Guideline number	**Guideline 55.007A**	Version	**3.0**
Title	**PV Office Processing for Clinical Investigations of Non CE/UKCA Marked medical Devices**		

1. Introduction

This guideline outlines the process to be followed when a Serious Adverse Event (SAE) report or Device Deficiency is submitted to the Pharmacovigilance (PV) Office for a sponsored clinical investigation of a medical device (CIMD)

All SAEs and a subset of device deficiencies in a CIMD must be reported to the Sponsor within 24 hours of awareness of the event, unless otherwise specified in the Safety Reporting Plan (Form 55.001A) or the study protocol.

Only device deficiencies that result in an SAE or that may have resulted in an SAE had circumstances been different are considered reportable to the Sponsor/MHRA. Other device deficiencies may be collected but these will be defined in the protocol and Safety Reporting Plan. These other device deficiencies if received should be filed but do not require onward reporting to the MHRA.

The Safety Reporting Plan should always be consulted when processing SAE or device deficiency reports as other study-specific arrangements may be in place.

2. PV Office Study Set-up

Following formal notification by the PV and Safety Manager, the PV Office will create a study folder in the relevant area of the filestore held at the Robertson Centre for Biostatistics (RCB)

The filestore folder should be named according to the following format:
ShortName_EudraCTNo_SponsorNo_CI Surname

3. SAE and Device Deficiency Receipt

Initial and follow-up SAE/reportable device deficiency reports can be submitted to the PV Office as follows:

- On a paper form (generic or study-specific) by email
- Using reporting procedures built into a study eCRF application

3.1 Paper reports:

a. Completed paper SAE and device deficiency report forms will be emailed to the PV Office
b. The handwritten report will be saved and reviewed by the PV Office following the processes detailed in sections 4 and 5
c. The PV Office will acknowledge receipt of the paper report by email. The acknowledgement email will include any queries resulting from the initial review by the PV Office and will be saved within the SAE folder as detailed in section 4
d. With regards to trials that use eCRF reporting procedures, the location staff responsible for submitting the report will be instructed to complete an SAE report via the trial eCRF

3.2 eCRF reports:

a. Where studies have reporting facilities built into an eCRF application, an automatic email alert will be triggered upon input of an SAE report by location staff. This alert is sent to the PV Office and relevant Sponsor and study personnel. The PV Office will save copies of the automatically generated emails in a chronological order, ensuring that the Report No is added to the file name to allow for easy identification
b. The PV Office will download a copy of the .pdf report from the eCRF application. This will be saved and reviewed by the PV Office following the processes detailed in sections 4 and 5

4. Tracking and Storage

All SAE/ device deficiency reports and related correspondence will be saved electronically in the relevant filestore folders.

For each parent SAE/device deficiency, a folder will be created as a sub-folder to the applicable participant number.

SAE reports will be saved as .pdf files and in a consistent format for each trial. At a minimum this must include the participant number and report number.

On receipt of an SAE report, a member of the PV Office will create an entry on the relevant SAE tracker spreadsheet. This entry will be attributed to the PV Office personnel handling the SAE and will be updated as and when additional information is provided.

5. PV Office SAE Review

5.1 Initial SAE Reports

PV Office personnel will perform the following checks on receipt of an initial SAE report:

a. If a paper report is received, are the trial and participant identifiers included on every page? If not, PV Office staff will contact the location and ask for the missing details to be added and a new copy sent through
b. Has the SAE been reported within 24 hours of the location becoming aware of the event? If not, PV Office personnel will remind the location of the need to report SAEs within 24 hours of awareness
c. Is there a diagnosis? If there is no text provided in the diagnosis field, or if the text indicates that the event is unknown or unconfirmed, this should be queried with location staff until resolution. Should any of the text require further review (i.e. the event appears to be complex, or does not appear to be consistent), the PV and Safety Manager (or Sponsor delegate) should be contacted
d. Has a narrative been provided and are any dates included consistent with date fields elsewhere on the report?
e. Has the seriousness criteria been assigned and is this consistent with the narrative?
f. Does the SAE have an outcome that is consistent with the seriousness criteria and narrative?
g. If the SAE states that the event is due to a device deficiency check to see if a device deficiency form has been submitted.

Should any of the above items be missing or inconsistent, the PV Office should query the information with the location personnel responsible for submitting the SAE and/or notify the PV and Safety Manager, as required.

Any event that has been reported as fatal of life threatening that has a causal relationship to the device must be immediately escalated to the CI and Sponsor PV and Safety Manager.

5.2 Initial Review of Causality and Expectedness

PV Office personnel will perform the following actions to ensure that the SAE is reviewed as per the regulatory requirements.

For all trials, causality **must** be provided by a local investigator, be it the Principal Investigator (PI) or another delegated investigator.

The Chief Investigator (CI)/Sponsor are responsible for the review of expectedness for all studies, the following steps should be followed:

a) Check for an assessment of causality by a local investigator at the location (PI or another clinician with relevant permissions). If this review has not been completed, this should be queried with the reporting location by the PV Office
b) Where an SAE has been assessed as related by the local investigator, the CI (or delegated clinician) should be notified of an event that requires their assessment of expectedness
c) In the event that the CI (or delegated clinician) does not review the SAE within 5 days from the date of Sponsor awareness, the PV and Safety Manager should be notified of an event that requires them to assess expectedness

Although the assessment of causality and expectedness should primarily be via the trial eCRF there may be circumstances where this is not possible, expediency is required, or where appropriate personnel cannot access the eCRF. In such cases relevant personnel may carry out their assessment

of causality and expectedness by email or, if required, via telephone. Where this occurs, the email or record of telephone report should be filed in the filestore alongside the relevant SAE. In such cases the person carrying out the assessment should also be reminded that they must also complete their assessment via the eCRF.

Should the local investigator assess an event as fatal of life threatening with a causal relationship to the device this must be immediately escalated to the CI and Sponsor PV and Safety Manager.

5.3 PV and Safety Manager

The PV and Safety Manager is responsible for:

a. For all events assigned as related, reviewing and confirming the expectedness assessment against the approved Reference Safety Information (RSI). Any inconsistencies should be raised with the investigator carrying out the assessment of expectedness. Should the PV and Safety Manager be unable to assess expectedness within to the required timelines (e.g. due to holiday or absence), the PV Office will contact the CI (or their delegate) to review and confirm the expectedness assessment of any related events unless the CI has already carried out the assessment of expectedness
b. Assessing events related to the medical device to determine whether the event indicates the need to take action to prevent harm to other users of the device and escalating to the CI if required.
c. Reviewing SAEs escalated by the PV administrators for narrative consistency and data discrepancies, including whether the SAE contains multiple events which require splitting
d. Reviewing SAEs escalated by the PV administrators to ensure that they meet protocol defined reporting requirements
e. Where an event is assigned as related to the device and unexpected as per the RSI (i.e. potential USADE), the PV and Safety Manager should discuss this with the reporting investigator. In all cases, should the event be classified as a USADE following these discussions, it should be reported to the REC

5.4 CI (or Clinical Delegate)

The CI (or their clinical delegate) is responsible for:

a) Assignment of expectedness for related SAEs in line with the protocol and Safety Reporting Plan
b) Providing a second opinion of causality where requested or where this is a requirement specified within the Safety Reporting Plan and trial protocol
c) Review of all SADEs/USADEs prior to submission to the MHRA and REC
d) Following escalation from the Sponsor PV and Safety Manager or PV administrators: Assessing events related to the medical device to determine whether the event indicates the need to take action to prevent harm to other users of the device

5.5 Follow-up SAE Reports

Upon receipt of a follow-up report for an SAE, the following checks should be made:

For events assessed by the local investigator as related:

a. Has there been a change in the assessment of causality from related to unrelated by the local investigator?
b. Have new event terms been added or has the event term changed significantly?

Should any of the above conditions be met, the follow-up report will require the expectedness of the event to be reassessed as per section 5.2. The SAE should be processed according to section 5.1 and within the timelines set out in section 6.

For events assessed by the local investigator as unrelated:

a. Has the assessment of causality changed from unrelated to related?

Should the above condition be met, the follow-up report will require reassessment of causality and expectedness as per section 5.2 and should be processed as per section 5.1 within the timelines set out in section 6.

Should the local investigator reassess an event as fatal of life threatening with a causal relationship to the device this must be immediately escalated to the CI and Sponsor PV and Safety Manager.

6. PV Office Review of Device Deficiencies,

6.1 Initial Reports

PV Office personnel will perform the following checks on receipt of an initial SAE report:

a. If a paper report is received, are the trial and participant identifiers included on every page? If not, PV Office staff will contact the location and ask for the missing details to be added and a new copy sent through
b. Has the type of deficiency been completed?
c. Is the device deficiency considered reportable to the Sponsor? i.e. did the event result in an SAE or could it have resulted in an SAE had circumstances been different. If the relevant questions have not been answered this should be chased. The event should be treated as reportable until evidenced otherwise.
d. If Sponsor reportable has the device deficiency (been reported within 24 hours of the location becoming aware of the event? If not, PV Office personnel will remind the location of the need to report device deficiencies within 24 hours of awareness
e. Is there a description of the deficiency? If there is no text provided this should be queried with location staff until resolution. Should any of the text require further review (i.e. the deficiency appears to be complex, or does not appear to be internally consistent), the PV and Safety Manager (or Sponsor delegate) should be contacted
f. Are any dates included consistent with date fields elsewhere on the report?
g. Does the device deficiency have an outcome that is consistent with the narrative?
h. If the device deficiency report indicates that the event resulted in an SAE check to see if the SAE has been reported.

Should any of the above items be missing or inconsistent, the PV Office should query the information with the location personnel responsible for submitting the SAE and/or notify the PV and Safety Manager, as required.

Device deficiencies that result in death, or that are life threatening must be immediately escalated to the CI and Sponsor PV and Safety Manager.

6.2 PI review of Device Deficiencies

For all reportable device deficiencies, review **must** be provided by a local investigator, be it the Principal Investigator (PI) or another delegated investigator. The timeline for this review is not defined within the regulation but where the event resulted in an SAE the timelines for SAE review should be followed i.e. sign off within 7 days.

6.3 Follow-up Device Deficiency Reports

Upon receipt of a follow-up report for a device deficiency a check should be performed to identify whether the status of the event has changed from non-reportable to reportable i.e. has the event now resulted in an SAE or could it have resulted in an SAE had circumstances been different?

If so, the follow-up report will require reassessment as per section 6.2. The SAE should be processed according to section 6.1 and within the timelines set out in section 6.1

Device deficiencies that result in death, or that are life threatening must be immediately escalated to the CI and Sponsor PV and Safety Manager.

7. PV Office Timelines for PI/CI Review

All SAEs and device deficiencies that may have potentially led to an SAE are participant to expedited reporting to the MHRA irrespective of causality within 7 days of sponsor awareness. SAEs and Device Deficiencies that indicate the need to take urgent action in order to prevent harm to other participants or users must be reported to the MHRA within 2 days. Furthermore any USADEs are reportable to the REC within 15 days. As such, all events should be reviewed by the PI and CI/Sponsor within 7 days of Sponsor awareness.

8. Reporting of SAEs/Device Deficiencies to the MHRA

The following events should be reported to the MHRA within 7 days of sponsor awareness of the event:

- Any SAE irrespective of causality
- Any device deficiency that is assessed as potentially resulting in an SAE
- Any follow ups to already reported events.

The following events should be reported to the MHRA within 2 days of Sponsor awareness of the event

- Any SAE (or device deficiency that resulted in an SAE) that indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it.

After processing the SAE, device deficiency report that may have potentially led to an SAE, or a follow up to these events a report of summarising reports received to date must be sent to the MHRA within seven days using the MEDDEV 2.7/3 SAE reporting table, or the MDCG 2020-10/2 SAE reporting form filed within the relevant filestore.

The report should completed by adding a line to the bottom line of the table, entering the relevant information and updating the No. of Patients enrolled to date, Date of report and No. of Invest. Devices used to date.

Each event should be listed individually and where follow up information is provided the existing line is updated to capture the further information.

Events are classified as a (added i.e. a new report), m (modified i.e. contains follow up information), and u (unchanged).

Where data has been updated from a previously submitted template the change should be marked in bold and highlighted in yellow.

At the time of submission a PDF copy of the relevant event will be attached to the MORE report

This listings are cumulative i.e. new reports and follow ups are added to a previously sent report. For each submission SAE reporting template should be saved in the filestore in the format 10-2 MDCG 2020-10-2 CI Summary Safety Report Form TRIALNAME YYMMDD v1.0.xlsx or MEDDEV 2_7_3_V1 TRIALNAME YYMMDD.xlsx depending on format used.

9. Submission of events to the MHRA via the MORE portal

All reportable events are submitted via the Manufacturers Online Reporting Environment (MORE) found here: https://more.mhra.gov.uk/login.

Once logged in events are submitted as follows:

1. Select “Reports”
2. Select “New report”
3. On the Select Report screen, pick “SAE” from the pull down menu
4. Click “Select”
5. Complete the Administrative Information Screen as follows:
    a. For the field GB or NI clinical investigation select “GB only” unless there are locations in Northern Ireland
    b. For the field Title of Clinical Investigation enter the full trial name
    c. For the field Report Type select “Other”
    d. For the field Reporting Period Quarterly select relevant quarter.
    e. For the field Year enter the year the event was reported
    f. For the field IRAS Project ID this can be found on the REC approval letter
    g. For the field MHRA Clinical investigation number enter the CTA/CI number found on the MHRA approval letter, Safety Reporting Plan, this will also be contained within the relevant field of the MEDDEV/MDCG form
    h. For the field Submitting Organisation Name enter NHS Greater Glasgow and Clyde
    i. For the field MS+NCA Reference Numbers for all participating Countries enter the CTA/CI number found on the MHRA approval letter and Safety Reporting Plan. If multiple countries add each reference number.
    j. For the field Reference Member State select GB
    k. For the field No. of patients enrolled to date total. Enter the total number of patients recruited
    l. Foe the field No. of patients enrolled to date per country. Enter the number of patients per country
    m. For the field No. of Invest. Devices to date total. Enter the number of patients on the investigative arm.
    n. For the field No. of Invest. Devices to date per country. Enter the number of patients on the investigative arm per country.
    o. For date of report field enter the date submitted to the MHRA.
    p. For device details select the Device Type as per the field device type on the MEDDEV 2.7/3 SAE reporting table, or the MDCG 2020-10/2 SAE reporting form

   q. For Device model enter the name of the device as per the MEDDEV 2.7/3 SAE reporting table, or the MDCG 2020-10/2 SAE reporting form
6. Under the attachments section select “Add” under the field Primary Attachment
7. Locate the version of the MEDDEV 2.7/3 SAE reporting table, or the MDCG 2020-10/2 SAE reporting form to be reported and copy the file name. This should be pasted into the File Name field.
8. Click “Select File”, select file to upload and choose Add.
9. Under the attachments section select “Add” under the field Supplementary Attachment
10. Locate the PDF copy of the SAE or device deficiency report to be submitted and copy the file name, this should be pasted into the File Name field.
11. Click “Select File”, select file to upload and choose Add.
12. Press Validate and Send
13. Go back to the dashboard and select Report Management.
14. The submitted report should be listed. Click on the report.
15. On the new pop up window, select Export PDF and file this in the filestore in the relevant location alongside the submitted report.

Note: There is no difference between submitting initial and follow up reports. The same process applies.

10. Submission of unexpected serious adverse device effects to the REC

Where an event is considered related to the medical device, or any trial specific procedures and has been assessed as unexpected by the CI/Sponsor the event must be reported to the REC within 15 days of Sponsor awareness. The SAE form should be transcribed onto the Non-CTIMP safety report to REC form found here:

https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/

Form: (Link may be participant to change)
https://www.hra.nhs.uk/documents/2466/Non_CTIMP_Safety_Report_Form_Accessible_September_2020_AA.odt

The CI should review and sign the form and this should be submitted to the REC. Contact details for the REC can be found within the Safety Reporting plan.

A copy of the non CTIMP safety report form should be saved within the filestore alongside the submitted SAE forms etc.

Guideline signatories

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Document history

Version	Date	Description	Retrospective Implementation
1.0	28/04/2021	Version 1.0 creation.	No
2.0	01/06/2023	Number corrected from 55.001H to 55.007A. Updated in line with change of system to MORE, added REC reporting	No
3.0	11/02/2026	Amended to include 2 day report processes and include updates to MHRA reporting processes.	No