1. Introduction

This Standard Operating Procedure (SOP) describes the process for identifying, documenting and reporting all Adverse Device Effects, Device deficiencies and Unexpected Adverse Device Effect where the University Hospitals of Leicester are acting as a HOST organisation or a research SITE and where the UHL is **NOT** the Sponsor.

1.1)
This SOP must not be used where UHL is acting as the research Sponsor. In this case SOP S-1041 UHL must be used (Trust reference - B16/2021)

1.2)
The outcome is that the UHL fulfills the requirements as a HOST Organisation or research SITE to identify, document and report all categories of Serious Adverse Device Effects and Device Malfunctions.

2. Scope

This SOP applies to all staff and external individuals involved in research activity HOSTED by UHL or where UHL is a research SITE.

3. Definitions

3.1) Adverse Event (AE)

Is defined as "any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment."

3.2) Serious Adverse Event (SAE)

In medical device studies a Serious Adverse Event (SAE) is defined by ISO14155:2011 guidelines for medical device studies as an untoward occurrence in a trial subject that:

- Led to a death
- A life-threating illness or injury, or
- A permanent impairment of a body structure or a body function
- In patient hospitalisation or prolonged in-patient hospitalisation
- Medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
- Led to foetal distress, foetal death or a congenital abnormality or birth defect.

(3.2.1)
NOTE 1: This also includes device deficiencies that might have led to a SAE if:

- Suitable action has not been taken
- Intervention has not been made
- If circumstances had been less fortunate

(3.2.2)
NOTE 2: A planned hospitalisation for a pre-existing condition, or procedure required by the Clinical Investigation Plan (CIP) without a serious deterioration in health is not considered to be a serious adverse event.

3.3) Adverse Device Effect (ADE)

An adverse device effect (ADE) is an adverse event that is deemed to be **related** to the use of an investigational medical device. 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.

(3.3.1)

An ADE includes any event that is a result of use error or intentional misuse. Use error refers to an act or omission of an act that results in a different device response than intended by the manufacturer or expected by the user. An unexpected physiological response of the subject does not in itself constitute a use error.

3.4) Serious Adverse Device Effect (SADE)

A SADE is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

3.5) 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 CIP or in the risk assessment.

3.6) Unanticipated Serious Adverse Device Effect (USADE)

A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the Risk Assessment and/or Investigator's

3.7) Device Deficiency

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.

3.8) Device Malfunction

Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or Clinical Investigation Plan (CIP).

(3.8.1)

Although these are the standard definitions of serious adverse events, the reporting requirements of each study may differ, dependent on the nature of the study and the patient population. Specific protocol and / or Sponsor reporting instructions should be followed.

4. Reporting Procedure

4.1) AE/ADE

AEs/ADEs must be documented in accordance with the Sponsor requirements. They should always be documented in the Case Report Form (CRF) and patients' medical records and observed to ensure that they do not escalate to a serious adverse event.

(4.1.1)

All serious adverse device effects and deficiencies in studies HOSTED by UHL or where UHL is the research SITE must be reported to the Sponsor in accordance with the Sponsor SOP.

5. SADE/USADE Reporting

5.1) HOSTED Non CE/UKCA studies where UHL is a research SITE

It is expected that all SADEs/USADEs be reported to the Sponsor within 24 Hours of being aware of the event in accordance with the Sponsor SOP.
UHL Research office requires an annual line listing of all events. A template is available for completion if the Sponsor is unable to produce a suitable listing.
(Appendix 1 SAE/SADE line listing and Appendix 2 Device Deficiency Line Listing)

(5.1.1)
Annual line listings should be completed and sent to the R&I Office on or within 28 days of the anniversary of UHL R&I Approval. UHL R&I will remind the study teams when this is due. Reminders will commence with effect from 1st January 2021. The line listing appended to an Annual Report can be sent provided that the information is UHL Specific. There is no requirement for an additional report to be generated.

(5.1.2)
In cases where there have been no SADEs or device deficiencies reported within the 12 month period, a NULL report for the study must be submitted.

(5.1.3)
It is the responsibility of the Principal Investigator (PI) at UHL to ensure that R&I Office is notified if there are unacceptable patterns of SADEs or device deficiencies emerging from a protocol which have the potential to affect the care or safety of the patient.

(5.1.4)
If a Sponsor takes the decision to prematurely stop or suspend a study, the PI must notify the R&I Office within 24 hours of notification.

5.2) HOSTED Studies for CE/UKCA marked Medical Device Studies where UHL is the research SITE

It is expected that all SADEs/USADEs or Medical Device Deficiencies be reported to the Sponsor in accordance with the Sponsor SOP.

(5.2.1)
UHL Research office requires an annual line listing of all events. A template is available for completion if the Sponsor is unable to produce a suitable listing.
(Appendix 1 SAE/SADE line listing and Appendix 2 Device Deficiency Line Listing)

(5.2.2)
Annual line listings should be completed and sent to the R&I Office on or within 28 days of the anniversary of UHL R&I Approval. UHL R&I will remind the study teams when this is due (Appendix 3). Reminders will commence with effect from 1st January 2022. The line listing appended to an Annual Report can be sent provided that the information is UHL Specific. There is no requirement for an additional report to be generated.

(5.2.3)
In cases where there have been no SADEs or device deficiencies reported within the 12 month period, a NULL report for the study must be submitted.

(5.2.4)
It is the responsibility of the Principal Investigator at UHL to ensure that R&I Office is notified if there are unacceptable patterns of SADEs or device deficiencies emerging from a protocol which have the potential to affect the care or safety of the patient.

(5.2.5)
If a Sponsor takes the decision to prematurely stop or suspend a study, the PI must notify the R&I Office within 24 hours of notification.

5.3) Device Deficiency / Malfunction

Where a device deficiency or Malfunction has occurred at the UHL site that requires the quarantine of the device/s; the device must not be returned to the manufacturer until the MHRA has been given the opportunity to carry out/complete an investigation, if required by the MHRA. In addition, the device should not be: All material evidence i.e. devices/parts removed, replaced or withdrawn from use following an incident, instructions for use, records of use, repair and maintenance records, packaging

5.4) Delegation of Authority Log

The Principal Investigator (PI) is responsible for the review and sign off of all serious adverse events and serious adverse device effects.
After discussion and agreement by the Sponsor; additional medically qualified individuals to be delegated the responsibility for reviewing and signing off the SADE and Device Deficiency forms. UHL requires that adequate processes are in place to ensure cover for SAE/SADE where either planned or unplanned leave is taken by the Principal Investigator.

(5.4.1)
This must be recorded on the Delegation of Authority Log which must be stored in the Investigator Site File (ISF).

6. Unexpected Serious Adverse Device Effect

Unexpected serious device effects are a subset of serious adverse device effects which are subject to strict mandatory reporting timelines to the Medicines and Healthcare products Regulatory Agency (MHRA) and the main Research Ethics Committee (REC).

(6.1)
In a study hosted by UHL or where UHL is a research SITE, it is expected that the Sponsors SOP will be followed.

(6.2)
As for all SADEs, a USADE must be reported to the Sponsor with immediate effect and within 24 hours of the research team becoming aware of it. The responsibility to report to the MHRA and the main REC is that of the Sponsor. In all cases of USADEs at UHL, notification must be made to the R&I Office within 24 hours of becoming aware of the USADE, and R&I kept informed of any action required, taken or proposed by any of the Investigators or the Sponsor.

7. R&I Office Process

As part of the Capacity and Capability review a Study Support Officer will add a reminder for ‘SADE, Device Deficiency Line Listing due’ to the Global Calendar in EDGE. The due date is the anniversary of HRA or where applicable MHRA (CTA) (whichever is the soonest) approval. The Global Calendar Entry will be categorised as ‘Audit’. An additional Global Calendar date will be added 31 days prior to the due date as ‘SADE, Device Deficiency Line Listing Due Notification’. NB as this process has been introduced in 2020 all studies active and reporting SADEs/Device Deficiencies on 1st January 2021 onwards will have the calendar entries added along with the relevant workflow. The delay

is to allow time to add the workflows and to accommodate additional pressure on resource due to COVID19.

(7.1)
When the notification appears on the calendar reminders listing a standard email Appendix 3 will be sent to the Research Team, copied to the PI requesting that the line listing for UHL be returned by the due date. If the Line Listing is not received a reminder email will be sent on the due date (Appendix 4)with a further follow-up sent 14 days later (Appendix 5).

(7.2)
If a Line listing is not received on the third request the Non-compliance SOP C-2013 UHL will be implemented at a Major finding.

(7.3)
Once received an acknowledgement email will be sent – Appendix 6 and completion of EDGE Workflow 'RICORP SAE Line Listing (Host) will be started. The Line Listing will be added to the files in Red Level of EDGE for the relevant study.

(7.4)
The Line Listing will be checked for completeness by the UHL Clinical Trials Monitor and training team. If complete, the Line Listing will be added to the next monthly R&I Governance Meeting Agenda, and in parallel sent to the Directors of R&I for a medical oversight review. If not complete a request to amend the document will be made with a deadline 7 days later (appendix 7). It is likely that there will be multiple reports received during the month and a single collated report will be produced. Any queries or points for clarification will be directed to the PI and Research Team as appropriate.

(7.5)
Where there are no further queries or points for clarification the reports will be filed within the meeting papers and the workflow completed. Where further clarification is required, this will be followed up with the PI and research team to conclusion. The Workflow will be updated and finalised as relevant.

8. Urgent Safety Measures (USM)

The Sponsor and Investigator may take appropriate urgent safety measures to protect clinical trial subjects from any immediate hazard to their health and safety. The measures must be taken immediately; Sponsor, MHRA, REC & HRA approvals are not required before implementation. However, they must be informed in writing, in the form of a substantial amendment within three days. It is expected that the R&I Office be notified of any USMs, the immediate action required, undertaken and any amendments following the USM.

9. Responsibilities

	Responsibility	Undertaken by	Activity
1	PI/Delegated individual	PI/Delegated individual	Report all serious adverse device effects or deficiencies to the Sponsor (except those identified as exempt)
2	PI/Delegated individual	PI/Delegated individual	Provide an annual line listing of SADEs/ device deficiencies to the R&I Office
3	PI/Delegated individual	PI/Delegated individual	Identify subjects by trial study number and initials, this information should be recorded on all reports. No personal identifiable data should be recorded on the SADE form or supporting documentation

10. Who Guideline Applies To

All staff within UHL and external to UHL who are delivering research.

11. Education and Training

The SOP is detailed so the process can be clearly followed. No flowchart is provided / required.

12. Education and Training

None

13. Monitoring Compliance

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
Sponsor Audit	Randomly chosen for audit	Carolyn Maloney	As and when	A report will be produced

14. Supporting Documents and Key References

SOP C-2031 Appendices 1, 2, 3, 4, 5, 6 & 7

SOP S-1041 (Trust reference B16/2021)

15. Key Words

Research, Innovation, EDGE, Safety Reporting, AE, SAE, SADE, USADE, ASADE, CE, UKCA

16. Contact and Review Details

CONTACT AND REVIEW DETAILS	
Guideline Lead (Name and Title) Lisa Wann R&I manager	**Executive Lead** **Medical Director**
Details of Changes made during review: **Review and update**	

17.

This line signifies the end of the document

17.1)

This table is used to track the development and approval and dissemination of the document and any changes made on revised / reviewed versions

17.2)

DEVELOPMENT AND APPROVAL RECORD FOR THIS DOCUMENT		
Author / Lead Officer:	Carolyn Maloney	**Job Title:** Head of Research Operations
Reviewed by:	UHL R&I Governance Meeting	
Approved by:	Professor Nigel Brunskill	**Date Approved: PGC 16.4.21**

REVIEW RECORD			
Date	**Issue No.**	**Reviewed By**	**Description Of Changes (If Any)**
Nov 2020	1	CM,LW,JJ	Update to new trust template

DISTRIBUTION RECORD:			
Date	**Name**	**Dept**	**Received**

Appendix 1 Medical Device SADE Line Listing

SAE/SADE Line Listing for UHL Hosted Medical Device Studies

EDGE Number: **IRAS Number:** **Site: Study Title:**

Patient Study ID	Date of Event	*SAE or Device Deficiency	Description of event	Relationship to procedure 1- Related 2- Not related	Relationship to device 1- Related 2- Not related	Expectedness Assessment 1-Expected 2-Unexpected	Outcome 1- Resolved 2- Resolved with sequelae 3- Ongoing 4-Fatal 5-Unknown	Date report sent to Sponsor

*Where Device deficiency is reported Appendix 2 must be completed and submitted with this report

Appendix 2 Device Deficiency Line Listing

Device Deficiency Line Listing for UHL Hosted Medical Device Studies

EDGE Number: **IRAS Number:** **Site Study Title:**

Patient Study ID	Date of Deficiency DD/MM/YYYY	Description of Deficiency	Indicate if Deficiency concerned: 1- Identity 2- 2. Quality 3- 3. Durability 4- Reliability 5- 5. Safety 6- Performance	Indicate if the deficiency is due to: 1. Malfunction 2.User error 3. Labelling	Deficiency outcome/action taken	Date report sent to Sponsor

Appendix 3 Template SADE Line Listing Initial reminder Email

Template email text to request Annual SADE Line Listing for UHL Hosted studies

Dear (add name of PI)

According to our records, the anniversary for HRA approval or Clinical trials Authorisation (MHRA Approval) (delete as appropriate) for your study is soon due:

EDGE ID XXXXXX

Study Title xxxxxxxx

UHL R&I will require a line listing of all Serious Adverse Device Effects and Device Deficiencies that have occurred at this site in the past 12 months. The Sponsor will need to submit an annual report to the regulatory authorities and part of this will include a complete listing of all SADEs and Device Deficiencies. Please would you liaise with them to extract the UHL SAEs in advance of the due date of XX/XX/XX.

Further detail is available in the SOP C-2031 UHL

Kind Regards

Appendix 4 Template SADE Line Listing second reminder email

Template email text for Second reminder Annual SADE and Device Deficiencies Line Listing for UHL Hosted studies

Dear (insert name of PI)

We wrote to you on xx/xx/xx requesting a line listing of all Serious Adverse Device Effect and Device Deficiencies for your study:

EDGE ID xxxxx

Study Title xxxxx

You may have overlooked the email (attached for your information)

I'd be grateful if you would give this your urgent attention.

Kind Regards

Dear (add name of PI)

According to our records, the anniversary for HRA approval or Clinical trials Authorisation (MHRA Approval) (delete as appropriate) for your study is soon due:

EDGE ID XXXXXX

Study Title xxxxxxxx

UHL R&I will require a line listing of all Serious Adverse Events that have occurred at this site in the past 12 months. The Sponsor will need to submit an annual report to the regulatory authorities and part of this will include a complete listing of all SAEs. Please would you liaise with them to extract the UHL SAEs in advance of the due date of XX/XX/XX.

Further detail is available in the SOP C-2002 UHL

Kind Regards

Appendix 5 Template SADE Line Listing Final Reminder email

Template email text for final reminder Annual SADE and Device Deficiencies Line Listing for UHL Hosted studies:

Dear (insert name of PI)

We wrote to you on xx/xx/xx reminding you of previous request on xx/xx/xx for a line listing of all Serious Adverse Device Effects and Device Deficiencies for your study:

EDGE ID xxxxx

Study Title xxxxx

You may have overlooked the emails (attached for your information)s but now require that you urgently give the request your attention.

Please respond with the line listing by XX/XX/XX. Please note that failure to comply with these requests may require that the UHL SOP C-2013 UHL Non Compliance be implemented at a Major finding which may affect your research applications in the future.

Kind regards

Appendix 6 Template Acknowledgement SAE Line Listing Email

Acknowledgement email SADE Line Listing for Hosted studies

Dear (insert name of PI)

Thank you for providing the SADE/ device deficiency Line Listing for your study:

EDGE ID: xxxxxx

Study Title: xxxxxxx

We will be in touch if we have any queries or need further clarification and will set a reminder to request similar next year, unless you notify us in the meantime that the study is no longer reporting SAEs or has closed.

Kind Regards

Appendix 7 Template SAE Line Listing request for further information email

Email request for further Information/ clarification with regards to submitted SADE Line Listing

Dear (insert name of PI)

Thank you for providing the SADE Line Listing for your study:

EDGE ID: xxxxxx

Study Title: xxxxxx

There are some omissions on the listing which need your urgent attention. Please would you make the following amendments and return to me by XX/XX/XX (7 days)

(List details of further information/clarification required)

Kind Regards