RECAST-3 – Working Practice Document
Title: Adverse event reporting, No. 006

The purpose of this Working Practice Document (WPD) is to describe the procedure to be used by all RECAST-3 investigators for the management of any trial related safety event. This WPD applies to the RECAST-3 trial coordinated by the Nottingham Stroke Trials Unit and is applicable to all participating sites.

Definitions

Adverse Events
An adverse event (AE) is any unfavourable and unintended sign, symptom, syndrome or illness that develops or worsens during the period of observation in the study.
An AE does include a / an:

1. Exacerbation of a pre-existing illness.
2. Increase in frequency or intensity of a pre-existing episodic event or condition.
3. Condition detected or diagnosed after medicinal product administration even though it may have been present prior to the start of the study.
4. Continuous persistent disease or symptoms present at baseline that worsen following the start of the study.

An AE does not include a / an:
1. Medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); but the condition that led to the procedure is an AE.
2. Pre-existing disease or conditions present or detected at the start of the study that did not worsen.
3. Situations where an untoward medical occurrence has not occurred (e.g., hospitalisations for cosmetic elective surgery, social and / or convenience admissions).
4. Disease or disorder being studied or sign or symptom associated with the disease or disorder unless more severe than expected for the participant's condition.
5. Overdose of concurrent medication without any signs or symptoms.

Adverse Device Effects
An adverse device effect (ADE) is defined as any untoward and unintended response to a medical device and includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device and any event that is a result of a user error.

Serious Adverse Events
A Serious Adverse Event (SAE) is any adverse event occurring following study mandated procedures, having received the treatment or intervention that results in any of the following outcomes:

1. Death
2. A life-threatening adverse event
3. Inpatient hospitalisation or prolongation of existing hospitalisation
4. A disability / incapacity

5. A congenital anomaly in the offspring of a participant

Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

All adverse events will be assessed for seriousness, expectedness and causality:

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

The following events are considered as safety or secondary end points, not SAEs per se:

- death;
- recurrent ischaemic stroke, transient ischaemic attack (TIA);
- intracranial haemorrhage, defined using the Heidelberg bleeding classification.[53]
- symptomatic swelling of the original infarct;[6]
- neurological deterioration;
- systemic embolism;
- neurovascular limb compromise secondary to RIC
- myocardial infarction
- AKI

All SAEs up to and including Day 7 will be collected. SAEs >1 week will not be collected; thereafter, only fatal SAEs and outcomes will be recorded and blindly adjudicated. All SAEs and safety outcomes will be reported on the database using the same SAE form.

Serious Adverse Device Effects

A **Serious Adverse Device Effect (SADE)** is defined as an adverse device effect that resulted in any of the consequences, characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune. Note that this definition captures “near misses” as well as actual incidents.

An **unexpected adverse device effect** is any adverse device effect, the specificity or severity of which is not consistent with the current Technical Dossier (or equivalent) or with the outcomes from prior clinical trials of RIC.

An **anticipated serious adverse device effect (ASADE)** is a serious adverse device effect, the specificity or severity of which has been identified in the current Technical Dossier (or equivalent) or with the outcomes from prior clinical trials of RIC.

An **unanticipated serious adverse device effect (USADE)** is any serious adverse device effect, the specificity or severity of which is not consistent with the current Technical Dossier (or equivalent) or with the outcomes from prior clinical trials of RIC.

Causality

Not related or improbable: a clinical event including laboratory test abnormality with temporal relationship to trial treatment / intervention administration which makes a causal relationship incompatible or for which other treatments, chemicals or disease provide a plausible explanation**.** This will be counted as "unrelated" for notification purposes.

Possible: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment / intervention administration which makes a causal relationship a reasonable possibility, but which could also be explained by other interventions, chemicals or concurrent disease. This will be counted as "related" for notification purposes.

Probable: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment / intervention administration which makes a causal relationship a reasonable possibility, and is unlikely to be due to other interventions, chemicals or concurrent disease. This will be counted as "related" for notification purposes.

Definite: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment / intervention administration which makes a causal relationship a reasonable possibility, and which can definitely not be attributed to other causes. This will be counted as "related" for notification purposes.

With regard to the criteria above, medical and scientific judgment shall be used in deciding whether prompt reporting is appropriate in that situation.

Reporting of adverse events

All adverse events (AEs) will be recorded as they are reported whether spontaneously volunteered or in response to questioning about wellbeing at trial visits. The questioning about AEs will cover the current visit as well as the period of time between the previous and the current visit. A note of any concomitant medication will also be made so that a full assessment of the AE can be made.

Abnormal laboratory test results that are deemed clinically significant by the investigator and that lead to a change or temporary or permanent discontinuation in the use of the device, or require intervention or diagnostic evaluation to assess the risk to the subject will be recorded as adverse events or adverse device effects in the CRF and instigate further investigation and follow up as appropriate.

All AEs, SAEs, ADEs and SADEs will be documented in the subject's medical records and CRF. All events must be followed until resolution, or for at least 30 days after discontinuation in use of the device, whichever comes first.

Participants will be asked to contact the study site immediately in the event of any SAEs or SADEs. The Chief Investigator shall be informed immediately of any serious events (via an

automated email sent from the database when the SAE form is submitted) and shall determine seriousness and relationship in conjunction with any treating medical practitioners.

In the event of a pregnancy occurring in a trial participant monitoring shall occur during the pregnancy and after delivery to ascertain any trial related adverse events in the mother or the offspring.

All adverse events and adverse device effects will be recorded and reported to the MHRA and REC as part of the annual reports.

SAEs and SADEs will be reported within the statutory timeframes to the MHRA and REC as stated below. The Chief Investigator will be responsible for all adverse event reporting.

The Chief Investigator will:

- Assess the event for seriousness, expectedness and relatedness to the trial device.
- Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action.
- If the event is deemed a SAE or SADE, shall, within 7 days, complete the appropriate adverse incident report form available from the MHRA web page and send to the MHRA
- If the event is deemed serious, related and/or unanticipated to the trial device, shall inform the REC using the reporting form found on the NRES web page within 15 days of knowledge of the event.
- Shall, within a further eight days send any follow-up information and reports to the MHRA and REC.
- Make any amendments as required to the study protocol and inform the REC as required

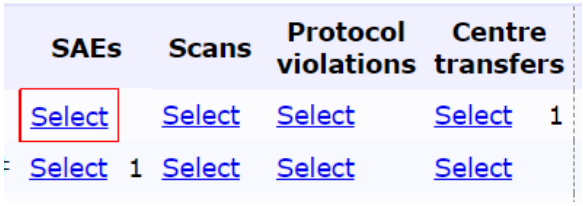
Participant removal from the study due to adverse events

Any participant who experiences an adverse event may be withdrawn from the study at the discretion of the Investigator.

Submitting an adverse event on the RECAST-3 database

SAEs and safety outcomes are all reported using the same SAE form on the RECAST-3 database.

Identify the participant you wish to submit an SAE/safety outcome for using the participant list on the RECAST-3 website, locate the SAEs column and use the **select** link.



This will show the SAE history page. This page lists all of the SAEs which have been submitted for the participant.

To submit a new SAE/safety outcome for the participant, select the **'Add new Serious Adverse Event record'** link.

Add new Serious Adverse Event record

History of Serious Adverse Events

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

Complete all details shown below, using the 'Decision Tree For Adverse Event Reporting – Medical Devices' as a guide for classifying the event (see Appendix 1).

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 1

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 *(dd-mmm-yyyy hh:mm 24hr)* - Day - - Month - - Year - :

Please categorise the event [Select...] Search

* *expected after remote ischaemic conditioning*
ǂ *safety outcome*

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

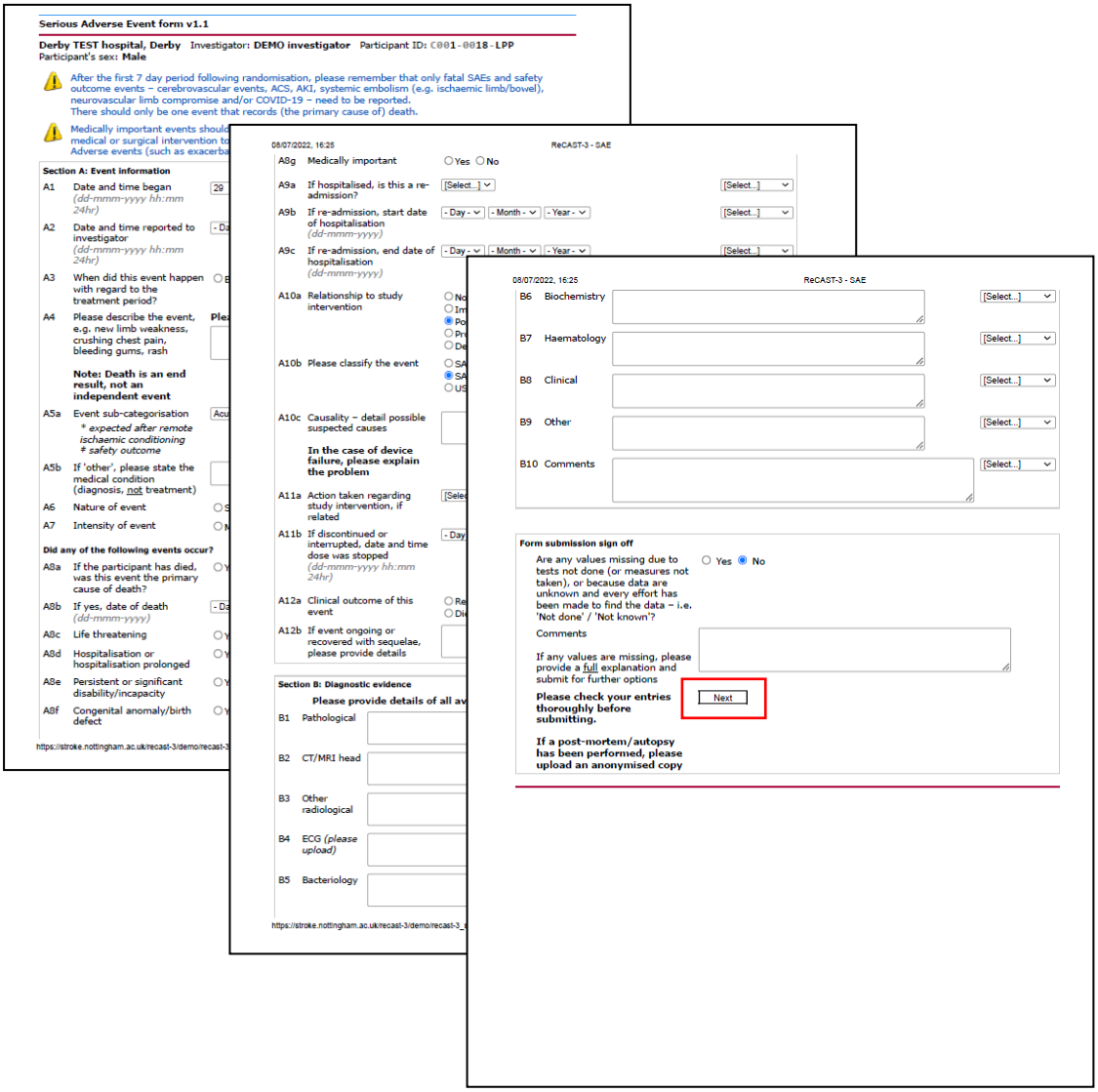
Relationship to study intervention View definitions
○ Not related
○ Improbable
○ Possible
○ Probable
○ Definite

Please classify the event
○ SADE
○ SAE
○ USADE
☐ For a USADE, please check box to confirm

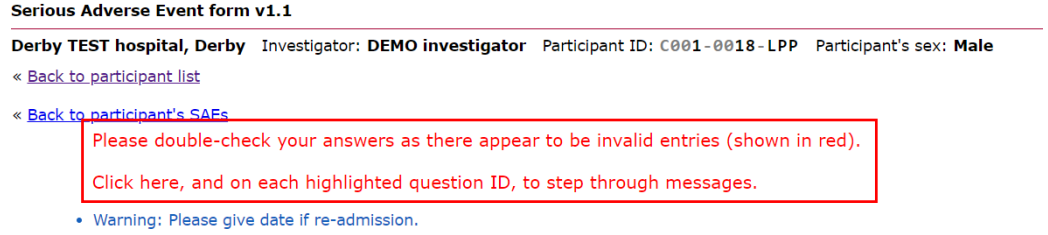
Continue

The Serious Adverse Event form **does not** support draft records.
The form **must** be submitted completely, otherwise the data will be lost.

After clicking continue, please proceed to complete all details on the Serious Adverse Event Form and click 'Next' at the bottom of the page.

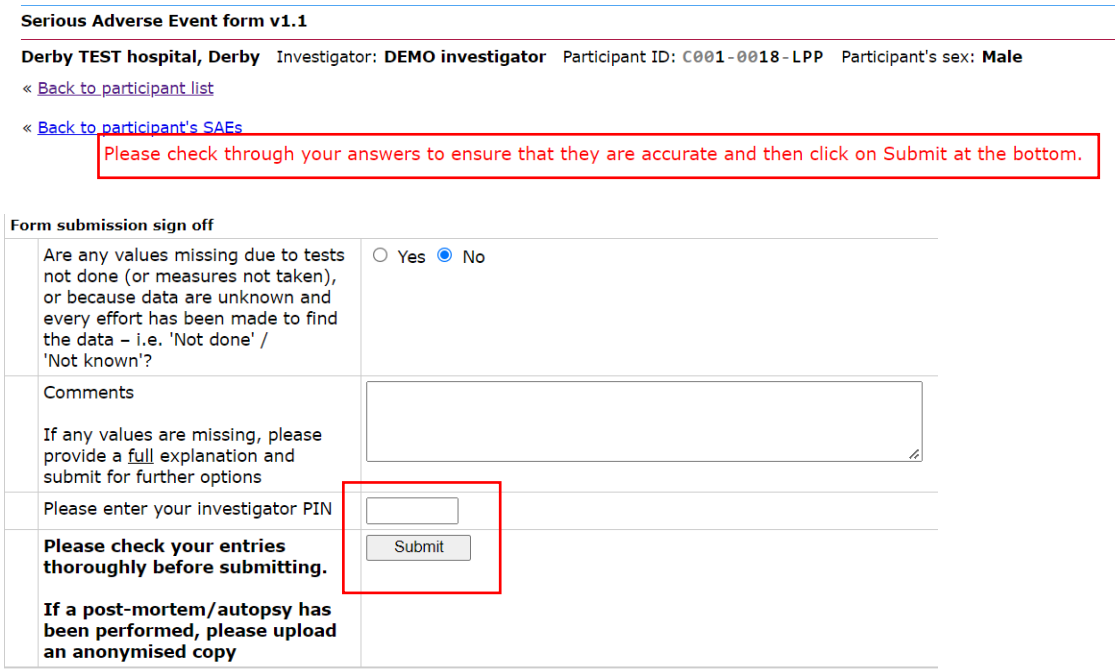


Once you have clicked 'Next', should there be any errors identified, these will be highlighted red, and the following message will be displayed at the top of the page:

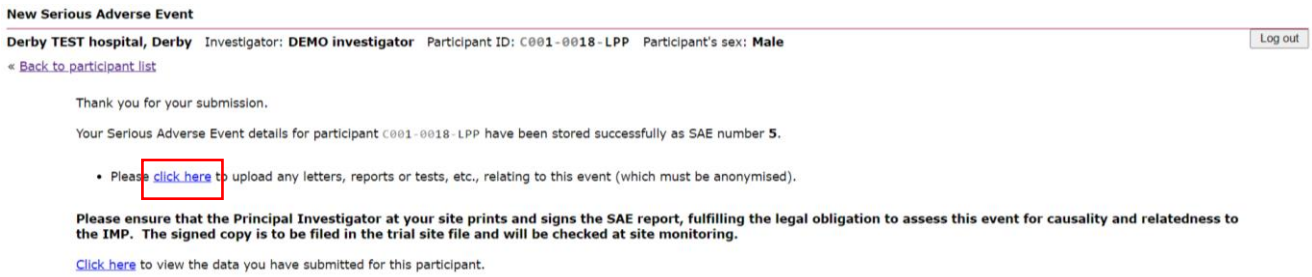


Please resolve any data queries and once again click 'Next' at the bottom of the page.

Once all queries have been resolved, you will be prompted to check through your answers to ensure that they are accurate before entering your investigator PIN and clicking on 'Submit' at the bottom of the page:

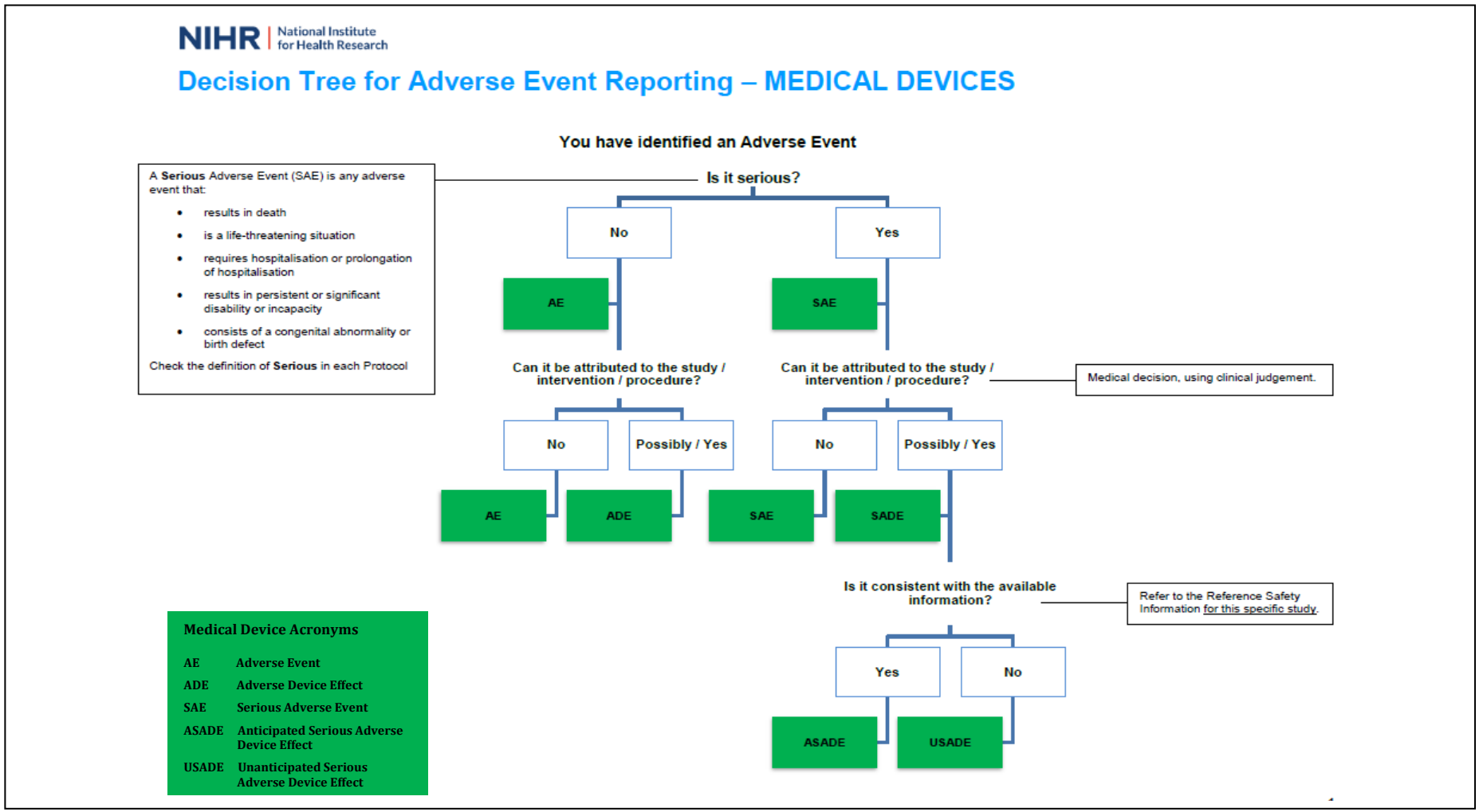


You will then see confirmation of your submission, with a link provided to upload any relevant anonymised documents:



You will receive an automated email confirming the SAE submission. The Principal Investigator, Chief Investigator, Database Programmer and Coordinating Centre will also receive the automated email notification.

Appendix 1


NIHR | National Institute for Health Research
Decision Tree for Adverse Event Reporting – MEDICAL DEVICES
You have identified an Adverse Event
A Serious Adverse Event (SAE) is any adverse event that:
results in death
is a life-threatening situation
requires hospitalisation or prolongation of hospitalisation
results in persistent or significant disability or incapacity
consists of a congenital abnormality or birth defect
Check the definition of Serious in each Protocol
Is it serious?
No
Yes
AE
SAE
Can it be attributed to the study / intervention / procedure?
Can it be attributed to the study / intervention / procedure?
Medical decision, using clinical judgement.
No
Possibly / Yes
No
Possibly / Yes
AE
ADE
SAE
SADE
Is it consistent with the available information?
Refer to the Reference Safety Information for this specific study.
Yes
No
ASADE
USADE
Medical Device Acronyms
AE Adverse Event
ADE Adverse Device Effect
SAE Serious Adverse Event
ASADE Anticipated Serious Adverse Device Effect
USADE Unanticipated Serious Adverse Device Effect