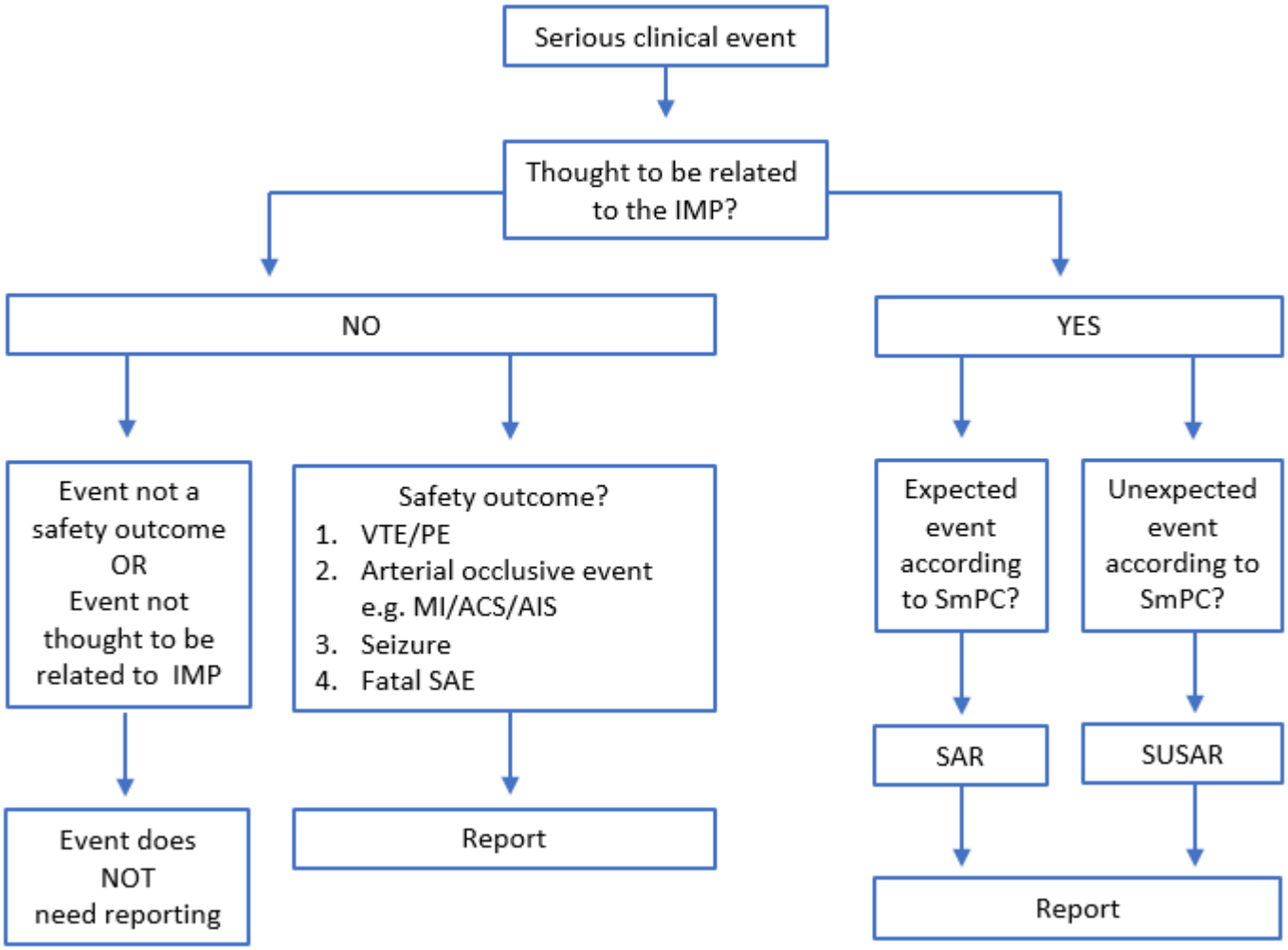
TICH-3 – Working Practice Document

Serious Adverse Event (SAE) Reporting
No. 010

Tranexamic acid (TXA) has an established safety record therefore we are only collecting data on focused safety outcomes. We have a legal responsibility to collect all safety events occurring within the first 7 days after randomisation (including SARs/SUSARs/fatal SAEs).

SAE Reporting Flowchart



Safety outcomes

- Venous occlusive events: VTE (Pulmonary embolism, Deep vein thrombosis)
- Ischaemic events (arterial thrombosis at any site, ischaemic stroke, transient ischaemic attack peripheral artery embolism, myocardial infarction, acute coronary syndrome)
- Seizures

REMEMBER If a safety outcome (e.g. seizure) occurs during infusion, the infusion must be stopped immediately

Fatal events

Please remember that fatal serious adverse events (SAEs) need to be reported until discharge from hospital, even if this is after 7 days.

Serious adverse reactions (SAR) or Suspected Unexpected Serious Adverse Reactions (SUSAR)

All events suspected to be related to the IMP will be assessed for seriousness, expectedness and causality against SmPC by local investigator.

Section 4.8 of the SmPC, date of last revision 02 February 2021, will act as the reference safety information https://stroke.nottingham.ac.uk/docs/TICH-3/MHRA_documents/TICH-3%20Focus%20Tranexamic%20Acid%20100mg%20ml%20Solution%20for%20Injection%20Summary%20of%20Product%20Characteristics%20%28SmPC%29%2020210202%20REVISION.pdf

For a list of expected events not subject to expedited reporting, please refer to Appendix 1 of the protocol – provided at the end of this WPD.

Before submission, please ensure that the event is discussed with a clinician, as you will be asked to provide evidence to support the submission. Examples of the evidence required for reporting are given in Appendix 2.

SAE reporting

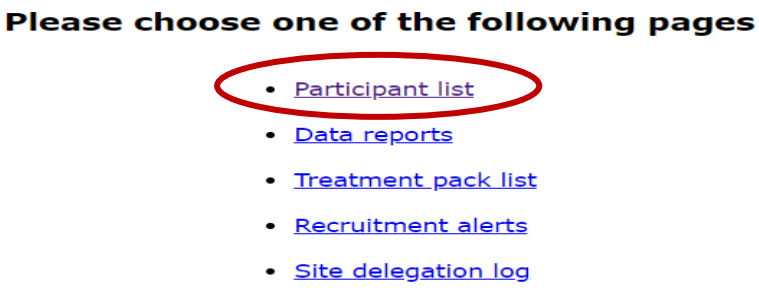
Investigators have a legal responsibility to report applicable SAEs to the chief investigator within 24 hours by completing the online form via the TICH-3 website. A copy of the report must be printed and signed by the PI at site and held in the Investigator Site File.

Serious Adverse Events (SAEs) that are not safety outcomes, SARS or SUSARS should not be reported

If a patient deteriorates the only events that need reporting are safety events (listed above). If the patient dies before discharge from hospital, then this would be a fatal SAE and reported using the death/discharge eCRF and submitting an SAE. For example, neurological deterioration due to haematoma enlargement/expansion (HE), intraventricular haemorrhage (IVH), or development of cerebral oedema known as perihematomal oedema (PHE) are all expected events after intracerebral haemorrhage ICH and therefore do not need reporting unless you think the deterioration is related to the drug or the patient dies.

How to submit an SAE via the TICH-3 website

1. Log into the TICH-3 website
2. Click on participant list



3. Click ‘select’ in the see column which corresponds to the correct participant ID that you are reporting the SAE for

Participant ID/age at randomisation	Event date	Treatment pack ID	Randomised	Contacts/ documents	Day 7 follow-up	Discharge/ death	SAEs	Brain scans	Protocol violations	Centre transfers	Day 180 follow-up
C001-0002-ONK 28	23 Feb 2022	80159	23 Feb 2022	Y NNY	1 Mar 2022	23 Feb 2022	Select 1	Select	Select	Select 1	21 Aug 2022
C001-0005-JER 110	1 Mar 2022	80090	1 Mar 2022	Y NNN	7 Mar 2022	7 Mar 2022	Select 1	Select	Select 1	Select	27 Aug 2022
C001-0006-OUT 79	1 Mar 2022	80100	1 Mar 2022	Y NNN	7 Mar 2022	-	Select	Select	Select	Select 1	27 Aug 2022
C001-0007-JLH 67	10 Mar 2022	80056	10 Mar 2022	Y NNN	16 Mar 2022	-	Select	Select	Select	Select	5 Sep 2022
C001-0008-LUW 22	17 Mar 2022	80145	17 Mar 2022	Y NNN	23 Mar 2022	17 Mar 2022	Select	Select	Select	Select	12 Sep 2022
C001-0009-EYH 58	5 May 2022	80162	5 May 2022	Y YNN	11 May 2022	-	‡ Select 1	Select	Select	Select	31 Oct 2022
C001-0001-CYR 60	15 Feb 2022	80114	15 Feb 2022	Y YYY	21 Feb 2022	22 Feb 2022	‡ Select 1	Select	Select 1	Select 3	22 Feb 2022

4. Click ‘Add new serious adverse event record’

Add new Serious Adverse Event record

History of Serious Adverse Events

SAE number	Date entered	Event began	Hospital-isation	Death (primary)	Event description	Sub-category
No SAEs have been submitted for this participant yet.						

5. Complete the SAE form

Serious Adverse Event – participant identity check

It is essential that the data collected are entered against the correct trial participant. Please complete the following questions to continue to the Serious Adverse Event CRF.

Trial number 6

Initials

Sex ○ Male ○ Female

Date of birth - Day - - Month - - Year -

Please provide the following details for the Serious Adverse Event to be added. This information will be copied across to the SAE form for you.

Date/time event began - Day - - Month - - Year - :
(dd-mmm-yyyy hh:mm 24hr)

Please categorise the event [Select...] Search

* *expected after tranexamic acid*
‡ *safety event*

Is this event the primary cause of death? ○ Yes ○ No

Relationship to study drug View definitions
○ Not related
○ Improbable
○ Possible
○ Probable
○ Definite

Please classify the event
○ SAR
○ SAE
○ SUSAR
☐ For a SUSAR, please check box to confirm

Continue

Appendix 1

List of events that are common after stroke and *do not need reporting unless they are thought to be a serious adverse reaction (SAR) or suspected unexpected serious adverse reaction (SUSAR)*. This list is not exhaustive and intended as a guide only. Section 4.8 of the SmPC for TXA, date of last revision 02 February 2021, will act as the reference safety information.

EXPECTED EVENTS NOT SUBJECT TO EXPEDITED SUSAR REPORTING			
After tranexamic acid the following events are expected and therefore not subject to expedited SUSAR reporting:			
Gastro-intestinal	**Cardiovascular**	**Central nervous system**	**General**
Abdominal pain	Arterial thrombosis any site	Convulsions	Anaphylaxis
Diarrhoea	Deep vein thrombosis (DVT)	Disturbance in colour vision	Fatigue
Gastrointestinal disturbance	Collapse	Dizziness	Flushing
Nausea	Hypotension	Headache	Hypersensitivity including oropharyngeal swelling, urticaria, angioedema
Vomiting	Ischaemic stroke	Seizure	Musculoskeletal pains
	Peripheral artery embolism		Rash
	Pulmonary embolism (PE)		
	Tachycardia		
	Venous thrombosis any site		

Appendix 2

Definitions of Safety events:

Venous thromboembolism (VTE): includes both deep vein thrombosis (DVT) and pulmonary embolism (PE).

Examples of evidence required:
Clinical detail and
DVT -

- ❖ Ultrasound
- ❖ Venography

PE –

- ❖ VQ (Ventilation Perfusion) Scan
- ❖ CTPA (CT Pulmonary Angiogram) scan

Stroke: A clinical syndrome characterised by rapidly developing clinical symptoms and/or signs of focal (and at times global) loss of cerebral function with symptoms lasting for more than 24 hours or leading to death, with no apparent cause other than that of vascular origin.
Classification is based on results of head CT/MRI imaging:

- Ischaemic
- Haemorrhagic
- Unknown – imaging not done

Recurrent Ischaemic Stroke: A stroke defined as above occurring greater than 72 hours after the qualifying stroke if the event is in the same vascular territory, or occurring at any time after the qualifying stroke if the event occurs in a different vascular territory.

TIA: A sudden focal neurological deficit of the brain or eye, presumed to be of vascular origin and lasts less than 24 hours.

NB. TIAs and stroke usually present with 'negative' symptoms (e.g. loss of motor power, loss of speech) as opposed to symptoms that are 'positive' in nature such as paraesthesia or limb jerking, which will usually have an alternative underlying cause.

Acute Coronary Syndromes

Criteria for acute, evolving or recent Myocardial Infarction (MI):
Either one of the following criteria satisfies the diagnosis for an acute, evolving or recent MI:

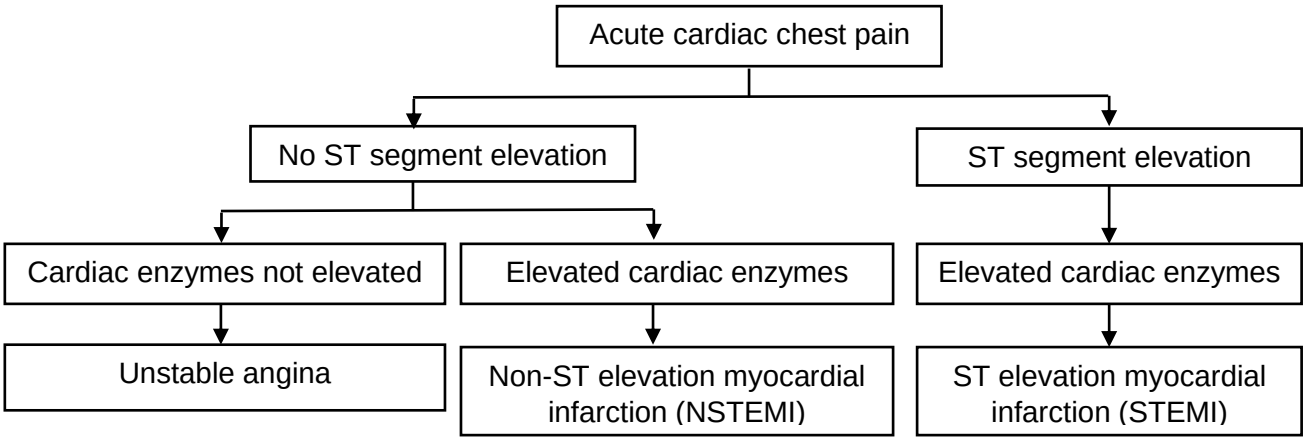
1. Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:

a) ischaemic symptoms;
b) development of pathologic Q waves on the ECG;
c) ECG changes indicative of ischemia (ST segment elevation or depression); or
d) coronary artery intervention (e.g. coronary angioplasty).

2. Pathologic findings of an acute MI.

Unstable Angina: Although there is no universally accepted definition of unstable angina, it has been described as a clinical syndrome between stable angina and acute myocardial infarction.

The diagram below will help distinguish between the types of acute coronary syndromes in patients presenting with acute cardiac chest pain:



Acute peripheral arterial disease (PAD): A sudden blockage of a peripheral artery. The blockage may result from a blood clot, embolism, dissection or trauma. Symptoms usually start suddenly. Acute peripheral arterial limb occlusion includes the 7 symptoms listed below:

- Severe pain
- Coldness
- Paraesthesia
- Loss of sensation
- Paleness in an extremity
- Lack of pulse in an extremity
- Blue skin in affect limb

It can also affect the arteries that carry blood from the kidneys and stomach.

Examples of evidence required:

- ❖ Clinical
- ❖ Radiological details e.g. angiogram

Seizures: Focal or generalised seizures, tonic clonic seizures or partial seizures, diagnosed clinically after review by an appropriately trained physician.

Examples of evidence required:

- ❖ Full clinical diagnosis details.