procedure for use of Octaplex

Doctor makes clinical assessment of patient on warfarin and bleeding.
Bleeding is considered life threatening

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- Send urgent INR, APTT, Fibrinogen, FBC and X match (as appropriate)
- Weigh patient or make estimate of weight
- Contact transfusion laboratory and request urgent results and inform laboratory that Octaplex is required. If possible, inform the laboratory:-
- Why the patient is on Warfarin (i.e. Stroke, DVT, PE, other thrombosis
- If the patient has a known allergy to heparin/ previous Heparin Induced Thrombocytopaenia (HIT)

↓

Request Octaplex via transfusion laboratory

If current INR known

• Request as per dosing algorithm taking into account patient's weight and current INR

If INR not known

• Ensure urgent INR sample has been sent. Request 1000iu octaplex for immediate management of the patient
• Once INR result know, **request remainder of the dose as indicated in the dosing algorithm**

NOTE: maximum total Octaplex dose = 3000IU in 24 hours

↓

Administer vitamin K 5mg iv

↓

Transfusion laboratory contacts doctor/clinical area to inform Octaplex available – doctor/nurse arranges **immediate** collection from blood bank

↓

Reconstitute in clinical area

↓

Administer as slow iv bolus (see section 13 for details)

↓

Repeat INR/clotting screen at 30 – 60 minutes

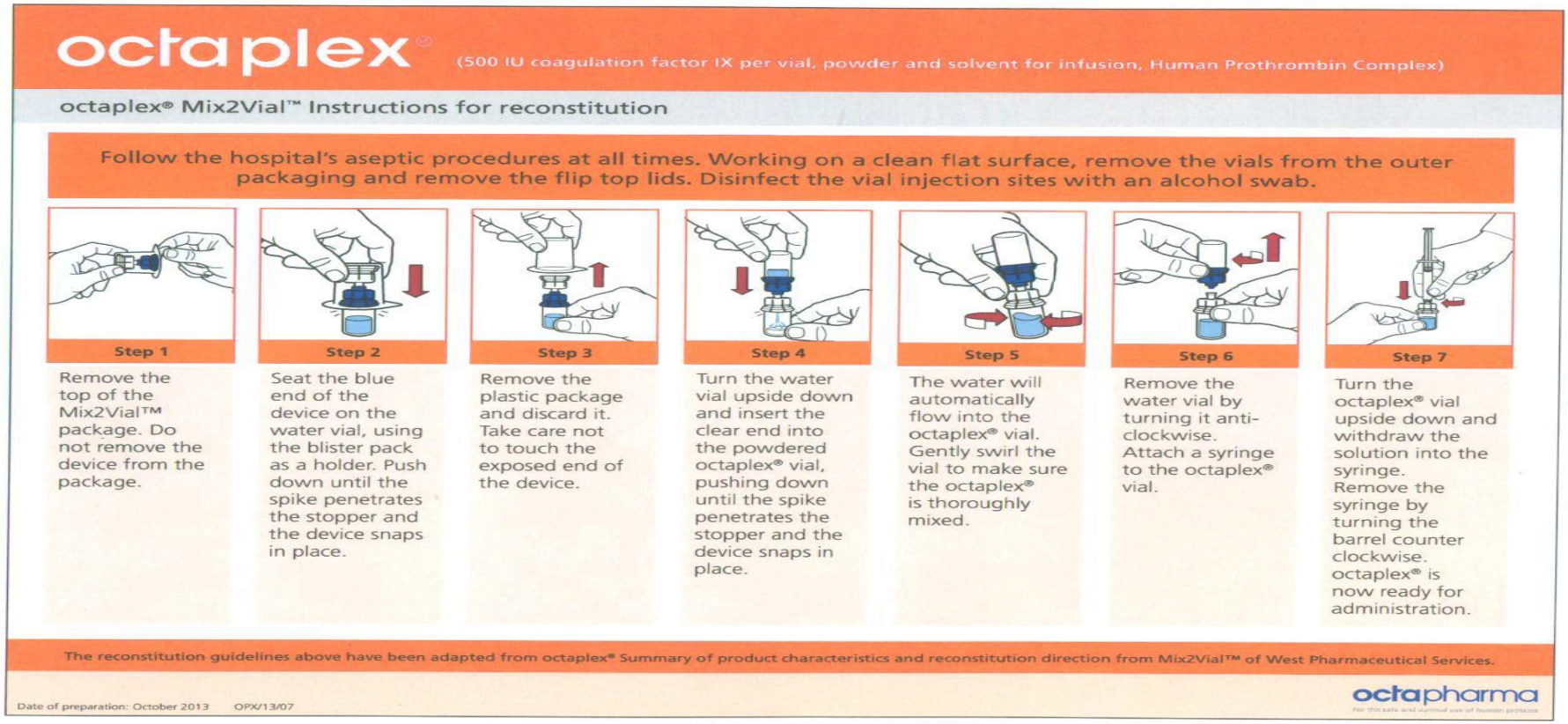
↓

Repeat INR/clotting screen at 6 hours and 18 hours
Monitor for signs of thrombosis and DIC

↓

Record clinical efficacy of Octaplex in medical notes

Appendix 3 – Mix2Vial™ needle free reconstitution



octaplex®

(500 IU coagulation factor IX per vial, powder and solvent for infusion, Human Prothrombin Complex)

octaplex® Mix2Vial™ Instructions for reconstitution

Follow the hospital's aseptic procedures at all times. Working on a clean flat surface, remove the vials from the outer packaging and remove the flip top lids. Disinfect the vial injection sites with an alcohol swab.

Step 1
Remove the top of the Mix2Vial™ package. Do not remove the device from the package.

Step 2
Seat the blue end of the device on the water vial, using the blister pack as a holder. Push down until the spike penetrates the stopper and the device snaps in place.

Step 3
Remove the plastic package and discard it. Take care not to touch the exposed end of the device.

Step 4
Turn the water vial upside down and insert the clear end into the powdered octaplex® vial, pushing down until the spike penetrates the stopper and the device snaps in place.

Step 5
The water will automatically flow into the octaplex® vial. Gently swirl the vial to make sure the octaplex® is thoroughly mixed.

Step 6
Remove the water vial by turning it anti-clockwise. Attach a syringe to the octaplex® vial.

Step 7
Turn the octaplex® vial upside down and withdraw the solution into the syringe. Remove the syringe by turning the barrel counter clockwise. octaplex® is now ready for administration.

The reconstitution guidelines above have been adapted from octaplex® Summary of product characteristics and reconstitution direction from Mix2Vial™ of West Pharmaceutical Services.

Date of preparation: October 2013 OPX/13/07

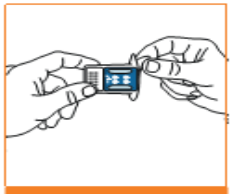
octapharma

Appendix 4- Nextaro® Transfer device

octaplex® Human Prothrombin Complex

Instructions for reconstitution using Nextaro®

Follow the hospital's aseptic procedures at all times. If necessary, allow the solvent (water for injections) and the powder in the closed vials to reach room temperature. This temperature should be maintained during reconstitution. Working on a clean flat surface, remove the vials from the outer packaging and remove the flip top lids. Disinfect the rubber stoppers on the vials appropriately.



Step 1

Peel away the lid of the outer package of the Nextaro®. Do not remove the device from the package.

Step 2

Place the solvent vial on an even surface and hold it firmly. Without removing the outer package, place the blue part of the Nextaro® on top of the solvent vial and press firmly down until it snaps into place.

Step 3

While holding onto the solvent vial, carefully remove the outer package from the Nextaro® being careful to leave the Nextaro® attached firmly to the solvent vial

Step 4

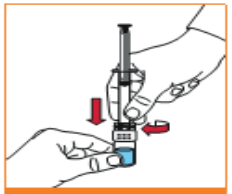
Place the powder vial on an even surface and hold it firmly. Take the solvent vial with the attached Nextaro® and turn it upside down. Place the white part of the Nextaro® connector on top of the powder vial and press firmly down until it snaps into place.

Step 5

The solvent flows automatically into the powder vial. With both vials still attached, gently swirl the powder vial until the product is dissolved. Octaplex® dissolves quickly at room temperature to a colourless to slightly blue solution.

Step 6

Unscrew the Nextaro® into two parts. Dispose of the empty solvent vial with the blue part of the Nextaro®. If the powder fails to dissolve completely or an aggregate is formed, do not use the preparation.



Step 7

Attach a syringe to the luer lock outlet on the white part of the Nextaro®. Turn the vial upside down and draw the solution into the syringe. Dispose of the Nextaro® and the empty vial.

The reconstitution guidelines above have been adapted from octaplex® Summary of Product Characteristics.

September 2020 2020.017.CC.C

octapharma

Quality Assurance Checklist - Version Number: 6 **Appendix: 4**

		Y/N/n/a	COMMENTS (where necessary)
1	**Title of document** Guidelines on the use of OCTAPLEX® (Prothrombin complex concentrate/PCC) for rapid reversal of warfarin in association with life threatening bleeding (C0254)		
2	**Type of document (e.g. Policy, guidance)**	Guideline	
	Is it clear whether the document type is a policy, guideline, procedure?	Yes	
3	**Introduction**		
	Are reasons for the development of the document clearly stated?	Yes	
4	**Content**		
	Is there a standard front cover?	Yes	
	Are the key points identified? (Policies only)	N/A	
	Is the document in the correct format?	Yes	
	Is the purpose of the document clear?	Yes	
	Is the scope clearly stated?	Yes	
	Are the definitions clearly explained?	Yes	
	Are the roles and responsibility clearly explained? (policies only)	N/A	
5	**Evidence Base**		
	Is the type of evidence to support the document explicitly identified?	Yes	
	Are key references cited?	Yes	
	Are associated documents referenced?	Yes	
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	Does the document identify which committee/ group will approve it?	Yes	
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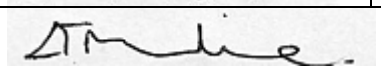
	Are there measurable standards or KPIs to support the monitoring of compliance with the effectiveness of the document?	Yes	
8	**Review date**		
	Is the review date identified?	Yes	
9	**Equality and Diversity (policies only)**		
	Is a completed Equality Impact Assessment	N/A	

If answers to any of the above questions is ‘no’, then this document is not ready for ratification, it needs further review.

Compliance Team:		
1.	Date of Compliance Team approval	18/06/2019
2.	Comments to author for any amendments	
3.	Name of compliance lead	Stanley Balachander, Quality governance and Policies Administrator.

Approval Committee: Hospital Transfusion Committee			
If the committee/group is happy to approve this document would the chair please sign below and send the document and the minutes from the approval committee to the author. To aid distribution all documentation should be sent electronically wherever possible.			
Name	L MENAPACE.	**Date**	10/5/21.
Signature			

Ratifying Committee: Quality Governance Operational Committee			
If the committee/group is happy to ratify this document would the chair please sign below and send the document and the minutes from the ratifying committee to the author. To aid distribution all documentation should be sent electronically wherever possible.			
Name	**Kanchan Rege**	**Date**	**08.07.21**
Signature