SOP number	**55.007**	Version	**3.0**
Title	**Safety Reporting In Clinical Trials Of Medical Devices Of Non CE/UKCA Marked Medical Devices Or CE/UKCA Marked Devices Used Outside Of Their Intended Purpose (Sponsored And Hosted Clinical Investigations).**		

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SOP category	NHS GG&C Sponsor Pharmacovigilance

Staff category

Staff Category	**R**	**A**	**C**	**I**
R&I Pharmacovigilance	X			
R&I Research Governance Manager		X		
R&I Innovation Lead			X	
Sponsor Research Co-Ordinators			X	
Project Managers			X	
Industry Collaboration Project Manager			X	
R&I Pharmacy			X	
R&I Monitoring			X	
Chief Investigator				X
Principal Investigator				X

1. Scope

This procedure applies to staff within the Glasgow Clinical Trials Unit (GCTU) involved in any aspect of safety reporting activity.

2. Purpose

Safety reporting for medical devices is similar to that within CTIMP trials albeit with some important differences. It relates to the detection, assessment, understanding and prevention of adverse effects, particularly long term and short term adverse device effects caused either directly or indirectly by a medical device.

The Medical Devices Regulations 2002 (Statutory Instrument 2002/618) was implemented on the 13th June 2002 and implemented the following EU directives:

- Medical Devices Directive 93/42/EEC
- Active Implantable Medical Devices Directive 90/385/EEC
- In Vitro Diagnostic Medical Devices Directive 98/79/EEC.

More recently, Directive 2007/47/EC amended the above directives with respect to clinical investigations of medical devices to further standardise clinical investigations and the safety reporting required for both CE/UKCA marked and non-CE/UKCA marked devices.

The purpose of this SOP is to describe the procedures to be followed to ensure that these regulatory requirements are met in clinical investigations of non-CE/UKCA marked medical devices or CE/UKCA marked devices to be used outside of their intended purpose sponsored by NHS Greater Glasgow and Clyde (NHS GGC) or co-sponsored with the University of Glasgow.

The Chief Investigator (CI) has overall responsibility for the conduct of the clinical investigation.

The Principal Investigator (PI), who may also be the CI in a single-location trial, has responsibility for the conduct of the clinical investigation at that location. This includes the assessment and reporting of adverse events as per the trial protocol.

In clinical investigations sponsored by NHS GGC or co-sponsored with the University of Glasgow, the delivery of safety reporting within the trial is delegated to the Chief Investigator (CI). However, the ultimate responsibility and accountability for safety reporting remains with NHS GGC under the co-sponsorship agreement.

The Pharmacovigilance (PV) Office is a support mechanism to facilitate, provide central coordination and allow oversight of safety reporting activity within CTIMPs and clinical investigations of non CE/UKCA marked medical devices sponsored by NHS Greater Glasgow and Clyde or co-sponsored with the University of Glasgow.

A safety-reporting plan (Form 55.001A) will be produced for each individual clinical investigation capturing the specific requirement for that study. This will be prepared by the pharmacovigilance and safety manager and should be in place prior to the study opening to recruitment.

3. Procedures

3.1 Definitions

Sponsor(s)

The individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical investigation.

Medical device

A medical device is any instrument, apparatus, implement, machine, appliance, implant, software, material, or other similar or related article:

3.1.1. (a) Intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of:

1. **Diagnosis, prevention, monitoring, treatment or alleviation of disease**
   Example: *Blood glucose monitor*
   ➤ Used to diagnose and monitor diabetes by measuring blood sugar levels.
2. **Diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury**
   Example: *Orthopaedic brace*
   ➤ Provides support and stabilization for injured joints or bones, aiding in recovery.
3. **Investigation, replacement, modification, or support of the anatomy or of a physiological process**
   Example: *Hip implant*
   ➤ Replaces a damaged hip joint, restoring mobility and anatomical function.
4. **Supporting or sustaining life**
   Example: *Ventilator*
   ➤ Sustains life by mechanically assisting or replacing spontaneous breathing.

5. **Control of conception**
   Example: *Intrauterine device (IUD)*
   ➤ A device placed in the uterus to prevent pregnancy.
6. **Disinfection of medical devices**
   Example: *Autoclave*
   ➤ Used to sterilize surgical instruments through high-pressure steam.

3.1.2. (b) Which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means:

Explanation:
This clause defines a medical device as one whose **primary mode of action** is not based on chemical interaction (e.g., drugs), immune response, or metabolism. However, the device may be **supported** by such means (e.g., used alongside medication).
Example: *Pacemaker*
➤ A pacemaker regulates heart rhythm through electrical impulses. It does not act pharmacologically, immunologically, or metabolically, though its function may be supported by medications like antiarrhythmics.

Investigational medical device
The medical device being assessed for safety or performance in a clinical investigation.
NOTE: This includes medical devices already on the market that are being evaluated for new intended uses, new populations, new materials or design changes.

Adverse Event (AE)
Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in participants, users or other persons whether or not related to the investigational medical device.

NOTE 1: This definition includes events related to the investigational device or the comparator.

NOTE 2: This definition includes events related to the procedures involved.

NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.

Serious Adverse Event (SAE)
Adverse event that:
a) Led to a death, injury or permanent impairment to a body structure or a body function.
b) Led to a serious deterioration in health of the participant, that either resulted in:
- A life-threatening illness or injury, or
- A permanent impairment of a body structure or a body function, or
- In-patient hospitalisation or prolongation of existing hospitalisation, or
- In medical or surgical intervention to prevent life threatening illness
c) Led to foetal distress, foetal death or a congenital abnormality or birth defect.

NOTE 1: Planned hospitalisation for pre-existing condition, or a procedure required by the Clinical Investigation Plan (CIP), without a serious deterioration in health, is not considered a serious adverse event.

Device deficiency
Inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, user error, or inadequacy in the information supplied by the manufacturer.

Adverse Device Effect (ADE)
Adverse event related to the use of an investigational medical device.

NOTE 1- This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.

NOTE 2- This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

Serious Adverse Device Effect (SADE)
An adverse effect related to the device that resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE)
A serious adverse effect related to the device that by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

NOTE: Anticipated SADE (ASADE): an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report

3.2 Responsibilities
The Pharmacovigilance office, chief investigator, and principal investigators are delegated specific responsibilities for safety reporting by the Sponsor and these are documented within the relevant agreements, the trial protocol, and during any study initiation. R&I coordinators and project managers have a responsibility to liaise with the Pharmacovigilance office during the setup of clinical investigations sponsored by NHS GG&C. Clinical trial monitors also have responsibilities for safety reporting as detailed below.

The PV office is responsible for:

- Working with the CI (and supplying manufacturer where applicable) to identify the information in the investigators brochure or risk analysis that will be used as the reference for assigning causality and expectedness.
- Checking annually for updates to the investigator brochure
- Working with the CI to write the trial protocol/investigation with a specific focus on safety reporting.
- Central data collection and verification of AEs, ADEs, SADEs, USADEs, and device deficiencies according to the trial protocol.
- If applicable, reporting safety information to the Chief Investigator, delegate or independent clinical reviewer for the ongoing assessment of the risk-benefit ratio.
- Expedited reporting of SAEs and DDs to the Competent Authority (MHRA in UK), main REC and Sponsor within required timelines.
- Reviewing SADEs and procedure related events for expectedness against the manufacturers information and/or protocol within 7 days of receipt by the Sponsor
- Notifying Investigators of any USADEs that occur within the trial.
- The unblinding of a participant for the purpose of expedited SAE reporting if applicable.

- Reporting events to the collaborating manufacturer in accordance with the trial contract (if applicable)
- Ensuring the contract has a return process in place with the manufacturer ,
- Reviewing device deficiencies to determine if a device should be returned for investigation
- Where the device incorporates an IMP, or is used in the delivery of a medicine e.g. spacer device for use with an inhaler liaise with pharmacy to review device deficiencies
- Checking for updates to the devices safety profile and communicating changes to the CI for assessment of the risk benefit ratio.
- Communicating changes associated with a change in the risk benefit ratio to locations via a substantial modification.
- Notifying Principal Investigators at location(s), the Sponsor, main REC and MHRA of findings that could adversely affect the health of participants, impact on the conduct of the trial or alter the authority's authorisation of the trial
- Monitoring location(s) compliance with safety reporting procedures and timelines
- Preparation of quarterly safety reports to the MHRA

The CI is responsible for:

- Assessing the investigators brochure or risk analysis for those adverse events that would be classed as expected during usage of the medical device.
- Assessing trial specific procedures to identify expected adverse events that may occur as a result of those procedures.
- Liaising with the Pharmacovigilance office to write those sections of the protocol relating to safety reporting.
- Upon the release of new safety information via the supplier of the medical device; assessing the risk/benefit of updated information and if necessary amending the protocol and/or safety reference documents accordingly.
- Review of SAEs within the trial in line with the protocol and agreeing the timelines for this with the Pharmacovigilance office.
- Reviewing USADEs and SADEs must be reviewed by the CI within 7 days of the PV office being notified of the event.
- SAEs indicating an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other participants, users or other persons* or follow up information to a previously reported SAE of this kind must be reviewed within 24 hours of the PV office making the CI aware of the event.
- Review DDs to identify any trends in reporting indicative of a potential issue with the device
- Reviewing quarterly safety reports prior to MHRA submission

Principal investigators are responsible for:

- Ensuring AEs are assessed for seriousness and causality and documented within the patient notes.
- Reporting device deficiencies to the Sponsor and assessing deficiencies to determine if they may have potentially resulted in an SAE
- For those AEs that become SAEs, ensuring that a review of causality and expectedness takes place within 24 hours for those events that indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other participants, users or other persons and within 7 days for all other events.
- Ensuring that all SAEs are reported to the sponsor within 24 hours of the location becoming aware of the event.

R&I coordinators and/or project managers are responsible for:

- Ensuring that the PV office is aware of clinical investigations of any non-CE/UKCA marked medical devices or CE/UKCA marked devices used outside of their intended purpose prior to the completion of the protocol for classification purposes.
- Ensuring that the PV office is involved in the risk assessment process for any sponsored clinical investigations of non-CE/UKCA /UKCA or CE/UKCA marked devices used outside of their intended purpose medical devices

Monitors are responsible for:

- Checking patient records for potential serious adverse events and/or device deficiencies in line with the monitoring plan and the safety reporting section of the protocol.

For clinical investigations of medical devices involving IMP only: R&I Sponsor Pharmacy Team is responsible for:

- Liaising and providing advice when any of the devices involve the use of medicines.
- Reviewing device deficiencies in collaboration with the PV and safety manager

3.3 Prior to study start

The proposed safety recording, notification and reporting procedures will be detailed within the CIP and will be reviewed by the Medicines and Healthcare products Regulatory Agency (MHRA) and Research Ethics Committee (REC) during the assessment process.

The CIP will document:

- What adverse events are to be recorded and reported? This decision will be the result of the risk assessment process. For low risk clinical investigations AEs should be reported within the patient notes, for high risk clinical investigations AEs should be collected on the eCRF.
- How adverse events will be identified (e.g. by enquiry at study visits, from lab reports).
- How adverse events are to be recorded in the CRF and/or patient records.
- How adverse events are to be assessed for seriousness, causality, expectedness and severity
- Any events classed as serious which should be excluded from expedited reporting. (If an incident is anticipated or likely as a result of the study population or condition, it can be excluded from the safety reporting process **only** if it is clearly identified as a likely outcome in the study protocol.)
- The period of time during which investigators should notify the sponsor of SAEs and DDs. This period of time will be dependent on the risks associated with the clinical investigation.
- Level of CI review of SAEs and the frequency of this review.
- Level of review by the Sponsor: Generally for SADES and DDs only.
- The document used to assess expectedness of any adverse reactions. In most cases this will be an Investigators Brochure, Risk Analysis Report, or may be the expected reactions to the device and/or procedures associated with that device listed within the protocol.
- Details of unblinding procedure if appropriate.
- The requirements for the expedited reporting of any adverse events assessed as a requiring submission to the MHRA and arrangements for the informing of investigators
- What device deficiencies are collected in the eCRF and how will these deficiencies be assessed?

Any delegation of safety reporting activities e.g. adverse event recording, assessment or reporting must be documented on a Delegation Log in the Location File.

For non-CE/UKCA marked medical devices or CE/UKCA marked devices used outside their intended purpose the pharmacovigilance and safety manager will be responsible for writing the safety reporting sections of the protocol in collaboration with the chief investigator.

3.4 During a trial (See Flow chart Appendix 1)

3.4.1 Adverse events.

Adverse events (AEs) are to be recorded, notified, assessed, reported, analysed, and managed in accordance with the approved study protocol.

The level of AE reporting is dependent on the risk of the trial in comparison to standard care, and the level of knowledge regarding the safety profile of the medical device. The CIP will document any adaptations to AE and SAE reporting along with the rationale for the changes to safety reporting levels.

Adverse events reported to trial staff must be documented in the CRF and/or participant medical records as required by the CIP.

All adverse events must be assessed for seriousness and causality. Serious Adverse Events (SAEs) must also be assessed for expectedness and severity.

For randomised double blind studies, AEs should be assessed as though the patient was using the medical device under investigation.

3.4.2 Assessment of seriousness.

This assessment is based on the regulatory definitions of seriousness. These definitions should be included in the clinical investigation plan.

An adverse event is serious if it:
a) Led to a death, injury or permanent impairment to a body structure or a body function

b) Led to a serious deterioration in health of the participant, that either resulted in:
- A life-threatening illness or injury[1], or
- A permanent impairment of a body structure or a body function, or
- In-patient hospitalisation[2] or prolonged an existing hospitalisation, or
- Required medical or surgical intervention to prevent life threatening illness

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

Note:

[1] Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the participant was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

[2] Hospitalisation is defined as an inpatient admission. Planned hospitalisation for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered a serious adverse event.

The term “severe” is often used to describe the intensity (clinical severity) of a specific event. This is not the same as “serious”, which is a regulatory definition based on patient/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

The reporter of the event may initially carry out the assessment of seriousness; however, the Principal Investigator or appropriately qualified clinician delegated this task must confirm this assessment at the time of their review.

3.4.3 Assessment of causality i.e. does it have a "reasonable causal relationship" with the medical device. The following categories are used:

Not related:	Any event that is clearly and definitely due to extraneous cause (e.g., disease, environment, etc.).
Possibly related:	Although a relationship to the medical device cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship makes other explanations possible.
Related:	The relationship with the use of the investigational device seems relevant and/or the event cannot be reasonably explained by another cause and could not be explained by the participants clinical or concurrent disease state (including concurrent treatments or drug use)

An adverse event thought to be related to the use of the medical device is an **Adverse Device Effect (ADE)**

A Serious Adverse Event suspected to be related to the use of the medical device is a **Serious Adverse Device Effect (SADE)**

The reporter of the event may perform an initial assessment of causality; however, final review of causality lies with the Principal Investigator or other local clinician delegated this task. They must review causality at the time of their review.

The Sponsor cannot downgrade the causality assessment provided by the local investigator and their team. Where the Sponsor disagrees with the investigator's causality assessment, the report will contain the opinion of both the investigator and Sponsor.

3.4.4 Assessment of expectedness.
If the ADE or SADE is thought to have a causal relationship to the device then clinical judgement along with the relevant document such as an investigators brochure or the CIP should be used to assign expectedness. The presence of any other factors that may confound the assessment should be taken into account for example any concurrent illnesses, concomitant medications, natural progression of a participants underlying disease, and any possible adverse effects of procedures utilised within the clinical investigation plan. If the event is listed within the CIP, protocol or IB as an anticipated effect then the event would be classed as expected. If; however, the event is not listed within the reference document or the event is of greater than expected severity, and the medical device is thought to have a causal relationship to the effect then this is classed as an Unanticipated Serious Device Effect and is subject to expedited reporting to the MHRA and main REC.

Anticipated: The medical device is thought to have a causal relationship with the event and the event is listed within the reference information used to assign causality
Unanticipated: The medical device is thought to have a causal relationship with the event and the event is NOT listed within the reference information.

Any AE that is assessed as **serious**, is suspected of having a **causal relationship** to the trial medication and is **unexpected** is an **Unanticipated Serious Adverse Device Effect** (**USADE**) and will require expedited reporting to the MHRA/ Ethics Committee.

3.4.5 Assessment of severity.
The intensity of the event should be assessed and described using the following categories:

Mild - awareness of event but easily tolerated
Moderate - discomfort enough to cause some interference with usual activity
Severe - inability to carry out usual activity

The reporter of the event may assess an event for severity; however, the Principal Investigator or appropriately qualified clinician delegated this task must confirm severity at the time of their review.

3.5 Device Deficiencies
As per UK Medical Devices Regulations 2002 (SI 2002 No 618, as amended) (UK MDR 2002), EU) Medical Devices Regulation 2017/745 (MDR) the manufacturer must report all device deficiencies to the MHRA where that deficiency might have led to a SAE if:

a) Suitable action had not been taken
b) Intervention had not been made
c) If circumstances had been less fortunate

In addition to the regulatory requirements there is a need to capture device deficiencies in order to monitor any issues arising that may require a change to the device, documentation related to the device, or the CIP.

As a general rule all device deficiencies (DDs) will be captured within the eCRF irrespective of their potential to result in an SAE.

Individual device deficiencies must be assessed by the local investigator as to whether they may have resulted in an SAE as per the criteria above. Device deficiencies may also be assessed by the Sponsor or CI to determine the need for expedited reporting. To simplify the assessment the reviewer must ask what may have potentially occurred had the participant not been part of a clinical investigation with the associated medical oversight, rescue strategies, mitigation strategies etc. Certain device deficiencies will always be considered reportable for example:

- A device is used to administer treatment to treat chronic conditions where that treatment is required to avoid in-patient admission or potentially life-threatening conditions then failure to complete that treatment for any reason would be considered reportable.
- A device administers treatment invasively via a needle or other means and that device has safeguards in place to avoid the exposed means of delivery. If the device safeguards fail, the device may present a risk of needlestick injury and this is reportable.
- Failure of a diagnostic device to identify a medical condition resulting in a participant not receiving treatment, or a diagnostic device incorrectly identifying a medical condition resulting in unnecessary exposure to potentially harmful treatment would be reportable.

3.6 Reporting Requirements

3.6.1 Reporting requirements for non CE/UKCA marked devices or CE/UKCA marked devices used outside of their indicated purpose.

Safety reporting for non CE/UKCA marked devices or for CE/UKCA marked devices used outside of their intended purpose is governed by UK Medical Devices Regulations 2002 (SI 2002 No 618, as amended)(UK MDR 2002), EU) Medical Devices Regulation 2017/745 (MDR), European Directives 90/385/EEC AND 93/42/EEC. In particular MEDDEV 2.7/3 Clinical Investigations: Serious Adverse Event Reporting outlines the reporting requirements for clinical investigations of this type.

Note: Where the clinical investigation also involves an IMP then the CTIMP regulations The Medicines for Human Use (Clinical Trials) Regulations 2004 and associated modifications are also applicable.

3.6.2 Reportable Events

The following events are considered reportable events subject to expedited reporting to the sponsor.

- Any SAE that occurs irrespective of the causality and expectedness
- Any Investigational Medical Device Deficiency that might have led to a SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate.
- Any new findings/updates in relation to already reported events.

All SAEs and device deficiencies must be notified to the sponsor PV office by the chief investigator or their delegate within 24 hours of them becoming aware of the event.

3.6.3 Notifying the sponsor

SAEs should be ideally reported via electronic CRF by users authorised to do so.

In the event that the eCRF system is not functional, or where an eCRF is not used then a sponsor approved SAE form may be used. This form will be provided to location at the time of set up. Alternatively details of any event can be emailed to pharmacovig@glasgowctu.org

Likewise Device deficiencies should ideally be reported via eCRF; where this is not possible they can be reported using a sponsor approved device deficiency form. This form will be provided to location at the time of set up. Alternatively details of any event can be emailed to pharmacovig@glasgowctu.org

SAE and device deficiency reports should be sent to the PV office by email to pharmacovig@glasgowctu.org

If necessary, a report may be provided by email to the PV Office. This must be followed up as soon as possible with a signed written (or electronic) report.
If the required information is not available at the time of initial reporting, the PI (or designee) must ensure that any missing information is forwarded to the PV Office as soon as this becomes available. The report should indicate that this information is follow-up information for a previously reported event. The follow up information can be sent as per the initial notification.

The principal investigator, or other medically qualified delegate should review and sign off the serious adverse event within 24 hours if the event indicates that the SAE may indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other participants, users or other person. For all other events, the SAE should be reviewed within 7 days.

In the absence of local clinical review, SAEs will be reported to the MHRA with 24 hour or 7 day time period, however, the Sponsor must ensure local clinical review takes place.

The CI and Sponsor may believe that an event indicates prompt action is required for others exposed to the medical device and may upgrade an event accordingly, reporting to the MHRA within 24 hours and implementing immediate mitigation strategies.

If the clinical investigation is blinded, the blind should be maintained when reporting to the sponsor unless it is necessary for the participants allocation to be unblinded to ensure the safety of the participant or others that may be at risk.

3.6.4 Processing of SAE and DDs

Upon entry onto the eCRF the event will be automatically assigned a unique reference by the system. The SAE/DD should be logged onto the relevant PV log on the day of receipt.

Confirmation of receipt of the events should be sent to the location within 2 business days of receipt and any missing information; particularly information regarding the causality and expectedness of the event and review by the PI/CI should be chased at this time.

The initial event should be filed in the PV Office filestore along with any follow-ups that are received and responses to any queries generated following SAE review.

In the event that an event is received indicating an imminent risk of death, serious injury, or serious illness and that could require prompt remedial action for other patients/participants, users or other persons then the pharmacovigilance and safety manager should be notified immediately along with the chief investigator, R&I senior management, and the manufacturer. See section 5.7.3 for further information regarding 2 day reports.

For all other events review and sign of by an authorised medically qualified investigator is required within 7 days of the PV office becoming aware of the event.

3.6.5 Expedited reporting of SAEs to the MHRA: Non CE/UKCA marked devices

The following events should be reported to the MHRA within 7 calendar days of the PV office becoming aware of the event:

- any SAE considered reportable as per the clinical investigation plan and/or protocol
- any Device Deficiency that might have led to a SAE if:
    - suitable action had not been taken or
    - intervention had not been made or
    - if circumstances had been less fortunate
- new findings/updates in relation to already reported events.

The following events should be reported to the MHRA within 2 calendar days of the PV office becoming aware of the event:

- any SAE or device deficiency that indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other participants, users or other persons* or follow up information to a previously reported SAE or device deficiency of this kind

*This includes events that are of significant and unexpected nature and may cause a public health risk or the possibility of multiple deaths occurring at short intervals For events meeting, or that are

suspected to meet this criteria the CI, PV and Safety Manager, and R&I Senior Management must be notified as soon as possible, see section 3.7.3

All SAEs and DDs reported to the sponsor must be submitted to the MHRA using the MDCG 2020-10/2 SAE reporting table found here: https://health.ec.europa.eu/document/download/bf136f27-27da-4a31-97c2-a5de741c3493_en?filename=md_mdcg_2020-10-2_guidance_safety_report_form_en.xlsx

A copy of the SAE or DD form should be submitted along with the cumulative line listing at the time of submission to the MHRA.

Events are to be processed as per Guideline 55.007A PV Office Processing for Clinical Investigations of Non CE/UKCA marked Medical Devices

One reporting form should be used for each clinical investigation plan.

The MHRA may request more detailed information upon reviewing the submitted reports and if requested this should be sent within the period of time stated in their request.

3.6.6 Expedited reporting of USADEs to the REC(s): Non CE/UKCA marked devices

An SAE occurring to a research participant at a UK trial location should be reported to the main REC if in the opinion of the Chief Investigator the event was:

Related: that is, it resulted from administration of the medical device or any of the research procedures

And

Unexpected: that is, the type of event is not listed in the protocol as an expected occurrence.

Reports of related and unexpected SAEs should be submitted within 15 calendar days of the PV officer becoming aware of the event, using the SAE report form for research other than clinical trials of investigational medicinal products (non-CTIMPs) published on the NRES website. http://www.hra.nhs.uk/?p=194813

If an SAE that was not initially deemed reportable to the REC is found to fit the criteria for expedited reporting, the PV office will submit the AE in a written report to the REC as soon as possible, but no later than 10 business days from the time the determination is made.

Individual reports of SAEs will be reviewed by the REC at a sub-committee or Committee meeting

In the event that an unanticipated adverse device effect presents an unreasonable risk to participants, the Sponsor may terminate all investigations or parts of investigations presenting that risk as soon as possible. Termination shall occur not later than 5 working days after the decision to halt the investigation is made and not later than 15 working days after the Sponsor received notice of the effect leading to the halt. The terminated study may only be resumed after approval from REC.

3.6.7 Reporting to other parties

Manufacturer

The manufacturer will be notified of all serious adverse events at the time the event is reported to the MHRA/REC unless alternative timelines are agreed at the time the contract is agreed.

Funder

As per the manufacturer

3.6.8 Other reportable events

Events may occur during a clinical investigation which do not fall within the definition of the SAE reporting requirements even though they may be relevant in terms of participant safety. Examples are:

- new events related to the conduct of a trial or the development of an IMP likely to affect the safety of subjects, such as:
- a significant hazard to the participant population such as lack of efficacy of a medical device used for the treatment of a life-threatening disease,
- a major safety finding from a newly completed animal study
- a temporary halt of the clinical investigation for safety reasons if the trial is conducted with the same investigational medicinal products in another country by the same sponsor, recommendations of the Data and Safety Monitoring Board, if any, where relevant for the safety of participants,

These events/observations are not to be reported as SAEs, but they might require other action, such as:

- urgent safety measures and their notification
- substantial modifications
- early termination of the clinical investigation

It is also recommended that the sponsor informs the MHRA and the Ethics Committee of any safety issues which might materially alter the current benefit-risk assessment of an IMP while not falling within the actions listed above.

3.7 Sponsor and CI oversight of events

3.7.1 SAEs

The Sponsor and CI must demonstrate an oversight of all serious adverse events and device deficiencies reported in a CIMD. The form this oversight takes is dependent on the risk/benefit ratio of the device. The following will apply for all studies:

- The Sponsor and CI will review all SADEs and procedure related SAEs to determine expectedness of the event prior to the 7 day reporting deadline to the MHRS
- The Sponsor and CI must take into account whether an SADE indicates is a risk to all other users of the device

Where a CIMD involves a device with a high risk/benefit ratio then additional levels of review may be required and this will be documented within the protocol. For example, the CI may be required to review all SAEs received within a defined timeframe.

For most CIMDs, the Sponsor will prepare aggregate data of non-related SAEs for review by the TMG to determine any unanticipated increases in events. Where possible event rates will be determined by arm to ensure that unelated events are balanced across participant groups.

The CI may be asked to review unrelated SAEs individually and where required this will be documented within the protocol along with associated timeframes.

3.7.2 Device Deficiencies

The Sponsor, CI, and manufacturer (where involved) must demonstrate an oversight of device deficiencies occurring within the CIMD to determine if:

a: amendments need to be made to the CIMD
b: there is an issue with the device or the associated documentation that needs to be investigated and rectified
c: there is a need to recall medical devices

In addition, the Sponsor and/or CI may wish to upgrade the assessment of a device deficiency should they believe that it may have resulted in an SAE under different circumstances.

For most CIMDs the opinion of the local investigator will be used to determine whether a device deficiency is reportable to the MHRA. The Sponsor will prepare aggregate listings of reported device deficiencies for review by the TMG to determine if action is required.

For CIMDs involving an IMP, or those involving devices with a high risk/benefit ratio the PV and Safety Manager, and the Sponsor Clinical Trial Pharmacist, and CI will review individual DDs in a timely manner to determine if an event requires upgrading and reporting to the MHRA. This level of review may be added in response to comments from the MHRA or findings from the TMG.

The level of device deficiency review will be documented within the CIP,

3.7.3 Sponsor review of 2 day reports to the MHRA

Following notification of an SAE or DD that meets the 2 day reporting requirement a meeting should be convened as soon as possible and recruitment to the study should be temporarily suspended.

In the first instance the project manager, governance manager, PV and safety manager, research coordinator, chief investigator (and co-investigators where applicable), and where IMP is involved the Sponsor Clinical Trial Pharmacist, should attend to determine the course of action. Following this discussion the manufacturer, where applicable, should be notified to inform them of the Sponsors decision and involve them in any recalls etc. that are required. The full decision making process should be documented within the trial risk assessment.

3.8 Unblinding

Unblinding arrangements should be detailed in the clinical investigation plan. Treatment allocation in the course of a clinical investigation should only be unblinded if this is relevant to the safety of the participant.

The blind should be maintained for persons responsible for the ongoing conduct of the study (such as the management, monitors, investigators) and those responsible for data analysis and interpretation of results at the conclusion of the study. Unblinded information should only be accessible to those who need to be involved in the safety reporting or persons performing ongoing safety evaluations during the trial.

3.9 Informing investigators of USADEs

All study investigators must be informed of USADEs that have occurred in the trial. This should be done in a timely manner and in a concise and practical way to ensure that investigators are kept full informed of all safety information.

In a single centre UK study where the sponsor has no other studies running with the same device, all other investigators at that location should be informed.
In multi-centre trials all principal investigators within the clinical investigation must be informed.

The PV office will forward a copy of any USADE reports with an accompanying cover letter to the CI for onward distribution to co-investigators.

Any immediate safety concerns must be communicated to all concerned investigators in an expedited fashion.

3.10 Pregnancy

The decision regarding the collection of pregnancy data should be made at the time of the risk assessment. Where the CIMD involves an IMP, or the use of potentially biologically active substances or a reagent where the participant may be exposed. R&I Sponsor Pharmacy should take part in these discussions. In the event that there is a risk of teratogenic effects from a medical device then CTIMP safety reporting shall be used to collect the necessary safety data.

If the decision is made to collect pregnancy data then the following reporting requirements would apply.

The CI /PI must collect pregnancy information for female trial participants or female partners of male participants. This includes those who become pregnant while participating in a clinical investigation of a medical device or during a stage where the foetus could have been exposed to that device.

Any pregnancy occurring in a female participant or female partner of a male participant who becomes pregnant while participating in the clinical investigation will be reported by the CI/PI to the PV Office (sponsor) using the Pregnancy Reporting Form (available at http://www.glasgowctu.org/data/Pregnancy_Notification.pdf) within two weeks of the CI first becoming aware of the pregnancy. The participant will also be followed to determine the outcome of the pregnancy and follow-up information forwarded to the PV office. It may be necessary to monitor the development of the newborn for an appropriate period post-delivery. Any resulting SAEs should be reported as per SAE reporting procedure above.

3.11 Notifying NHS Trust/Health Board

Although not a requirement of the Clinical Trials Regulations, the Principal Investigator at each centre participating in a trial should ensure that their NHS Trust/Health Board are notified, in accordance with the Trust / Board clinical incident reporting policy, of any relevant patient safety incidents that occur in the clinical investigation..

4. Referenced Documents

- International Conference on Harmonisation (1996) Harmonised Tripartite Guideline for Good Clinical Practice
- The Scottish Executive Health Department Research Governance Framework for Health and Community Care (Second Edition, 2006)
- Medicines and Healthcare products Regulatory Agency, Good Clinical Practice Guide, UK: TSO, 2012.
- Medical Devices Regulations 2002 (SI 2002 No 618, as amended) (UK MDR 2002) incorporating
- Medical Devices Directive 93/42/EEC
- Active Implantable Medical Devices Directive 90/385/EEC
- In Vitro Diagnostic Medical Devices Directive 98/79/EEC.
- ISO14155 Clinical investigation of medical devices for human subjects - Good clinical practice (2020)
- Guideline 55.007A – PV Office Processing for Clinical Investigations of Non CE Marked medical devices

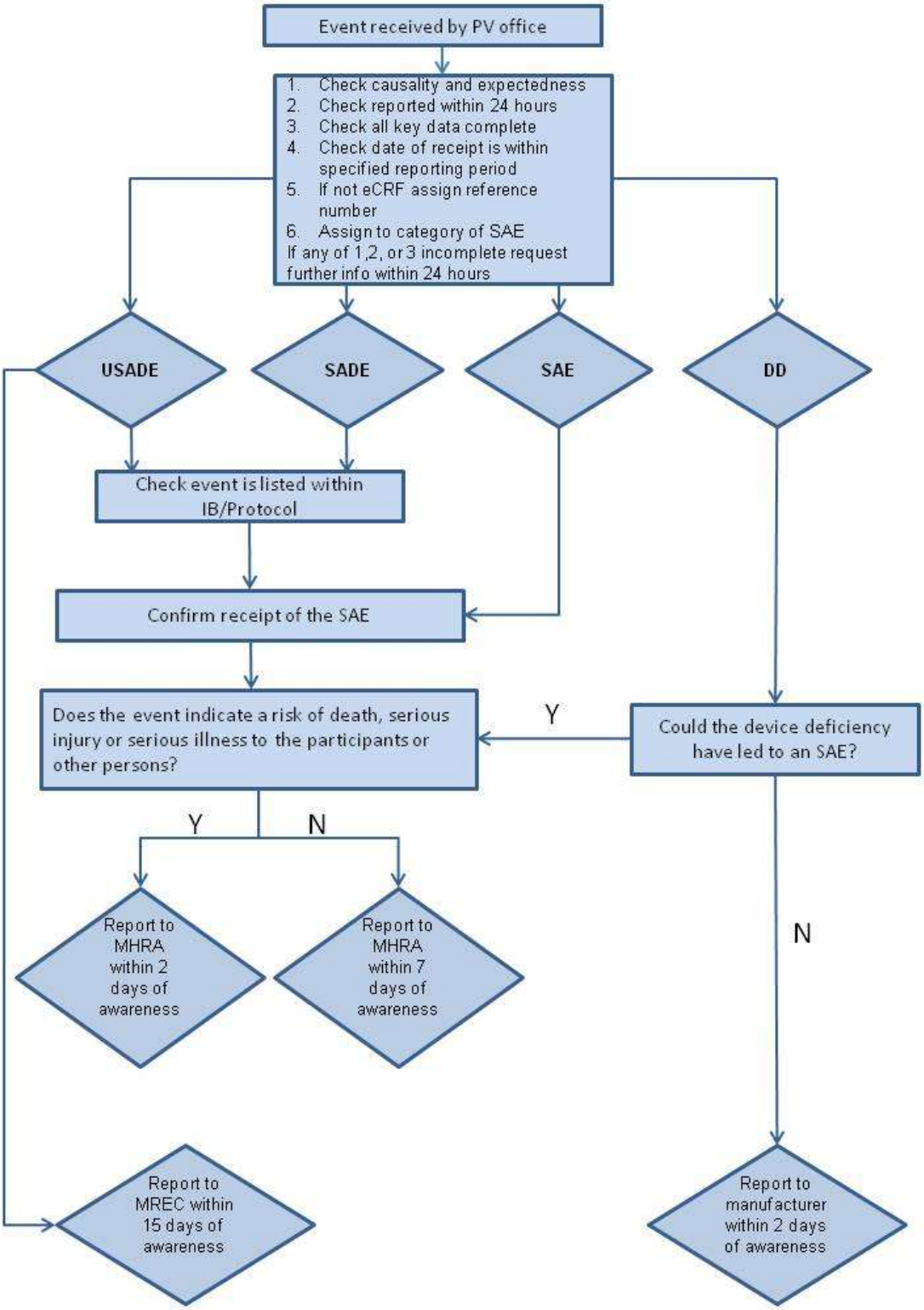
5. Related Documents

N/A

6. Document History

Version	Date	Description	Retrospective Implementation
1.0	15/07/2016	Release of first version	No
2.0	19/07/2018	Amended in line with PV Manager review of MEDDEV regulations.	No
3.0	11/02/2026	Amended in line with changes to regulations, updated sections around 2 days reports etc.	No

Appendix 1: Medical device reporting flowchart



The number of days listed in each scenario is calendar days.