Whittington Health NHS

Emergency reversal of anticoagulant therapy (Bleeding & Emergency Surgery)

Subject:	Anticoagulation Therapy – Emergency Reversal
Policy Number	
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Policy Executive Owner:	Divisional Director ICAM
Designation of Author:	Farrukh Shah, Consultant Haematologist, Alsion Thomas, Haematology SpR
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Version Control Sheet

Version	Date	Author	Status	Comment
1.0	15.11.14	Alison Thomas, Farrukh Shah		Change from FFP to PCC for all emergency warfarin reversal. Addition of guidance for bleeding on new oral anticoagulants and fibrinolytic drugs. Inclusion of information previously contained in separate Beriplex guideline.

Abbreviations:

APTR: Activated partial thromboplastin time ratio

FBC: Full blood count

FFP: Fresh frozen plasma

LMWH: Low molecular weight heparin

NOACs: New oral anticoagulants

PCC: Prothrombin complex concentrate

PT: Prothrombin time

UFH: Unfractionated heparin

➢ Criteria for use

This guideline applies to the management of adult patients who require reversal of anticoagulant therapy due to:

- Bleeding
- The need for emergency surgery which cannot be delayed

The management of bleeding comprises:

- General measures for all patients
- Drug-specific measures (vitamin K antagonists, heparins, fondaparinux, new oral anticoagulants, anti-platelet agents and anti-fibrinolytics).

➢ Related guidelines:

Please see Whittington Health Guidelines:

Therapeutic Anticoagulation Guidelines: Warfarin, LMWH, UFH, Rivaroxaban

"Peri-operative management of adults on anticoagulant therapy"

"Major Haemorrhage in Adults"

➢ General principles

Major bleeding on patients receiving anticoagulant therapy is a major cause of morbidity and mortality. **Senior input from the patient's own team and haematology must be sought in all cases of major bleeding on anticoagulant therapy**.

Specific reversal agents for anti-coagulants:

Specific agents to reverse the effects of anticoagulants are only available for the following antiocagulants:

- Vitamin K antagonists (e.g. warfarin): prothrombin complex concentrate (PCC), vitamin K (phytomenadione)
- Heparins (unfractionated and low molecular weight): protamine

Anticoagulants for which there is no specific reversal agent:

- New oral anticoagulants (NOACs) e.g. rivaroxaban, apixaban, dabigatran
- Fondaparinux

General haemostatic measures are the mainstay of management. Prothrombin complex concentrate (for reversal of NOACs) or recombinant FVIIa (for reversal of fondaparinux) may be considered in the context of life-threatening or on-going major bleeding on a case-by-case basis. **These are unlicensed indications and must be agreed by the patient's consultant and a consultant haematologist.**

Fresh frozen plasma (FFP) has no proven efficacy in reversal of anticoagulant effect of drugs other than vitamin K antagonists. It should ONLY be used for reversal of vitamin K antagonists where PCC is unavailable.

Patient safety reporting:

All instances of bleeding on anticoagulant therapy must be reported on DATIX.

➢ Management of bleeding - general measures:

Definition of a major bleed:

Life, limb or sight-threatening bleeding that requires complete reversal of anticoagulation (1). This includes: intracranial, retro-peritoneal, intraspinal, intra-ocular, pericardial or intramuscular with compartment syndrome (2).

General measures in the management of bleeding for all anti-thrombotics (3)

- Stop the anti-thrombotic drug
- Document timing and amount of last drug dose and presence of pre-existing renal or hepatic impairment
- Assess source of bleeding
- Request: FBC, PT, APTR, renal function. INR for warfarin.
- Correct haemodynamic compromise: IV fluids, red cell transfusion (aim Hb>7)
- Apply mechanical pressure if possible.

Issues to address once bleeding controlled:

- Unexpected bleeding on therapeutic anticoagulant (i.e. not supra-therapeutic) – always investigate possibility of underlying cause (e.g. unsuspected renal or GI tract pathology
- Review compliance with medication and factors that may contribute to poor control
- Review ongoing treatment:
    - Risks and benefits of on-going anticoagulation
    - Choice of anticoagulant, dosing and monitoring arrangements

➢ Bleeding on warfarin

The management algorithm for bleeding on warfarin is summarised in **Appendix 1 (1;3).**

Risk of bleeding on warfarin increases significantly with INR results >5,0. The management of bleeding depends on the severity of bleeding and the INR.

- Emergency reversal in major bleeding is with 25U/kg PCC (Beriplex) and 5mg IV vitamin K (phytomenadione)
- Fresh frozen plasma (FFP) produces sub-optimal anticoagulation reversal and should only be used if PCC is not available
- Anti-coagulation reversal for non-major bleeding should be with 1-3mg IV vitamin K (phytomenadione)
- Patients with an INR >5 who are not bleeding should have 1-2 doses of warfarin withheld and their maintenance dose should be reduced.
- Asymptomatic patients with INR ≥8.0 should receive 1-5mg oral vitamin K (phytomenadione). Re-check INR following day.
- Cause of the elevated INR should be investigated

Other vitamin K antagoinsts: phenprocoumon, acenocoumarol (sinthrome), phenindione

- These other vitamin K antagoinists are commonly used in other countries. They have the same mechanism of action as warfarin
- Emergency reversal as for warfarin.

➢ Bleeding on heparins (unfractionated and low molecular weight)

Protamine sulphate:

- Protamine sulphate rapidly reverses unfractionated heparin (UFH) and partially reverses low molecular weight heparin (LMWH – about 60% reversal).
- Protamine can cause severe allergic reactions including anaphylaxis, hypertension, bronchospasm and skin reactions in up to 10% patients.
- ***Contra-indications:*** previous exposure to protamine sulphate (including protamine insulin preparations), vasectomy and fish allergy.
- Give slower than 5mg/min, minimum time 5 minutes.
- Maximum dose – 50mg over 10 minutes.
- Protamine has an anticoagulant effect in overdose
- Protamine is available from: ITU, Mary Seacole North and South, Montouschi and the emergency drugs cupboard.

Reversal of unfractionated heparin (UFH)

- The half-life of IV unfractionated heparin is 45-90 minutes when at therapeutic range.
- **Treatment is often achieved simply by stopping UFH and general measures**.
- UFH can be rapidly reversed with protamine sulphate. Protamine dose may be calculated from quantity of UFH administered in the 2 hours prior to reversal. **Give 1mg of protamine per 100 units of UFH**
    - e.g. bleeding during an IV infusion of 1250 units/hr requires 25mg protamine.
- If 2-6hr since infusion stopped and UFH thought to be cause of bleed, consider reduced dose of protamine e.g. 0.25mg per 100 units of UFH. ***Seek haematology advice***
- Half-life of protamine is 7 minutes (shorter than half life of UFH) – so repeat administration may be required.
- Repeat APTT 15 minutes after protamine administration.

Reversal of low molecular weight heparin (3):

- The half –life of LMWH is approximately 4 hours.
- Anti-Xa levels are not measured in house and therefore the results are unlikely to be available in time to affect initial management.
- Potential reversal with protamine **MUST BE DISCUSSED WITH HAEMATOLOGY**
- **LMWH given within last 8 hours:**
    - give protamine sulphate 1mg per 100 anti-Xa units of LMWH (100 units tinzaparin = 100 anti-Xa units). Maximum dose 50mg protamine sulphate.
    - If ineffective, consider further protamine sulphate 0.5mg per 100 anti-Xa units of LMWH.
    - If life-threatening bleeding despite protamine sulphate and time frame suggests residual effect from LMWH consider recombinant FVIIa (**unlicensed indication**)
- **LMWH given >8 hours ago**:
    - consider smaller doses of protamine sulphate (e.g. 50% if within 8-12 hours). Protamine sulphate may not be required if >12 hours post last dose.

➢ Bleeding on fondaparinux

- There is no specific antidote for fondaparinux
- Stop fondaparinux
- Employ general haemostatic measures
- In LIFE-THREATENING bleeding consider recombinant FVIIa (Novoseven®) (**unlicensed indication**). **MUST BE DISCUSSED WITH CONSULTANT HAEMATOLOGIST**

➢ Bleeding on new oral anticoagulants (NOACs)

The algorithm for management of bleeding in patients taking NOACs is shown in **Appendix 3**

General considerations:

- There is no specific antidote to NOACs. The mainstay of management is stopping the drug and general haemostatic measures
- Prothrombin complex concentrate should be considered in life-threatening or on-going major bleeding. **Unlicensed indication**
- Careful attention should be paid to the time of the last dose and renal function to help gauge the likely anticoagulant effect of the drug.
- Consider activated charcoal if within 2 hours of ingestion

Effect of NOACs on coagulation screen (PT and APTT)(4;5):

- *Dabigatran;* The APTT is usually prolonged by therapeutic doses of dabigatran, even at trough, but not in all patients. The thrombin time is considerably prolonged by dabigatran and a normal thrombin time suggests the level of dabigatran is likely to be very low (4).
- *Rivaroxaban and apixaban* prolong the APTT and PT; the PT tends to be more sensitive. Some patients on rivaroxaban and apixaban will have normal PT and APTT despite therapeutic drug levels.

➢ Bleeding on anti-platelet drugs

- Although anti-platelet agents have short plasma half-lives they may have a prolonged biological effect due to irreversible platelet inhibition
- No specific reversal agents.
- General haemostatic measures should be employed. Stop anti-platelet agents (discuss with cardiology first)
- Time to normal platelet function after discontinuation(3):
    - NSAIDS – 24hr
    - Aspirin , clopidogrel and prasugrel: 5-7 days
    - Dipyridamole: 24hr
- Consider platelet transfusion as an additional measure for critical bleeding or prevention of bleeding before emergency surgery

➢ Bleeding on fibrinolytic drugs

- Licensed anti-fibrinolytics: alteplase, tenecteplase, reteplase, urokinase, streptokinase. All function indirectly by promoting generation of plasmin which then mediates clot lysis.

- Although fibrinolytic drugs themselves have short half-lives the effect on coagulation is much longer and haemostasis may not return to normal until approximately 48 hours post administration.

For major bleeding (e.g. intracerebral) within 48 hours of administration of anti-fibrinolytics(3):

- Stop infusion of fibrinolytic drugs and other anti-thrombotic drugs
- Contact consultant haematologist. Inform patient's own consultant
- Urgently send: FBC, coagulation screen, thrombin time
- Administer FFP 12ml/kg
- Administer IV tranexamic acid 1g tds
- If depletion of fibrinogen, administer cryoprecipitate.

➢ Emergency surgery

General principles:

- Is the procedure for a bleeding-related complication (e.g. upper GI bleed)? If yes – follow guidelines for bleeding of anticoagulants above
- Consider:
    - What anticoagulant is the patient taking and when was the last dose taken?
    - How urgent is the surgery?
        - Within 6 hours
        - Within 24 hours
        - After 24 hours

Neuraxial blockades (e.g. spinal, epidural, lumbar puncture) **should not be performed** in patients on anticoagulants, or who may require anticoagulants in the post-operative period, who require emergency surgery unless deemed safe by the anaesthetic consultant and haematology consultant

Management of patients on warfarin requiring emergency surgery:

- **INR<1.5:** Safe to proceed
- **INR >1.5 and surgery must proceed within next 6 hours:**
    - Stop warfarin
    - Give IV vitamin K (phytomenadione) 2-5mg.
    - Contact haematologist to authorise use of prothrombin complex concentrate (25IU/kg) (**See appendix 2**)
    - Repeat INR 10 minutes post PCC administration.
    - If INR >1.5 contact haematology for advice
- **INR>1.5 and surgery must proceed within next 6-12 hours:**
    - Stop warfarin
    - Give IV vitamin K (phytomenadione) 2-5mg IV
    - Repeat INR at 6 hours
    - If INR>1.5, discuss with haematologist regarding PCC
- **INR>1.5 and surgery required in >12 hours time:**
    - Stop warfarin
    - Give vitamin K (phytomenadione) 2-5mg IV/PO
    - Repeat INR at 6-8 hours
    - If INR>1.5, consider further vitamin K (phytomenadione)
    - Check INR pre-procedure. If remains >1.5, discuss with haematology.

Patients on therapeutic LMWH:

- If >24 hours since last dose of LMWH and creatinine clearance >30ml/min – safe to proceed with surgery
- If <24 hours since last dose of LMWH, discuss with haematology

Patients on other anticoagulants:

- Must be discussed with the haematology consultant on call by the anaesthetic consultant and surgical consultant.

➢ Contacts (inside and outside the Trust including out-of-hours contacts)

Haematology SpRs: bleep 3060 or bleep 3037

Haematology consultants: via switchboard

Out of hours: on call haematologist via switchboard.

➢ References (evidence upon which the guideline is based)

(1) Keeling D, Baglin T, Tait C, Watson H, Perry D, Baglin C, et al. Guidelines on oral anticoagulation with warfarin - fourth edition. Br J Haematol 2011 Aug;154(3):311-24.

(2) Schulman S, Angeras U, Bergqvist D, Eriksson B, Lassen MR, Fisher W. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. J Thromb Haemost 2010 Jan;8(1):202-4.

(3) Makris M, Van Veen JJ, Tait CR, Mumford AD, Laffan M. Guideline on the management of bleeding in patients on antithrombotic agents. Br J Haematol 2013 Jan;160(1):35-46.

(4) Kitchen S, Gray E, Mackie I, Baglin T, Makris M. Measurement of non-coumarin anticoagulants and their effects on tests of Haemostasis: Guidance from the British Committee for Standards in Haematology. Br J Haematol 2014 Sep;166(6):830-41.

(5) Baglin T, Keeling D, Kitchen S. Effects on routine coagulation screens and assessment of anticoagulant intensity in patients taking oral dabigatran or rivaroxaban: guidance from the British Committee for Standards in Haematology. Br J Haematol 2012 Nov;159(4):427-9.

➢ Compliance with this guideline (how and when the guideline will be monitored e.g. audit and which committee the results will be reported to) Please use the tool provided at the end of this template

- Use of Beriplex
- Major bleeds on warfarin
- Bleeding events on rivaroxaban
- Bleeding events on low molecular weight heparin

APPENDIX 1: MANGEMENT OF BLEEDING ON WARFARIN

How severe is the bleeding?

Life threatening or major bleeding at any INR
Intra-cerebral or intra-cavity bleed

- Resuscitate as necessary
- Stop warfarin
- Check INR
- Give Beriplex ® 25 units/kg. Contact haematology to authorise product release.
- Beriplex to be collected from transfusion laboratory by staff trained to collect blood products
- Give 5mg IV vitamin K (phytomenadione, Konakion MM)
- Repeat INR 10 minutes after administration PCC.
- Contact haematology if INR still >1.5.
- Repeat INR 6-8 hours dose of Beriplex (short half life)

Head injuries:
Patients on warfarin with a strong suspicion of intracerebral haematoma after a clear head injury should have their warfarin reversed with Beriplex immediately and before CT and INR results are available

Contact details:
Haematology SpRs: bleep 3060 or 3037
Haematology Consultant: via switchboard

Non-major bleeding

- Give vitamin K 1mg orally (consider higher dose if INR >7).
- Omit anticoagulant
- General haemostatic measures
- Repeat INR at 24 hours

No bleeding but INR >5

What is the INR?

INR 5-7

- Omit oral warfarin for number of days indicated in **Warfarin prescribing guideline**
- Consider 1mg vitamin K PO in patients at high risk of bleeding (e.g. elderly)
- Reduce maintenance dose

INR ≥8.0

- Give vitamin K 1mg orally
- Omit oral anticoagulant on that day.
- Recheck INR following day

Vitamin K (phytomenadione): Obtain from pharmacy or emergency drugs cupboard

General Haemostatic Measures:

- Stop the anti-thrombotic drug
- Document timing and amount of the last drug dose and presence of existing renal or hepatic dysfunction
- Assess source of bleeding
- Request: FBC, U&E, coagulation screen, INR
- Correct haemodynamic compromise with IV fluids (± red cells to maintain Hb >70g/L)
- Apply mechanical pressure if possible
- Use endoscopic, radiological or surgical measures

FOR GUIDANCE ON ADMINISTRATION OF BERIPLEX (PROTHROMBIN COMPLEX CONCENTRATE SEE APPENDIX 2. Patient's written consent required

APPENDIX 2: ADMINISTRATION OF BERIPLEX® (PROTHROMBIN COMPLEX CONCENTRATE)

General principles:

- Beriplex ® (prothrombin complex concentrate) contains the blood factors II, VII, IX and X. It rapidly and specifically replaces the vitamin-K dependent clotting factors depleted by warfarin to correct the INR
- Beriplex is a blood product. It is not blood group specific.

Before use:

- **The need for PCC must be discussed with the patient's consultant.**
- **Use MUST be authorised by the Consultant Haematologist on call (via haematology SpR in hours).**
- **Written consent required for all patients.**

Contra-indications:

Absolute: History of heparin induced thrombocytopenia
Known allergy to heparin or citrate (present as excipients)
IgA deficiency (contains traces of IgA)

Relative: Disseminated intravascular coagulation (DIC) or high risk of thrombosis: e.g. recent thrombosis or myocardial infarction

Availability:

Available from the Transfusion Laboratory.
May only be collected from the Transfusion Laboratory by staff authorised to collect blood components

Dosing:

The dose used in Whittington Health is: 25 units/kg, rounded to the nearest 500 unit vial as below. **Maximum single dose should not exceed 5000 units.**

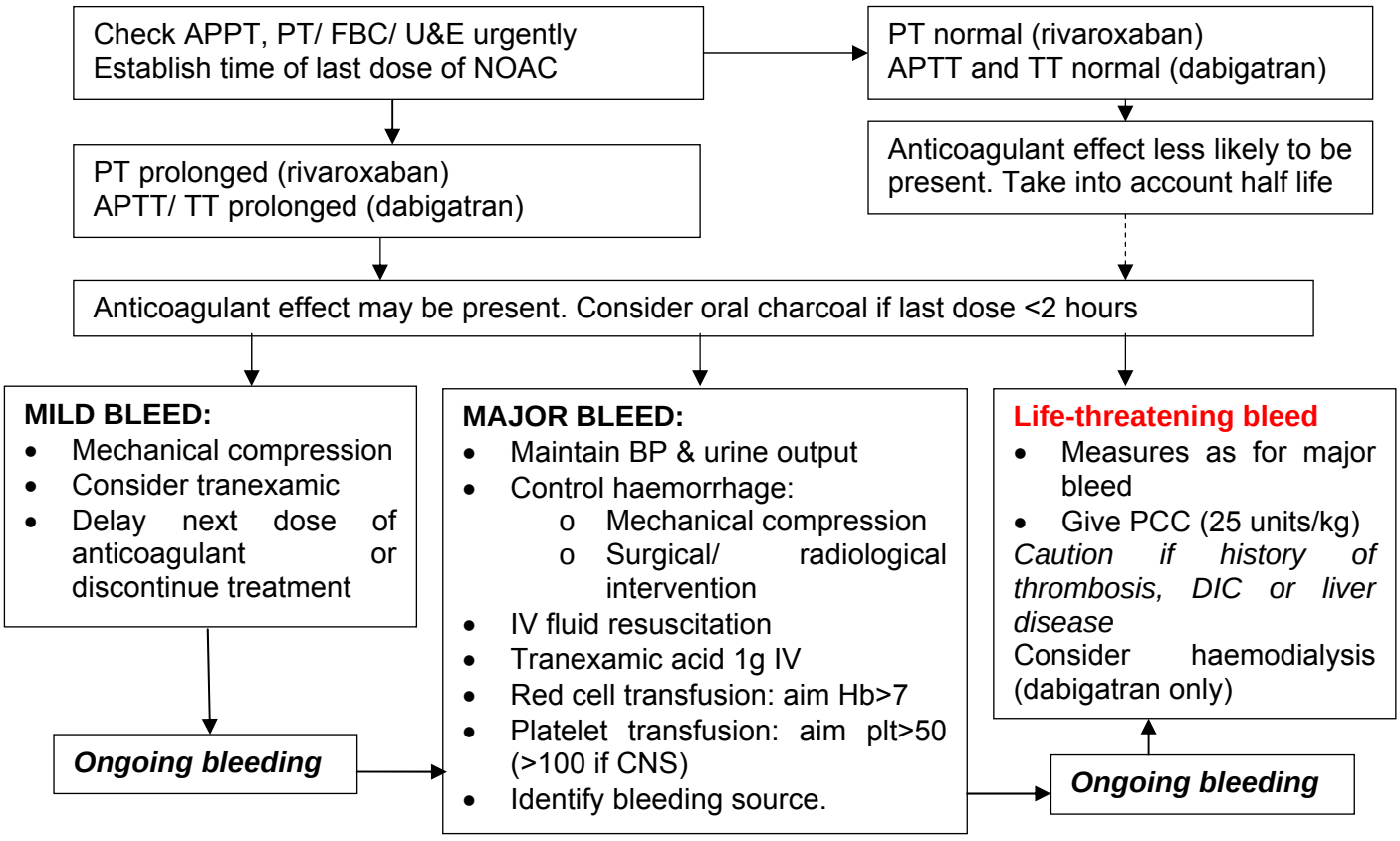
Weight (kg)	Total dose	No 500iu vials	Ml water for injection	Infusion time
50-60	1500	3	60	7 min
61-80	2000	4	80	10 min
81-100	2500	5	100	12 min
101-120	3000	6	120	14 min

Administration:

- Reconstitute using the contents of the pack with each vial (water for injection, vial of powder and double ended needle). **Instructions contained within each pack.**
- Draw up into a 60ml syringe. Administer via a syringe driver at the infusion rate stated.
- Monitor heart rate before and during infusion
- Flush cannula after infusion completed.
- Record the batch number of each vial administered on the drug chart
- Repeat coagulation screen 10 minutes after completion of infusion
- If post infusion INR >1.5, discuss with haematology.
- Repeat INR 6-8 hours post Beriplex administration (**Beriplex has a short half life**)

APPENDIX 3: MANAGEMENT OF BLEEDING ON NEW ORAL ANTICOAGULANTS (RIVAROXABAN, DABIGATRAN, APIXABAN)

The patient's own consultant and the on call haematologist must be contacted in all cases of major or life-threatening bleeding associated with NOACs
Vitamin K and protamine will not reverse the activity of NOACs



Major bleed:
Symptomatic bleeding in a critical area or organ e.g. intracranial, intraspinal, retroperitoneal

General Haemostatic Measures:
- Stop the anti-thrombotic drug
- Document timing and amount of the last drug dose and presence of existing renal or hepatic dysfunction
- Assess source of bleeding
- Request: FBC, U&E, coagulation screen, INR
- Correct haemodynamic compromise with IV fluids (± red cells to maintain Hb >70g/L)
- Apply mechanical pressure if possible
- Use endoscopic, radiological or surgical measures

Half-lives (may be prolonged in renal failure):
- Rivaroxaban: 5-13 hours
- Dabigatran: 11-22 hours
- Apixaban: 9-14 hours

PROTHROMBIN COMPLEX CONCENTRATE IS UNLICENSED FOR REVERSAL OF NOACs. Approval of haematology consultant and patient's own consultant required.

Contact details:
Haematology SpRs: bleep 3060 or 3037
Haematology Consultant: via switchboard

FOR GUIDANCE ON ADMINISTRATION OF BERIPLEX (PROTHROMBIN COMPLEX CONCENTRATE SEE APPENDIX 2. Patient's written consent required

To be completed and attached to any procedural document when submitted to the appropriate committee for consideration and approval

		Yes/No	Comments
1.	**Does the procedural document affect one group less or more favourably than another on the basis of:**		
	• Race	No	
	• Ethnic origins (including gypsies and travellers)	No	
	• Nationality	No	
	• Gender	No	
	• Culture	No	
	• Religion or belief	No	
	• Sexual orientation including lesbian, gay and bisexual people	No	
	• Age	No	
	• Disability - learning disabilities, physical disability, sensory impairment and mental health problems	No	
2.	**Is there any evidence that some groups are affected differently?**	No	
3.	**If you have identified potential discrimination, are any exceptions valid, legal and/or justifiable?**	No	
4.	**Is the impact of the procedural document likely to be negative?**	No	
5.	**If so can the impact be avoided?**	N/A	
6.	**What alternatives are there to achieving the procedural document without the impact?**	N/A	
7.	**Can we reduce the impact by taking different action?**	N/A	

If you have identified a potential discriminatory impact of this procedural document, please refer it to the Director of Human Resources, together with any suggestions as to the action required to avoid/reduce this impact.

For advice in respect of answering the above questions, please contact the Director of Human Resources.

Checklist for the Review and Approval of Procedural Document

To be completed and attached to any procedural document when submitted to the relevant committee for consideration and approval.

	Title of document being reviewed:	Yes/No	Comments
1.	**Title**		
	Is the title clear and unambiguous?	Yes	
	Is it clear whether the document is a guideline, policy, protocol or standard?	Yes	
2.	**Rationale**		
	Are reasons for development of the document stated?	Yes	
3.	**Development Process**		
	Is it clear that the relevant people/groups have been involved in the development of the document?	Yes	
	Are people involved in the development?	Yes	
	Is there evidence of consultation with stakeholders and users?	Yes	
4.	**Content**		
	Is the objective of the document clear?	Yes	
	Is the target population clear and unambiguous?	Yes	
	Are the intended outcomes described?	Yes	
5.	**Evidence Base**		
	Are key references cited in full?	N/A	
	Are supporting documents referenced?	N/A	
6.	**Approval**		
	Does the document identify which committee/ group will approve it?	Yes	
7.	**Dissemination and Implementation**		
	Is there an outline/plan to identify how this will be done?	Yes	
8.	**Document Control**		
	Does the document identify where it will be held?	Yes	
9.	**Process to Monitor Compliance and Effectiveness**		

	Title of document being reviewed:	Yes/No	Comments
	Are there measurable standards or KPIs to support the monitoring of compliance with and effectiveness of the document?	Yes	
	Is there a plan to review or audit compliance with the document?	Yes	
10.	**Review Date**		
	Is the review date identified?	Yes	
	Is the frequency of review identified? If so is it acceptable?	Yes	
11.	**Overall Responsibility for the Document**		
	Is it clear who will be responsible for co-ordinating the dissemination, implementation and review of the document?	Yes	

Executive Sponsor Approval			
If you approve the document, please sign and date it and forward to the author. Procedural documents will not be forwarded for ratification without Executive Sponsor Approval			
Name		Date	
Signature			
Relevant Committee Approval			
The Director of Nursing and Patient Experience's signature below confirms that this procedural document was ratified by the appropriate Governance Committee.			
Name		Date	
Signature			
Responsible Committee Approval – only applies to reviewed procedural documents with minor changes			
The Committee Chair's signature below confirms that this procedural document was ratified by the responsible Committee			
Name		Date	
Name of Committee		Name & role of Committee Chair	
Signature			

Tool to Develop Monitoring Arrangements for Policies and guidelines

What key element(s) need(s) monitoring as per local approved policy or guidance?	Who will lead on this aspect of monitoring? Name the lead and what is the role of the multidisciplinary team or others if any.	What tool will be used to monitor/check/observe/Assess/inspect/ authenticate that everything is working according to this key element from the approved policy?	How often is the need to monitor each element? How often is the need complete a report ? How often is the need to share the report?	What committee will the completed report go to?
Element to be monitored	**Lead**	**Tool**	**Frequency**	**Reporting arrangements**
Use of Beriplex	**Transfusion Lead**		**Annually**	**Hospital Transfusion Committee**
Bleeding events on anticoagulation (warfarin, LMWH, UFH & NOACs)	**Thrombosis Lead & anticoagulant pharmacist**		**Annually**	**Thrombosis Committee**