Safety Reporting for NuTH Sponsored Clinical Investigations of Medical Devices

NJRO-REG-SOP-002

Contents

1. Background/Introduction

In order to ensure compliance with the Medical Device Regulations (2002) and the 'Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice' (ISO 14155:2011), all adverse events which occur during the course of a study involving medical devices under clinical investigation must be recorded and reported appropriately in order to ensure that patient safety is maintained.

2. Purpose

The purpose of this Standard Operating Procedure (SOP) is to describe the processes for assessing, recording and reporting safety information for NuTH sponsored trials involving medical devices, and to ensure that these trials comply with Good Clinical Practice (GCP) and all relevant legislation, including:

- Medical Devices Regulations (2002)
- Medical Devices Directive 90/385/EEC
- Medical Devices Directive 93/42/EEC
- European Commission: Guidelines on Medical Devices; MEDDEV 2.7/3
- EN ISO 14155:2011 'Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice'

It is acknowledged that the new EU Regulations for medical devices 2017/745 (MDR) and in vitro diagnostic medical devices 2017/746 (IVDR) 'entered into force' on the 25th May 2017, which is when the three (MDR) and five year (IVDR) transition periods began. As such, the MDR and IVDR will fully apply in EU member states from 26th May 2020 and 2022. Throughout this transition period, NuTH as Sponsor will work towards full compliance.

3. Scope of Document

This SOP applies to Chief Investigators, Delivery teams, Trial Management staff and Sponsor representatives from the Regulatory Compliance Team (RCT) who are involved in any aspect of safety reporting for medical device trials that fall under the Medical Device Regulations (2002). This specifically refers to studies that involve non-CE marked devices or CE marked devices that are being used outside the intended use(s) covered by the CE marking.

4. Definitions

4.1 The following definitions have been adapted from the European Commission's Guidelines on Medical Devices, DEDDEV 2.7/3:

4.1.1 **Medical Device**: any instrument, apparatus, appliance, software, material or other article used alone or combined for humans to:

- Diagnose, prevent, monitor, treat or alleviate disease
- Diagnose, monitor, treat, alleviate or compensate for an injury or handicap
- Investigate, replace or modify the anatomy or a physiological process
- Control conception

A medical device does not achieve its principal intended action by pharmacological, immunological or metabolic means although it may be assisted by these.

4.1.2 **Investigational Medical Device**: A Medical device being assessed for safety and/or performance in a clinical investigation. This encompasses medical devices already on the market that are being evaluated for new intended uses, new populations, new materials or design alterations.

4.1.3 **Adverse Event (AE)**: Any untoward medical occurrence, unintended disease/injury or any untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons whether or not related to the investigational medical device. This includes events related to the investigational device, the comparator and/or any procedures involved (i.e. any procedure in the clinical investigation plan). For users or other persons this is restricted to events related to the investigational medical device.

4.1.4 **Adverse Device Effect (ADE)**: An adverse event related to the use of a medical device under clinical investigation. This includes any AE resulting from insufficiencies or inadequacies in the instructions for use, deployment, implantation, installation, operation or any malfunction of the investigational medical device.

4.1.5 **Device Deficiency (DD)**: Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labelling.

4.1.6 **Serious Adverse Device Effect (SADE)**: An adverse device effect that has resulted in any of the consequences characteristic of a Serious Adverse Event (SAE) (see section 4.1.7 below).

4.1.7 **Serious Adverse Event (SAE)**: An adverse event that:

a) Led to death
b) Led to a serious deterioration in health that either
   - Resulted in a life-threatening illness or injury
   - Resulted in a permanent impairment of a body structure or body function
   - Required inpatient hospitalisation or prolongation of existing hospitalisation
   - Resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or function

c) Led to fetal distress, fetal death or a congenital abnormality or birth defect

This includes device deficiencies that might have led to an SAE if suitable action had not been taken, intervention had not been made or if circumstances had been less fortunate. However, a planned hospitalisation for a pre-existing condition or a procedure required by the clinical investigation plan without a serious deterioration in health is not considered to be an SAE.

4.1.8 **Anticipated Serious Adverse Device Effect (ASADE)**: A Serious Adverse Device Effect which by its nature, incidence, severity or outcome has been previously identified in the current version of the risk analysis report or Investigator Brochure.

4.1.9 **Unanticipated Serious Adverse Device Effect (USADE)**: Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the Investigator Brochure or risk analysis report.

5. Roles & Responsibilities

5.1 The RCT on behalf of Sponsor are responsible for the ongoing safety evaluation of the Medical Device under investigation.

5.2 However, specific tasks associated with the safety reporting process for medical devices under clinical investigation may be delegated to the Chief Investigator (CI) or Trial Management Team via a Delegation of Sponsor Duties Agreement. This will be stored within the Sponsor Oversight File (SOF) for each individual study, and will be signed off by the RCT, the Trial Management Team and the CI to ensure that all parties agree to their assigned roles.

5.3 The Data Monitoring Committee (DMC) or Trial Oversight Committee (TOC) where applicable, are responsible for the overarching review of safety data.

6. Procedures

6.1 Study set up and Safety Considerations

6.1.1 Safety reporting requirements should be determined during protocol development and should be documented within the Protocol and Sponsor Risk Assessment prior to conducting a clinical investigation of a medical device.

6.1.2 It is important to ensure that all relevant parties (including the CI, Trial Management Team, Sponsor, Statisticians etc.) have sufficient input in to these discussions. Therefore safety reporting should feature as an early agenda item during the Trial Management Group (TMG) meetings in order to ensure that safety reporting procedures are robust.

6.1.3 Risk Assessment

6.1.3.1 A documented Sponsor Risk Assessment should be completed during protocol development in order to ensure that any risks associated with the Investigational Medical Device or the associated study procedures can be mitigated (see 'Clinical Trial Risk Assessment for High Risk, NuTH FT Sponsored Trials' SOP).

6.1.3.2 The risks identified within the Sponsor Risk Assessment should be balanced against any anticipated benefits to the participants.

6.1.3.3 The Risk Assessment must also be updated in response to all relevant study proceedings (e.g. substantial amendments, serious breaches, audit findings etc.) in order to reflect any new risks that arise during the conduct of the clinical investigation.

6.1.3.4 The study protocol (clinical investigation plan), Investigator Brochure (IB) and Patient Information Sheet (PIS) should also identify any anticipated / expected ADEs, and should be updated in line with the Sponsor Risk Assessment in order to reflect any new risks that arise during the conduct of the clinical investigation.

6.1.4 Data Monitoring Committee (DMC)

6.1.4.1 The CI and Trial Management Team should establish a DMC prior to the start of a trial involving a medical device under clinical investigation in order to provide oversight regarding the ethical and safety considerations of patients throughout the study.

6.1.4.2 They should also prepare a DMC Charter which should identify specific responsibilities of the DMC. It should also establish the frequency of meetings, documented outputs (e.g. minutes) and the handling of emergency situations.

6.1.4.3 Throughout the trial, regular reports of data must be compiled and presented to the DMC or TOC as appropriate. The DMC/TOC should use the information to identify any potential safety signals that may require further action in relation to the device. Any potential safety signals must be reported to the RCT via the safety reporting inbox: tnu-tr.safetyreporting@nhs.net.

6.2 Identifying, Recording and Reporting Requirements

6.2.1 It is the responsibility of the Principal Investigator (PI) at a site (or their designee as identified via the site Delegation Log held within the Investigator Site File), to identify, record and report AEs as stated in the study protocol / clinical investigation plan.

6.2.2 Unless otherwise stated in the protocol, details of all AEs must be recorded in the patient's medical notes and via an electronic case report form (eCRF) where applicable.

6.2.3 If an AE is deemed 'serious' by the PI or designee (see section 4.1.7), the SAE must be reported to the CI, delegated Clinical Trials Unit (CTU), and/or Sponsor's pharmacovigilance representative (as defined by the protocol) immediately or within 24 hours of being made aware of the event. (The exception to this are those SAEs identified in the protocol as not requiring immediate reporting.)

6.2.4 The initial SAE report can be made verbally but must be promptly followed with a detailed, written report.

6.2.5 SAEs/SADEs/ASADEs/USADEs occurring in NuTH FT sponsored studies must be notified to the RCT in accordance with the agreed Risk Assessment and current protocol. For those trials managed by the CI, a copy of the SAE form must be submitted directly to Sponsor via email to tnu-tr.safetyreporting@nhs.net.

6.2.6 For those trials managed by a CTU, the RCT on behalf of Sponsor and the CTU will determine the best method for notification. Examples may include automatic notification via the Soho66 Fax service or transfer of information via secure email to the Sponsor Safety Reporting Inbox: tnu-tr.safetyreporting@nhs.net.

6.2.7 All reports for SAEs occurring in NuTH FT sponsored studies will be reviewed by an appropriately qualified member of the RCT/NuTH FT R&D Department to check that all essential information has been completed (e.g. event term, severity, seriousness, causality, expectedness, authorisations by appropriated delegated investigator etc.).

6.2.8 As Sponsor's representative, the RCT will put systems in place to ensure that all SAEs/SADEs/ASADEs/USADEs are tracked appropriately and that they are reported correctly within the regulatory timelines and followed up until conclusion.

6.2.9 All confirmed SAEs/SADEs/ASADEs/USADEs will be logged by the RCT and a receipt will be returned to the CI and/or Trial Management Team (as appropriate). The confirmation of receipt should include an SAE reference number along with any requests for any missing information or necessary clarifications. The SAE form and any related correspondence should be filed in the TMF and SOF as appropriate.

6.3 Assessment of Adverse Events

6.3.1 Each AE must be assessed for seriousness, severity, causality and expectedness by an appropriately trained and delegated investigator.

6.3.2 Seriousness Assessment

6.3.2.1 The Investigator, or an appropriately trained designee, should make an assessment of seriousness as outlined in section 4.1.7.

6.3.3 Severity Assessment

6.3.3.1 The Investigator, or designee, should make an assessment of severity for each AE using the following criteria:

Intensity	**Description**
Mild	An event easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities
Moderate	An event sufficiently discomforting to interfere with normal everyday activities
Severe	An event that prevents normal everyday activities

6.3.4 Causality Assessment

6.3.4.1 The relationship between the investigational medical device (including comparator treatments) and the occurrence of each AE must be assessed and categorised by the Principal Investigator (or delegate).

6.3.4.2 Each AE should be categorised as follows:

- Not related: No relationship with the investigational device; other factor(s) certainly or probably causative.
- Possibly Related: The nature of the event, underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the device.

6.3.5 Expectedness Assessment

6.3.5.1 For all AEs deemed 'serious' and 'device or procedure related' (SADEs), they must then be assessed to determine if the event is 'Anticipated' or 'Unanticipated'.

6.3.5.2 For all SADEs, the Risk Assessment or Protocol can be used by the investigator as a basis for identifying anticipated/unanticipated ADEs characterised by their nature, incidence, severity and outcome.

6.3.5.3 The investigator must document the version of the Risk Assessment / protocol used to perform the expectedness assessment. This should be recorded on the study SAE form.

6.3.6 Event Categorisation

6.3.6.1 The below table can be used when categorising adverse events:

<table>
<tr><th>Adverse Events</th><th>Non-device related</th><th colspan="2">Device or procedure related</th></tr>
<tr><td>Non-serious</td><td>AE</td><td colspan="2">ADE</td></tr>
<tr><td rowspan="3">Serious</td><td rowspan="3">SAE</td><td colspan="2">SADE</td></tr>
<tr><td>Anticipated</td><td>Unanticipated</td></tr>
<tr><td>ASADE</td><td>USADE</td></tr>
</table>

6.3.6.2 The flow charts contained within Appendix 2 and Appendix 3 can also be used when categorising all AEs and DDs that arise during a clinical investigation of a medical device.

6.3.7 Follow up of SAEs/SADEs

6.3.7.1 All SAEs/SADEs must be followed up until resolution, even if the patient has withdrawn from the study. An SAE/SADE would be considered 'resolved' if it has:

- Completely resolved
- Recovered with sequelae
- If it is stable and no change is anticipated
- If the participant has died

6.3.7.2 The frequency of follow up for unresolved SAEs/SADEs will be determined on an individual basis depending upon the nature of the event and the amount and type of missing information.

6.4 Expedited Reporting of SADEs, USADEs and Device Deficiencies to the Competent Authority (CA) and Research Ethics Committee (REC)

6.4.1 Notifications to the Competent Authority (Medicines and Healthcare products Regulatory Agency - MHRA)

6.4.1.1 According to Annex 7 of Directive 90/385/EEC, Annex X of Directive 93/42/EEC and Regulation 16(10)(a) of the Medical Devices Regulations 2002 (SI 618), the following events must be fully recorded and immediately notified to all competent authorities of the Member States in which the clinical investigation is being performed:

- Any SAE
- Any Investigational Medical Device Deficiency that might have led to an SAE if:
  Suitable action had not been taken;
  The intervention had not been made;
  Or if circumstances had been less fortunate
- New findings/updates in relation to already reported events

6.4.1.2 The Sponsor must report to all National Competent Authorities (i.e. MHRA for the UK) where the clinical investigation has commenced.

6.4.1.3 Any SAEs (SADEs/USADEs) which indicate an imminent risk of death, serious injury or serious illness and that require prompt remedial action for the other patients/participants, users or other persons or a new finding in relation to an already reported event must be reported immediately, but no later than **2 calendar days** after Sponsor awareness of a new reportable event or of new information in relation to an already reported event. It is the responsibility of the RCT on behalf of Sponsor to notify the MHRA of such events, although this task may be delegated to the Trial Management Team via a Delegation of Sponsor Duties Agreement.

6.4.1.4 Any other reportable events as outlined above or any new findings/updates relating to such events must be reported immediately, but no later than **7 calendar days** following the date of Sponsor awareness. Again, the RCT is responsible for reporting such events to the Competent Authority, although this task may be delegated to the Trial Management team via a Delegation of Sponsor Duties Agreement.

6.4.1.5 The RCT (or appropriate delegate) will be responsible for completing the SAE tabulation form and submitting this to the National Competent

Authorities (NCA) relevant to all states in which the clinical investigation is taking place. The NCA for the UK is the MHRA. The reporting form template which must be submitted to the MHRA is contained within Appendix 1. This SAE tabulation provides a cumulative overview of the reportable events for an individual clinical investigation and will be updated and transmitted to all competent authorities each time a new reported event (or a new update to an already reported event) is to be reported. The reporting form is study specific and covers only a given clinical investigation, defined by a distinct clinical investigation plan.

6.4.1.6 When completing the SAE tabulation form, the RCT (or appropriate delegate) must identify the new and updated information in the 'status' column (see Appendix 1):

- a = added (new reportable event)
- m = modified (new finding or update to an already reported event)
- u = unchanged

6.4.1.7 Any changes made to a line in the SAE tabulation form should be highlighted in bold and/or colour in the respective column.

6.4.1.8 The SAE tabulation should be submitted as an Excel document to the participating Competent Authorities. For the UK, this should be submitted to the MHRA via the following email address: aic@mhra.gsi.gov.uk

6.4.2 Notifications to the Research Ethics Committee (REC)

6.4.2.1 For medical device trials that fall under the Medical Device Regulations (2002), only SAEs/SADEs that are **related** to the administration of the medical device or study procedures and **unexpected** (i.e. not listed in the Risk Assessment or Protocol as an expected occurrence) should be submitted to the REC.

6.4.2.2 Related and unexpected SAEs should be submitted to the REC using the 'non-CTIMP safety report to REC form', which can be located via the HRA website: https://www.hra.nhs.uk/.

6.4.2.3 Related and unexpected SAEs should be submitted to the REC within **15 days** of the CI becoming aware of the event.

6.4.2.4 Again, the RCT is responsible for reporting such events to the REC, although this task may be delegated to the Trial Management team via a Delegation of Sponsor Duties Agreement.

6.5 Investigator Notification

6.5.1 In the case of a multicentre clinical investigation, the Sponsor or delegate (as confirmed in the study specific Delegation of Sponsor Duties Agreement) must ensure that all Principal Investigators (PIs) are informed in writing of all SADEs, USADEs and DDs that occur at all investigator sites.

6.5.2 Documented evidence of investigator review must be filed within the investigator site file, whether this is through signing and dating the report itself or by simply responding to the email distribution confirming their review.

6.5.3 The Trial Management Team must obtain acknowledgement from sites to confirm that investigators have reviewed the SADEs/USADEs/DDs. This confirmation should be stored within the Trial Master File (TMF).

6.6 Reporting events via DATIX

6.6.1 All USADEs occurring in NuTH FT sponsored studies, whether experienced by patients from NuTH FT or another Trust hosting the study, must also be reported via the electronic incident reporting system, DATIX.

6.6.2 The incident type should be entered as 'Research Incident/Accident'; Directorate as 'Medical Director's Directorate'; Speciality as 'Research Development and Governance'; Site as 'Regent Point'; and Location as 'Research Buildings' (entries selected from the drop down menus).

6.6.3 Reporting via DATIX is the responsibility of an appropriately qualified member of the NuTH FT RCT. (See also NuTH FT 'Managing and Reporting of Accidents and Incidents' Policy).

6.7 SAE Reconciliation

6.7.1 SAE/SADE reconciliation should be conducted by the Trial Management Team (or as specified by the Delegation of Sponsor Duties Agreement located in the Sponsor Oversight File) on a regular basis.

6.7.2 This reconciliation process should incorporate a review of information contained within the SAE/SADE report and ensuring that this consistent with information held within the study database.

6.7.3 Specific data items to be reconciled, the frequency of reconciliation and the process by which SAE/SADE reconciliation will be achieved should be discussed and agreed by the TMG (including Sponsor), and formally documented in the Data Management Plan.

6.8 Device Deficiencies

6.8.1 All DDs (as defined in 4.1.5) should be reported to the RCT via the safety reporting inbox: tnu-tr.safetyreporting@nhs.net

6.8.2 The following DDs are subject to expedited reporting to the CA and REC:

6.8.2.1 DD that might have led to an SAE if:

Suitable action had not been taken

Intervention had not been made

If circumstances had been less fortunate

6.8.3 Expedited reporting timelines for DDs mirror those within sections 6.4.1 and 6.4.2.

6.8.4 As with SADEs/USADEs, the RCT remain responsible for reporting all relevant DDs to the CA and REC.

6.9 Medical Device Quarantine

6.9.1 If an ADE is defined as serious (i.e. a SADE) or a DD that could have led to a SADE/USADE, the investigator must quarantine the device as soon as possible. This involves segregating the device from other equipment and labelling it as 'not for use' with relevant contact details included.

6.9.2 Until the Competent Authority (MHRA) and Sponsor have been given the opportunity to carry out an investigation:

- The device and all associated items (including relevant packaging materials) should be quarantined
- They should not be repaired, discarded or returned to the manufacturer without agreement from Sponsor
- All material evidence (including devices/parts removed, replaced or withdrawn from use following an incident; instructions for use; records of use; packaging materials or other means of batch identification etc.) must be:
    - Clearly identified and labelled (including the competent authority/Sponsor/manufacture reference number if needed)

- Securely packaged and stored

6.9.3 Material evidence should not be altered or interfered with in any way, expect for safety reasons or to prevent loss.

6.9.4 Where appropriate, a record should be made of all readings, settings, position of switches, valves, dials, gauges and indicators, together with any photographic evidence and eye witness reports.

6.9.5 Documentation relating to such evidence should be retained in the Trial Master File (TMF) and Sponsor Oversite File (SOF) where appropriate.

6.9.6 If the Device is sent to the Competent Authority (only if specifically requested), documentation regarding shipment and receipt of the device should also be retained.

7. References

Medical Devices Regulations (2002)

Medical Device Directive 90/385/EEC

Medical Device Directive 93/42/EEC

International Standards Organisation (ISO) 14155:2011 'Clinical investigation of medical devices for human subjects. Good clinical practice'

European Commission guidelines on medical devices MEDDEV 2.7/3

8. Appendices

Appendix 1: MHRA SAE Reporting Form

Appendix 2: Categorising Adverse Events

Appendix 3: Categorising Device Deficiencies

The Newcastle upon Tyne Hospitals NHS Foundation Trust

Newcastle University

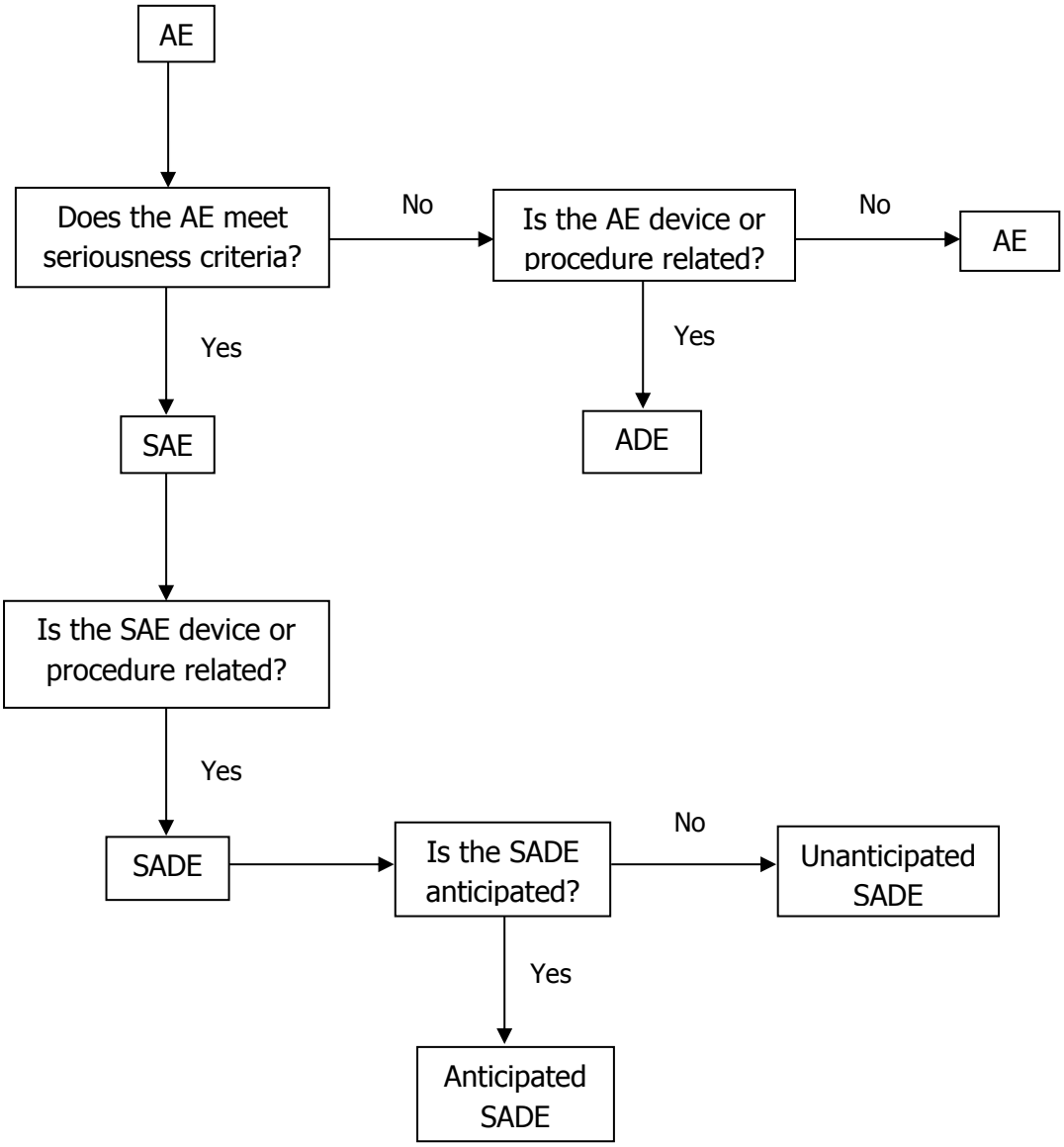
Appendix 1: MHRA SAE Reporting Form

MEDDEV 2.7/3 SAE Report Table v2																		
EUDAMED - ID:																		
Title of Clinical Investigation:																		
CIP Number:																		
Contact person (Name, Address, E-Mail, Telephone Number)											**Device type:**							
MS+NCA Reference Numbers for all participating Countries:											**Reference Member State:**							
No. of Patients enrolled to date total:		**No. of Patients enrolled to date** (date of report) **per country:**									**No. of Invest. Devices used to date total:**		**No. of Invest. Devices used to date per country:**					
Date of Report:	dd/mm/yyyy																	
Status: A, M, U	**Date Sponsor received Report of SAE (dd/mm/yyyy)**	**Countrycode**	**Study Center**	**Patient ID Code**	**SAE ID Code**	**Date of Procedure/ First Use (dd/mm/yyyy)**	**Date of Event Onset (dd/mm/yyyy)**	**SAE OR Dev. Def.**	**Description of event**	**action/ treatment/patient outcome**	**Relationship to Procedure:** not related **OR** unlikely **OR** possible **OR** probable **OR** causal relations	**Relationship to Investigational Device:** not related **OR** unlikely **OR** possible **OR** probable **OR** causal relations	**Unanticipated aADE:** Yes **OR** No	**Treatment Arm:** Investigational Device/ Control Group/ blinded/ n.a.	**Event Status:** Resolved/ Resolved with Sequelae/ Ongoing/De	**Date of Event Resolution (dd/mm/yyyy)**		

Note 1: Submission of this report does not, in itself, represent a conclusion by the sponsor or the competent authority that the content of this report is complete or that the device(s) listed failed in any manner and/or that the device(s) caused or contributed to the alleged death or deterioration in the state of the health of any person.

Note 2: If additional columns are added to this form (for instance to include the opinion of the investigators), please add them next to the existing columns on the right. This form may be subjected to automatic analysis and addition of columns in between may interfere with automatic analysis. Widthening of columns can be applied without alteration of the order.

Appendix 2: Categorising Adverse Events



Appendix 3: Categorising Device Deficiencies