Group arrangements:
Salford Royal NHS Foundation Trust (SRFT)
Pennine Acute Hospitals NHS Trust (PAT)

Northern Care Alliance NHS Group

Thrombolysis in acute ischaemic stroke awareness and management of angioedema

Lead Author:	Craig J Smith, Professor of Stroke Medicine
Additional author(s)	Gareth Thomas, Jane Molloy, Glyn Smurthwaite, James Palmer
Division/ Department:	Division of Neurosciences and Renal Services
Applies to: (Please delete)	Salford Royal Care Organisation
Approving Committee:	Stroke Clinical Governance Subgroup
Date approved:	26/09/2019
Expiry date:	October 2022

Contents

FIGURE 1

ACUTE ISCHAEMIC STROKE PATIENT ELIGIBLE FOR THROMBOLYSIS
STROKE TEAM BRING THROMBOLYSIS BOX

↓

?AT RISK OF ANGIOEDEMA?

Existing treatment with ACE-I
Ischaemia involving insula

↓

INFORM SECOND ON-CALL ANAESTHETIST:
Wireless baton mobile 61852

Commence thrombolysis observations including:
?STRIDOR
HEMIFACIAL/LINGUAL ANGIOEDEMA CHART

↓

DEVELOPMENT OF ANY SIGNS OF ANGIOEDEMA:

STOP tPA *IMMEDIATELY*

Administer first-line Rx:

- **HIGH-FLOW OXYGEN**
- **CHLORPHENAMINE 10mg iv**
- **HYDROCORTISONE 200mg iv**
- **5ml of 1:1000 NEBULISED ADRENALINE driven by 100% oxygen (repeat as required 2-3 hourly) ***

-Assess severity and risk of airway compromise
-Contact the CARDIAC ARREST TEAM immediately (2222)
-Inform second on-call anaesthetist (or ICU SpR)
-Inform stroke consultant if not already present

TRANSFER TO POST-ANAESTHESIA CARE UNIT (PACU)
LEVEL 3 THEATRE RECOVERY (65079/64663)

Consider C1-esterase inhibitor 1000units iv over 10-15mins, followed by further 500units iv PRN;
0.5ml of 1:1000 ADRENALINE IM

↓

ONGOING MANAGEMENT
Review on a case by case basis with senior medical staff

Continue for a minimum of ***24hours:***

- Chlorphenamine 10mg iv tds
- Hydrocortisone 100mg iv tds
- Nebulised adrenaline PRN*

Consider discontinuing ACE-I/statin longer-term
Complete Trust audit form, yellow card reporting, EPR coding

*** ENSURE EYE PROTECTION APPLIED TO PATIENT (see text)**

1. Overview (What is this guideline about?)

- Thrombolysis with iv tissue plasminogen-activator (tPA) for ischaemic stroke is usually administered in a level 1 care environment (Emergency Department and/or Acute Stroke Unit), as there is no specific recommendation otherwise[1]
- Angioedema, manifesting as hemi-facial/ orolingual swelling is a recognised complication of stroke thrombolysis with tPA which may progress to life-threatening airway compromise
- Preceding treatment with angiotensin-converting enzyme inhibitors (ACE-Is) and presence of insula/frontal cortical ischaemia on pre-treatment CT increase the likelihood of angioedema developing
- All patients eligible for thrombolysis will be assessed for their risk of developing angioedema by the attending senior stroke team doctor. This risk should be discussed and documented with the patient and/or family
- In those patients eligible for tPA identified as at-risk of developing angioedema, the second on-call anaesthetist will be informed of the patient details, location and timing of tPA treatment
- Patients developing angioedema will receive appropriate urgent medical treatment and timely anaesthetic review in an appropriate environment, as outlined in this policy

2. Scope (Where will this document be used?)

- All clinical medical and nursing staff involved in the administration of thrombolysis in acute ischaemic stroke
- All anaesthetic, critical care and theatre recovery unit staff
- All cardiac arrest and resuscitation-team staff
- All blood-bank/haematology/transfusion staff

Associated Documents

- Thrombolysis in acute ischaemic stroke assessment and eligibility for IV alteplase TWCG6(12)

3. Background (Why is this document important?)

Scope of the policy

Patients receiving thrombolysis with tPA for ischaemic stroke may develop the potentially life-threatening complication of hemi-facial/ orolingual angioedema.

The purpose of this protocol is to consolidate best evidence-based guidance to inform the assessment of risk of angioedema, and its management, in patients receiving thrombolysis for acute ischaemic stroke. The protocol aims to provide:

1. A Trust framework facilitating urgent assessment of risk
2. An agreed management algorithm for patients developing angioedema
3. Governance and audit systems to ensure protocol adherence and to monitor processes of care.

Background

The incidence of angioedema in patients receiving tPA for ischemic stroke has been reported as 1.3 to 8%[2-5]. It usually manifests as mild, transient painless hemifacial swelling starting in the tongue, usually contralateral to the ischaemic hemisphere, and resolves within 24hours[2].

Data from observational studies suggest life-threatening airway compromise requiring anaesthetic intervention is rare; occurring in around 0.2 to 1% of all patients receiving tPA, or around 13% of those developing angioedema[2,3,5,6].

In a recent single-centre study at Salford Royal, the incidence of angioedema at SRFT was approximately 8%, ranging from 5 to 189mins after initiation of tPA[5].

The pathophysiological basis of angioedema following tPA in stroke is unclear. tPA generates plasmin, which leads to formation of bradykinin, a powerful vasodilatory peptide[7] metabolised by angiotensin converting-enzyme (ACE). ACE-inhibitors (ACE-I) have been associated with non-hereditary angioedema and may therefore enhance the risk of tPA-induced angioedema in stroke by potentiating bradykinin levels.

Autonomic dysregulation associated with acute stroke has also been proposed as a contributory factor although the mechanisms and importance remain unclear.

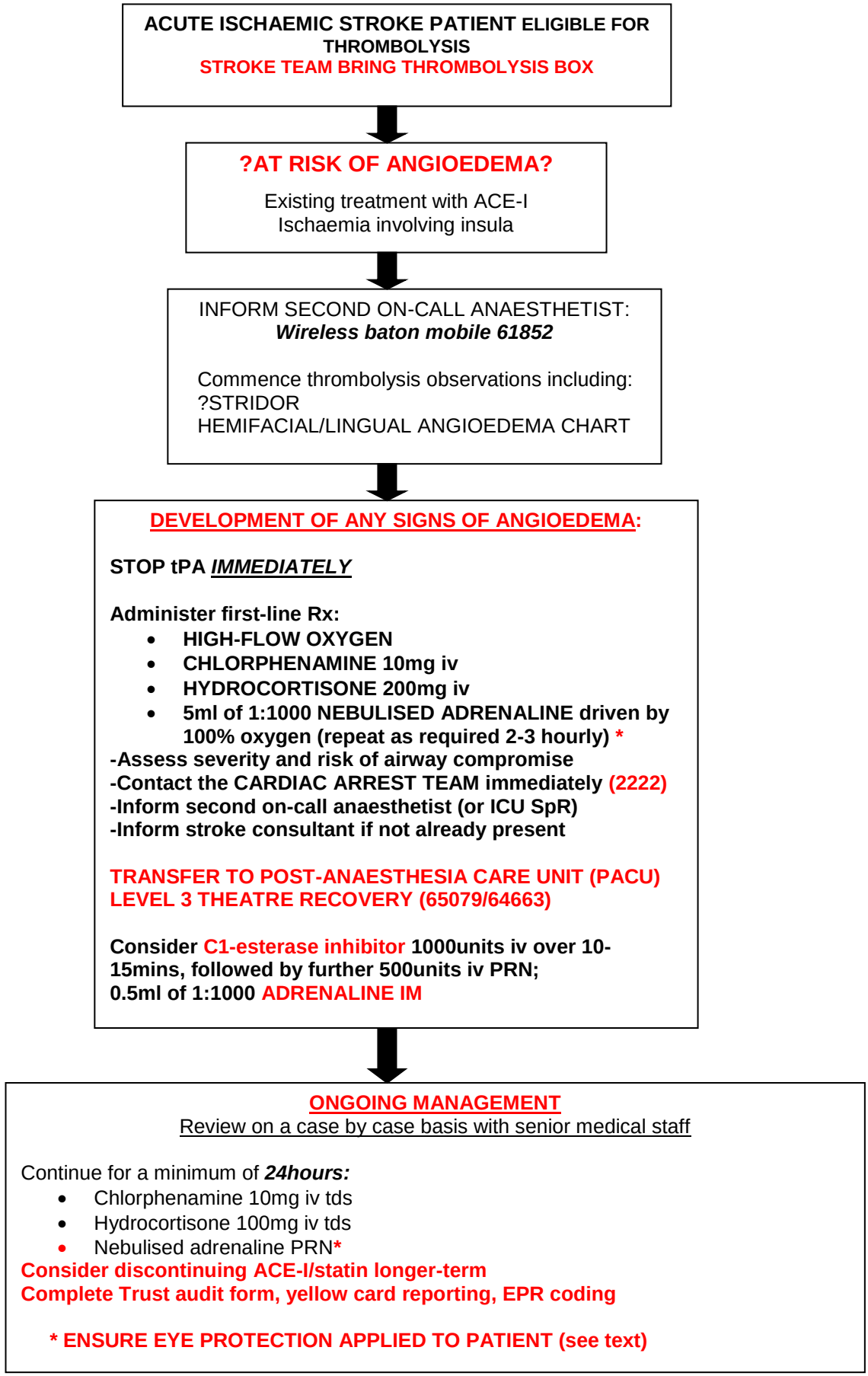
Existing treatment with ACE-I (RR 13.6; 95% CI 3 to 62.7) and signs of acute insula/frontal ischemia (RR 9.1; 1.4 to 30) predicted development of angioedema[2] in one relatively small study of patients receiving tPA in acute ischaemic stroke. A subsequent study confirmed the association between ACE-I and angioedmea[5].

4. What is new in this version?

"Guideline reviewed and updated with no important changes to content".

5. Guideline

5.1 FIGURE 1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INFORM SECOND ON-CALL ANAESTHETIST:
Wireless baton mobile 61852
Commence thrombolysis observations including:
?STRIDOR
HEMIFACIAL/LINGUAL ANGIOEDEMA CHART
DEVELOPMENT OF ANY SIGNS OF ANGIOEDEMA:
STOP tPA IMMEDIATELY
Administer first-line Rx:
HIGH-FLOW OXYGEN
CHLORPHENAMINE 10mg iv
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5ml of 1:1000 NEBULISED ADRENALINE driven by 100% oxygen (repeat as required 2-3 hourly) *
-Assess severity and risk of airway compromise
-Contact the CARDIAC ARREST TEAM immediately (2222)
-Inform second on-call anaesthetist (or ICU SpR)
-Inform stroke consultant if not already present
TRANSFER TO POST-ANAESTHESIA CARE UNIT (PACU)
LEVEL 3 THEATRE RECOVERY (65079/64663)
Consider C1-esterase inhibitor 1000units iv over 10-15mins, followed by further 500units iv PRN;
0.5ml of 1:1000 ADRENALINE IM
ONGOING MANAGEMENT
Review on a case by case basis with senior medical staff
Continue for a minimum of 24hours:
Chlorphenamine 10mg iv tds
Hydrocortisone 100mg iv tds
Nebulised adrenaline PRN*
Consider discontinuing ACE-I/statin longer-term
Complete Trust audit form, yellow card reporting, EPR coding
* ENSURE EYE PROTECTION APPLIED TO PATIENT (see text)

5.2 FIGURE 2

Acute Stroke Unit (ASU)	***Extension 64788/ 62149***
Hyperacute Stroke Unit (HASU) B3	***Extension 61913/ 61903***
On-call stroke consultant	***Pager via switchboard or ASU***
On-call stroke registrar	***Baton pager 07623 606 541***
Second on-call anaesthetist	***Baton wireless mobile 61852***
ICU SpR	***Extension 65045/ 65046***
PACU, level 3 theatres	***Extension 65079/ 64663***
Emergency room: resus area	***Extension 64849 / 62451***
Blood bank (0900-1730)	***Extension 64994***
On-call haematology technician (1730-0900)	***Bleep 3077***

5.3 Assessment of patients at-risk of angioedema

The drugs required for empirical urgent first-line treatment of angioedema[8] (FIGURE 1) are contained within the thrombolysis packs. These are kept on the ASU and routinely taken when assessing suitability for thrombolysis.

All patients eligible for thrombolysis will be screened for risk of angioedema.

Known treatment with an ACE-I (any dose or formulation; if the full drug history is unknown assume the patient is taking ACE-I until proven otherwise) and/or those with clear evidence of early ischemia involving the insula cortex will trigger the following:

The second on-call anaesthetist will be contacted using the baton mobile phone (see FIGURE 1 and 2) to inform them:

- That tPA is commencing in a patient potentially at-risk of angioedema
- The exact location of the patient

5.4 Commencing thrombolysis with tPA

Monitoring of thrombolysis will proceed as usual with the addition of the facial/lingual swelling observation chart (APPENDIX 1) for ALL patients.

Note that maintenance of normal oxygen saturations should NOT be interpreted as absence of laryngeal oedema/ early airway compromise.

5.5 If ANY features of angioedema develop (FIGURE 1)

- Stop tPA immediately (if not already)
- Commence first-line medical treatment[7] (see FIGURE 1 and below)
- Contact the cardiac arrest team urgently (2222)
- Contact the second on-call anaesthetist. Contact the ITU SpR if the second on-call anaesthetist is unavailable
- Contact the senior stroke team doctor if not already present

1) Adrenaline, 5ml of 1:1000 (=5mg), should be given nebulised in 100% oxygen. Staff must ensure eye protection (wet swab/paper towel/goggles) for any patients that receive nebulised adrenaline.

2) The severity of angioedema and threat of impending airway compromise should be evaluated as follows (and documented on EPR):

   - **Mild:** unilateral involvement, without progression to involve bilateral structures or airway compromise
   - **Moderate:** bilateral involvement but without progression to impending or actual airway compromise
   - **Severe:** impending or actual airway compromise

3) If there is no response to nebulised adrenaline within 5 minutes of administration or if symptoms worsen, consider adrenaline IM at a dose of 500mcg (0.5ml of 1:1000) and early use of C1 esterase inhibitor (see below). If a patient is being treated in the Emergency Dept. and staff with the skills required to provide advance airway management are immediately available then the decision to call the cardiac arrest team rests with the senior clinician in attendance. However, the on call anaesthetist should be called. If the skills for advanced airway management are not immediately available, then proceed as below in section 4).

4) If the second on-call anaesthetist or ICU SpR is able to attend, they should assess the patient's airway prior to transferring the patient to the Post-Anaesthesia Care Unit (PACU) in level 3 theatres for further management. If they are unable to attend urgently, the patient should be transferred to the PACU without delay where the anaesthetist is likely to be able to assist.

5) If angioedema becomes refractory to first-line treatment, or there is any concern regarding impending airway compromise, iv C1 esterase inhibitor concentrate 1000units should be obtained urgently from blood bank and administered over 10-15mins, with a further 500units iv if necessary. During office hours the blood bank should be contacted directly (ex: 64994). The on-call Haematology technician should be contacted out-of hours (bleep 3077).

6) There is a lack of evidence to inform whether to continue or stop ACE-I or statins in the longer-term in this situation. The decision should therefore be made on an individual patient basis, documented appropriately on EPR and communicated to the GP/ receiving medical team if repatriated.

5.6 Standards

A. Thrombolysis with iv tPA is usually administered in a level 1 care environment (Emergency Department and/or the Acute Stroke Unit) as there is no specific recommendation otherwise[1]

B. The thrombolysis box, containing the appropriate first-line drugs for treatment of angioedema, will be taken to the bedside whenever stroke unit staff assess patients for suitability of thrombolysis

C. All patients eligible for thrombolysis will be assessed for their risk of developing angioedema by the attending senior stroke team doctor. This MUST be discussed with the patient and /or family and documented on EPR

D. In those patients eligible for tPA identified as at-risk of developing angioedema, the second on-call anaesthetist will be informed of the patient details, location and timing of tPA treatment

E. Patients developing angioedema will receive appropriate medical treatment and timely anaesthetic review in an appropriate environment

6. Roles & responsibilities

Stroke clinical staff: to be aware of (1) the risk and potential consequences of angioedema following tPA and to advise patients and families of the risk; (2) the existence of this policy including urgent drug management and liaison with anaesthetic colleagues.

Anaesthetic/ critical care/ theatre recovery unit staff: to be aware of this policy and the potential need to provide resuscitation skills, in particular airway management in patients at risk of, or developing angioedema following tPA.

Cardiac arrest/resuscitation team: to be aware of this policy including urgent drug management and liaison with anaesthetic/ ICU and stroke colleagues.

Stroke ward manager & nursing staff: to ensure awareness of (1) this policy;
(2) its implications for patient monitoring and safety; (3) indications for alerting senior medical/anaesthetic staff; (4) liaison with pharmacy.

Blood bank/ Haematology staff: to be aware (1) of the indication for use of C1 esterase inhibitor as a second-line treatment for refractory angioedema; (2) that a request for C1esterase inhibitor concentrate may be received from stroke unit staff.

7. Monitoring document effectiveness

There will be continuous, prospective audit of all patients receiving tPA within the current Trust Mortality and Morbidity program for Stroke. Occurrence of angioedema will be coded as a complication on EPR, and reported as a suspected adverse drug reaction via the Medicines and Healthcare products Regulatory Agency yellow card reporting system (http://yellowcard.mhra.gov.uk/).

The policy will be monitored and reviewed by the Stroke Clinical Governance and Critical Care Groups on a 2-yearly basis unless new evidence is published in the interim.

8. Abbreviations and definitions

Please refer to text.

9. References

To be read in conjunction with the following documents:
NICE guidance – diagnosis and initial management of Stroke and TIA
http://www.nice.org.uk/nicemedia/pdf/CG68FullGuideline.pdf

(1) National Institute for Health and Clinical Excellence. Alteplase for the treatment of acute ischaemic stroke. Technology Appraisal 122; June 2007

(2) Hill MD, Lye T, Moss H, et al. Hemi-orolingual angioedema and ACE inhibition after alteplase treatment of stroke. Neurology 2003; 60: 1525-1527

(3) Hill MD, Buchan AM, for the Canadian Alteplase for Stroke Effectiveness Study (CASES) Investigators. Thrombolysis for acute ischemic stroke: results of the Canadian Alteplase for Stroke Effectiveness Study. Canadian Medical Association Journal 2005; 172: 1307-1312

(4) Ottomeyer C, Hennerici MG, Szabo K. Raising awareness of orolingual angiodema as a complication of thrombolysis in acute stroke patients. Cerebrovascular Disorders 2009; 27:307-308

(5) Hurford R, Rezvani S, Kreimei M, et al. Incidence, predictors and clinical characteristics of orolingual angio-oedema complicating thrombolysis with tissue plasminogen activator for ischaemic stroke. J Neurol Neurosurg Psychiatry 2015;
86: 520-523

(6) Engelter ST, Fluri F, Buitrago-Téllez C, et al. Life-threatening orolingual angioedema during thrombolysis in acute ischemic stroke. Journal of Neurology 2005; 252: 1167-1170

(7) Molinaro G, Gervais N, Adam A. Biochemical basis of angioedema associated with recombinant tissue plasminogen activator treatment: an in vitro experimental approach. Stroke 2002; 33: 1712-1716

(8) Emergency Treatment of Anaphylactic Reactions. Guidelines for healthcare providers. Resuscitation Council (UK). London, 2008.

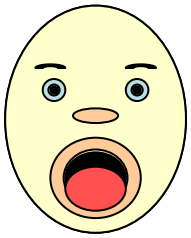
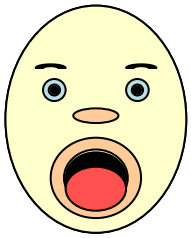
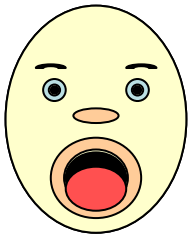
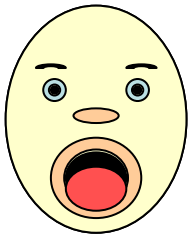
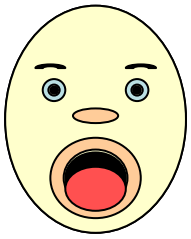
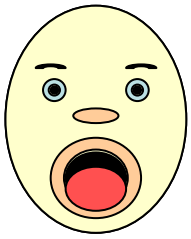
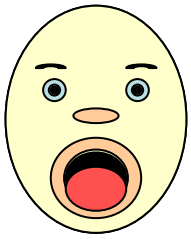
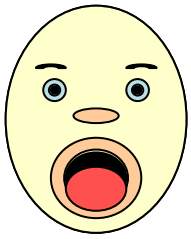
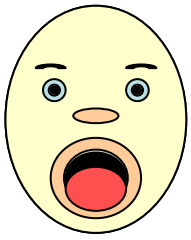
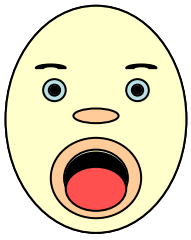
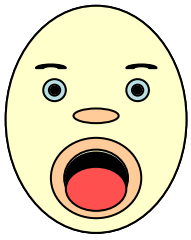
10. Appendices

Appendix 1

We are very grateful to Sister Sally Marshall for kindly contributing the **angioedema observation chart**

Indicate extent of any area of swelling to the face/ lips/ tongue by shading the picture. Stop tPA urgently and refer to the angioedema protocol.

Patient Name: **Hospital No:**

Time/Date…….. …..……hr/mins post TPA  No Swelling noted ☐ Name:	Time/Date…….. …..…hr/mins post TPA  No Swelling noted ☐ Name:	Time/Date…….. ……..hr/mins post TPA  No Swelling noted ☐ Name:	Time/Date…….. ……..…hr/mins post TPA  No Swelling noted ☐ Name:
Time/Date…….. ……hr/mins post TPA  No Swelling noted ☐ Name:	Time/Date…….. ……hr/mins post TPA  No Swelling noted ☐ Name:	Time/Date…….. ……..…hr/mins post TPA  No Swelling noted ☐ Name:	Time/Date…….. ……..…hr/mins post TPA  No Swelling noted ☐ Name:
Time/Date…….. ……..…hr/mins post TPA  No Swelling noted ☐ Name:	Time/Date…….. ……hr/mins post TPA  No Swelling noted ☐ Name:	Time/Date…….. ……hr/mins post TPA  No Swelling noted ☐ Name:	Time/Date…….. ……..…hr/mins post TPA  No Swelling noted ☐ Name:

11. Document Control Information

All sections must be completed by the author prior to submission for approval

Lead Author:	Craig J Smith Professor of Stroke Medicine		
Lead author contact details:	ex 64044/60623; craig.smith@srft.nhs.uk		
Consultation List the persons or groups who have contributed to this guideline. (please state which Care Organisation)	**Name of person or group**	**Role / Department / Committee (Care Org)**	**Date**
	Craig Smith	MCCN	2008-2019
	Gareth Thomas	Critical Care, Salford	2008-2019
	James Palmer	Anaesthesia, Salford	2009-2019
	Jane Molloy	MCCN	2008-2019
	Glyn Smurthwaite	Anaesthesia, Salford	2008-2019
	Hana Alachkar	Previously Immunology, Salford	2008-2018
Endorsement List the persons or groups who have seen given their support to this guideline. (please state which Care Organisation)	**Name of person or group**	**Role / Department / Committee (Care Org)**	**Date**
	Version 6: Paula Beech	Lead, Stroke Clinical Governance Group	26/09/2019
	Version 5: Paul Chadwick	Lead, Medicines Management Group	October 2017
	Version 4: John MacDonald	Lead, Medicines Management Group	October 2015
	Version 3: Craig Smith	Lead, Stroke Clinical Governance Group	October 2013
	Version 2: Paul Chadwick	Lead, Medicines Management Group	October 2011
	Version 1: Steve Waldeck	Clinical Effectiveness Committee	October 2009
Keywords / phrases:	ischaemic stroke; thrombolysis; tissue plasminogen activator; tPA; angioedema; airway; intubation; anaesthetist; PACU; stroke; ICU; C1 esterase; ACE inhibitor; statin; ASU; Emergency Department		
Communication plan:	The Stroke Unit Ward Manager and Clinical Stroke lead will hold the implementation plan. The Stroke Clinical Governance Group will review progress in implementation. Staff working within Stroke, Anaesthetics, Theatre Recovery (PACU), Neuro-HDU, Intensive Care and General Internal Medicine on-call services will be made aware through the Clinical Governance framework. Stroke service nursing staff will be made aware of the protocol through in-service training and Stroke study days. All relevant pharmacy staff will be made aware of the policy by the lead pharmacist for stroke services and a copy of the policy will also be added to the pharmacy on-call files. All Blood Bank /Haematology technical staff will be made aware that a request for C1esterase inhibitor concentrate may be received from the stroke unit. The policy will be implemented from the date of Clinical Effectiveness Committee approval.		
Document review arrangements:	This document will be reviewed by the author, or a nominated person, at least once every three years or earlier should a change in legislation, best practice or other change in circumstance dictate.		

This section will be completed following committee approval

Guideline Approval:	Name of Approving Committee: Stroke Clinical Governance Subgroup	
	Chairperson: Paula Beech	
	Approval date: 26/09/2019	
	Formal Committee decision √	Chairperson's approval √

12. Equality Impact Assessment (EqIA) screening tool

Legislation requires that our documents consider the potential to affect groups differently, and eliminate or minimise this where possible. This process helps to reduce health inequalities by identifying where steps can be taken to ensure the same access, experience and outcomes are achieved across all groups of people. This may require you to do things differently for some groups to reduce any potential differences.

1a) Have you undertaken any consultation/ involvement with service users, staff or other groups in relation to this document?	No
1b) Have any amendments been made as a result?	N/A
2) Does this guideline have the potential to affect any of the groups below differently or negatively? No	

Protected Group	Yes	No	Unsure	Reasons for decision
Age *(e.g. are specific age groups excluded? Would the same process affect age groups in different ways?)*		X		
Sex *(e.g. is gender neutral language used in the way the guideline or information leaflet is written?)*		X		
Race *(e.g. any specific needs identified for certain groups such as dress, diet, individual care needs? Are interpretation and translation services required and do staff know how to book these?)*		X		
Religion & Belief *(e.g. Jehovah Witness stance on blood transfusions; dietary needs that may conflict with medication offered.)*		X		
Sexual orientation *(e.g. is inclusive language used? Are there different access/prevalence rates?)*		X		
Pregnancy & Maternity *(e.g. are procedures suitable for pregnant and/or breastfeeding women?)*		X		
Marital status/civil partnership *(e.g. would there be any difference because the individual is/is not married/in a civil partnership?)*		X		
Gender Reassignment *(e.g. are there particular tests related to gender? Is confidentiality of the patient or staff member maintained?)*		X		
Human Rights *(e.g. does it uphold the principles of Fairness, Respect, Equality, Dignity and Autonomy?)*		X		
Carers *(e.g. is sufficient notice built in so can take time off work to attend appointment?)*		X		
Socio/economic *(e.g. would there be any requirement or expectation that may not be able to be met by those on low or limited income, such as costs incurred?)*		X		
Disability *(e.g. are information/questionnaires/consent forms available in different formats upon request? Are waiting areas suitable?) Includes hearing and/or visual impairments, physical disability, neurodevelopmental impairments e.g. autism, mental health conditions, and long term conditions e.g. cancer.*		X		

Are there any adjustments that need to be made to ensure that people with disabilities have the same access to and outcomes from the service or employment activities as those without disabilities? *(e.g. allow extra time for appointments, allow advocates to be present in the room, having access to visual aids, removing requirement to wait in unsuitable environments, etc.)*		**X**	

3) Where you have identified that there are potential differences, what steps have you taken to mitigate these? N/A

4) Where you have identified adjustments would need to be made for those with disabilities, what action has been taken? N/A

5) Where the policy, procedure, guidelines, patient information leaflet or project impacts on patients how have you ensured that you have met the Accessible Information Standard – please state below:

N/A

……

EDI Team/Champion only*: does the above ensure compliance with Accessible Information Standard*

- Yes
- No

If no what additional mitigation is required:

Will this guideline require a full impact assessment? No

Please state your rationale for the decision: No potential to affect any group differently

(*a full impact assessment will be required if you are unsure of the potential to affect a group differently, or if you believe there is a potential for it to affect a group differently and do not know how to mitigate against this - Please contact the Inclusion and Equality team for advice on* equality@pat.nhs.uk)

Author: Type/sign: CRAIG J SMITH Date: 24/10/19

Sign off from Equality Champion: Date: