Gloucestershire Hospitals
NHS Foundation Trust

SOP 19: Periodic Safety reporting to Regulatory Authorities

SOP reference:	SOP 19	
Version:	3.0	
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	18/10/2023	
Implementation date of current version:	22/11/2023	
Date of Review:	22/11/2025	

IT IS THE RESPONSIBILITY OF ALL USERS OF THIS SOP TO ENSURE THAT THE CORRECT VERSION IS BEING USED

All staff should regularly check the Research & Development Webpage for information relating to the implementation of new or revised versions. Staff must ensure that they are adequately trained in the new procedure and must make sure that all copies of superseded version are promptly withdrawn from use unless notified otherwise by the SOP Controller.

The definitive version of all Gloucestershire Hospitals NHS Foundation Trust SOPs appear online. If you are reading this in printed form, check that the version number and date below is the most recent one as shown on the R&D website:

Research at our hospitals (gloshospitals.nhs.uk)

The Gloucestershire Hospitals NHS Foundation Trust wishes to acknowledge York Hospitals NHS Foundation Trust and University Hospitals Bristol NHS Foundation Trust who gave permission to use their templates in the development of these SOPs.

Version History Log

This area will be updated with details of all changes made to the SOP whether due for full review or not.

Version	Details of Change	Date Implemented
1.0	Original SOP	09/02/2017
2.0	Rebranding to GHNHSFT, updating of contact details and reference documents	31/03/2018
3.0	Updated SOP title Removal of Urgent Safety measures information into a new separate SOP Removal of end of trial report as this is information is contained within SOP TD 04 End of Trial Procedures for both sponsored and hosted trials Added information regarding submission to HRA Information regarding devices Removal of appendices Inserted information about a shortened DSUR Removal of SOP categories and change of reference codes	22/11/2023

This SOP will be reviewed every two years unless changes to any relevant legislation require otherwise

Glossary

APR	Annual Progress Report
CI	Chief Investigator
CTA	Clinical Trials Application
CWoW	Combined Ways of Working
DIBD	Development International Birth Date
DSUR	Development Safety Update Report
GHNHSFT	Gloucestershire Hospitals NHS Foundation Trust
HRA	Health Research Authority
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
ISF	Investigator Site File
MHRA	Medicines and Healthcare Products Regulatory Agency
REC	Research Ethics Committee
RSI	Reference Safety Information
SARs	Serious Adverse Reactions
SmPC	Summary of Product Characteristics
TMF	Trial Master File

Contents

1. Introduction, Background and Purpose

Pharmacovigilance is the science of collecting, monitoring, researching, assessing and evaluating information on the adverse effects of medicines, with a view to identifying information about potential new hazards and preventing harm to subjects. Pharmacovigilance is of the utmost importance in clinical trials to ensure both the safety of the trial subjects and the safety of current and future patients.

Effective pharmacovigilance facilitates an ongoing assessment of the risk-benefit ratio of a trial in relation to the Investigational Medicinal Product (IMP) /device and the trial procedures. Emerging safety data allow the sponsor to safely manage the trial by introducing amendments to the protocol and providing updated information to the investigators and subjects where necessary and allows them to assess whether it continues to be safe to conduct the trial.

After a research study has received all necessary approvals for it to proceed, various bodies and organisations will be interested in its progress. In many (but not all) cases, progress reports must be submitted to regulatory bodies including the Research Ethics Committee (REC), the Medicines and Healthcare Products Regulatory Agency (MHRA) and the Health Research Authority (HRA).

2. Who should use this SOP

This SOP should be used by all staff involved in research studies sponsored or co-sponsored by the Trust, in addition to GHNHSFT R&D Department.

Section 5 describes how and when elements of this SOP may also be applicable to externally-sponsored studies hosted by the Trust.

3. When this SOP should be used

This SOP should be used when the Trust is the sponsor or co-sponsor. In addition, see Section 5 for applicability to externally-sponsored studies hosted by the Trust.

The ‘sponsor representative’ for the Trust is a member of the R&D Governance Department.

4. Development Safety Update Report (DSUR) for CTIMPs only

For all CTIMP studies, Reporting requirements differ depending on the type of trial, as follows:

A shortened DSUR can be submitted for:

- Individual trials authorised under the Notification Scheme which are not part of a multi-study development programme (i.e., Type A trials)
- Phase 4 national (UK only) trials of licensed products, that commanded a low fee from the MHRA, and where all participants have completed treatment and are only in follow up.

These DSURs can be submitted using the HRA Progress Report Template. A covering letter must be included that indicates an Annual Progress Report (APR) is being submitted in lieu of a full DSUR, and must include the EudraCT number and Clinical Trial Application (CTA) reference number. A list of all serious adverse reactions should be included in section 6 of the report.
A full DSUR must be submitted for other trials.

4.1 Background to the DSUR

The DSUR is intended to be a common standard for periodic reporting on drugs under development (including marketed drugs that are under further study) among the International Conference on Harmonisation (ICH) regions.

The DSUR is intended to present a comprehensive annual review and evaluation of pertinent safety information collected during the reporting period related to a drug under investigation, by:

- examining whether the information obtained by the sponsor during the reporting period is in accord with previous knowledge of the investigational drug's safety;
- describing new safety issues that could have an impact on the protection of clinical trial subjects;
- summarising the current understanding and management of identified and potential risks;
- providing an update on the status of the clinical investigation/development programme and study results.

A DSUR should be concise and provide information to assure regulators that sponsors are adequately monitoring and evaluating the evolving safety profile of the investigational drug. All safety issues discovered during the reporting period should be discussed in the text of the DSUR; however, it should not be used to provide the initial notification of significant new safety information or provide the means by which new safety issues are detected.

4.2 Responsibility and timelines for submission of DSUR

Responsibility for preparation and submission of the DSUR within the specified timescales is delegated to the CI. Reports must be provided at yearly intervals for the duration of the trial, from trial authorisation until termination.

The 'Development International Birth Date' (DIBD) determines the start of the annual reporting period for the DSUR. This date is the Sponsor's first authorisation to conduct a clinical trial in any country worldwide. The data lock point of the DSUR should therefore be the last day of the one-year reporting period.

The DSUR must be submitted to all concerned regulatory authorities **no later than 60 calendar days** after the DSUR data lock point.

The due date of the DSUR must be clearly documented in the Investigator Site File (ISF)/Trial Master File (TMF).

4.3 DSURs for Combination Therapies

In general, a single DSUR should be prepared for clinical trials involving a fixed combination product (i.e., a product consisting of at least two active ingredients in a fixed dose that is administered in a single dosage form). If the sponsor is also conducting clinical trials with individual component(s) of the fixed combination product, separate DSUR(s) should be submitted for each component

4.4 Reference Safety Information

The Investigator's Brochure (IB) in effect at the start of the reporting period is the reference document to determine whether the information received during the reporting period remains consistent with previous knowledge of the investigational drug's safety profile. The IB version number and date must be stated in the DSUR. When an IB is not required for a study, the Summary of Product Characteristics (SmPC) should serve as the reference safety information and version information given similarly.

The Reference Safety Information (RSI) is a list of medical events used for the assessment of the expectedness of 'suspected' Serious Adverse Reactions (SARs) that occur in clinical trials. The RSI is a specific section in the IB or the list of expected adverse reactions contained in the Summary of Product Characteristics (SmPC) , and is submitted as part of the CTA application.

The IB in effect at the start of the reporting period should serve as the reference for safety information. The DSUR should clearly indicate the version number and date of the IB used for this purpose.

The RSI in the IB or SMPC if used instead, must be reviewed by the CI at least once a year i.e., at the end of the DSUR reporting period. This RSI review should be clearly documented in the Trial Master File. If there are any changes to the RSI,

a substantial amendment is required to be submitted to the MHRA and approved before it is implemented in the trial.

4.5 Completing the DSUR

Comprehensive details of what to include in a full DSUR can be found in the ICH guidelines. Please see references.

4.6 Submitting the DSUR

The CI must send the DSUR to the following:

- Emailed to the Sponsor, GHNHSFT R&D Governance department ghn-tr.glos.rdsu@nhs.net to agree content
- Upload to the MHRA via the MHRA submission online portal. Please contact the GHNHSFT R&D department for MHRA submission account registration
- Email the executive summary to the Research Ethics Committee (REC) which gave a favourable opinion of the research (the main REC)
- For studies using the Combined Ways of Working (CWoW) system the DSUR can be submitted via the reporting section in the Integrated Research Application System (IRAS). This should also include a cover letter. If preferred, it is also possible to submit DSURs via the Human Medicines Portal. Please note DSURs should either be submitted for a project in IRAS or on the Human Medicines Portal, not both.

The MHRA and HRA websites must be checked for up to date submission requirements prior to the time of DSUR submission.

A copy of the signed DSUR must be retained in the TMF together with evidence of submission.

5. Annual Progress Report (APR) (all studies)

Progress reports to REC are required for studies that are;

- More than two years in duration
- Research tissue banks
- Research databases

There is no requirement for a progress report for:

- Proportionate review studies (of any duration)
- Studies lasting two years or less. If an amendment is made to extend a study beyond two years, progress reports are required to be submitted from the point the study is extended.

Progress reports must be submitted to the REC which granted the favourable opinion and is the responsibility of the CI. The due date for reports is 12 months after the date on which the favourable opinion was given and each year thereafter until the end of the trial.

The CI will email an electronic copy to the REC within 30 days of the end of the reporting period. The report should be submitted to the Sponsor, GHNHSFT ghn-tr.glos.rdsu@nhs.net for review and approval before being submitted to the REC.

The HRA has produced templates which must be used, available via the HRA website:

Progress reports - Health Research Authority (hra.nhs.uk). There are different templates for different study types.

A copy of the signed APR must be retained in the TMF together.

6. Device Trial Summary Reports

For device trials, requirements for submitting summary reports to the MHRA are detailed in the letter of no objection from the MHRA. The letter outlines the format these reports should follow, as well as the required frequency for submitting these reports. The responsibility for submitting these reports to the MHRA will be agreed contractually and will usually be that of the device manufacturer.

7. References:

www.hra.nhs.uk/resources/during-and-after-your-study/nhs-rec-annual-progress-report-forms/

E2F Step 5 Note for guidance on development safety update report (europa.eu)

Safety and progress reports (CTIMPs) procedural table - Health Research Authority (hra.nhs.uk)

https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/progress-reports/