Standard Operating Procedure			**55.002**
Preparation and submission of the Development Safety Update Report (Glasgow Clinical Trials Unit)			
Version	5.0		
Prepared by	Marc Jones	Signature	Date
Approved by	Caroline Watson	Signature	Date
Released by	Julie Brittenden	Signature	Date

1. SOP Category

NGS GG&C Sponsor Pharmacovigilance

2. Staff Category

Pharmacovigilance Office
R&D Governance
Clinical Trials Pharmacist
R&D Coordinators (Sponsor Representative)
Project Managers
Clinical Trials Monitors
Chief Investigators

3. Scope

This procedure applies to NHS GGC staff with sponsor responsibilities.
Chief Investigators will be provided with a copy of this SOP for their information.

4. Purpose

The purpose of the SOP is to describe the procedure for the preparation and submission of the Development Safety Update Report (DSUR) for CTIMPs sponsored by NHS GGC or co-sponsored with the University of Glasgow and supported by the Glasgow Clinical Trials Unit (GCTU) Pharmacovigilance Office. Procedures for sponsored/co-sponsored CTIMPS supported by the CRUK-CTU Pharmacovigilance Office are described in CRUK-CTU SOPs.

The Medicines for Human Use (Clinical Trials) Regulations 2004 transposed EU Directive 2001/20/EC into UK law and set out specific requirements for pharmacovigilance in clinical trials of investigational medicinal products (CTIMPs). This includes the requirement for the sponsor of a CTIMP to submit an annual list of suspected serious adverse reactions and a report on the safety of the subjects in the trial to the licensing authority (Medicines and Healthcare products Regulatory Agency (MHRA) in the UK) and the Research Ethics Committee (REC) which approved a trial as soon as is practicable (and within 60 days) of the anniversary of the issue of the Clinical Trials Authorisation.

All submissions of annual safety reports must be in the DSUR format.
ICH guideline E2F on development safety update report provides detailed guidance of the format and content of the report

The Sponsor of a CTIMP is responsible for the preparation, content and submission of the DSUR. The Sponsor can delegate the writing of the DSUR to a 3rd party (e.g. a pharmaceutical

company or contract research organisation) but a detailed contractual agreement must be in place.

In CTIMPs sponsored by NHS GGC or co-sponsored with the University of Glasgow, the delivery of pharmacovigilance activity within the trial is delegated to the Chief Investigator (CI). This includes the submission of the DSUR.

5. Procedure

5.1 Periodicity of the DSUR

5.1.1 Start of reporting

The start of the annual reporting period for the period for the DSUR is the month and date of the Development International Birth Date (DIBD). This is the date of the sponsor's first authorisation to conduct a clinical trial using the IMP in any country worldwide. For CTIMPs sponsored by NHS GGC or co-sponsored with the University of Glasgow this will be the Clinical Trials Authorisation (CTA) date for the trial.

If a CTIMP has not started by due date of the report, only an explanatory letter to the MHRA/REC is required.

If a CTIMP is completed within a time period shorter than 1 year, (for example a Phase I trial) a DSUR does not have to be produced.

If a CTIMP is suspended on the due date of the DSUR, a report must still be submitted.

5.1.2 Data lock point

The data lock point of the DSUR is the last day of the one-year reporting period.

5.1.3 End of reporting

For CTIMPs sponsored by NHS GGC or co-sponsored with the University of Glasgow DSURs will be submitted until the End of Trial as detailed in the study protocol. In most cases it will be the date of the last visit of the last patient undergoing the trial. Any exceptions to this should be justified in the protocol. e.g. for a licensed IMP where follow-up is until death the MHRA will consider a request for no DSUR to be submitted during the follow-up period.

Note: Other Competent Authorities may not support this option

There is no requirement to submit a final safety report with the end of trial declaration.

5.2 DSURs for combination therapies.

DSURs are Investigational Medicinal Product (IMP) specific. In trials involving multi-drug therapy the Sponsor, in conjunction with the CI, should select the most appropriate format for the report on a trial specific basis. The rationale for the selected approach should be included in the report. Further guidance is available in ICH E2F: Note for guidance on development safety update reports

5.3 DSURs for trials with the same IMP

In CTIMPs sponsored by NHS GGC or co-sponsored with the University of Glasgow DSURS will be trial specific. Where more than one trial is being conducted with the same IMP an individual DSUR will be submitted for each trial in line with the CTA date for that trial. A justification for this approach should be included in the report.

5.4 DSURS for blinded trials

Where unblinded information is included in a DSUR e.g. Line listings with details of unblinded SUSARS, unblinded personnel must only review an initial draft of the DSUR, prior to the addition of any unblinded information. The final review of the DSUR, with unblinded information included, must only be made by unblinded personnel.

A separate final blinded copy will be prepared and forwarded to the CI for filing in the CI Site File.

5.5 Content and format of a DSUR

The recommended content and format of a DSUR and guidance on the contents of each section is included in the ICH guideline E2F.

The DSUR should be concise and provide information to assure the regulators that the sponsor is adequately monitoring and evaluating the evolving safety profile of the investigational drug.

All sections should be completed. In situations where the sponsor does not have access to the information to be included in specific sections (e.g., sponsor-investigators might not have information on manufacturing issues, non-clinical data, and marketing status), this should be stated in the DSUR.

The recommended table of contents for the DSUR is:

Title page
Executive Summary
Table of Contents
1. Introduction
2. Worldwide Marketing Approval Status
3. Actions Taken in the Reporting Period for Safety Reasons
4. Changes to Reference Safety Information
5. Inventory of Clinical Trials Ongoing and Completed during the Reporting Period
6. Estimated Cumulative Exposure
   - 6.1 Cumulative Subject Exposure in the Development Programme
   - 6.2 Patient Exposure from Marketing Experience
7. Data in Line Listings and Summary Tabulations
   - 7.1 Reference Information
   - 7.2 Line Listings of Serious Adverse Reactions during the Reporting Period
   - 7.3 Cumulative Summary Tabulations of Serious Adverse Events
8. Significant Findings from Clinical Trials during the Reporting Period
   - 8.1 Completed Clinical Trials
   - 8.2 Ongoing Clinical Trials
   - 8.3 Long-term Follow-up
   - 8.4 Other Therapeutic Use of Investigational Drug
   - 8.5 New Safety Data Related to Combination Therapies
9. Safety Findings from Non-interventional Studies
10. Other Clinical Trial/Study Safety Information
11. Safety Findings from Marketing Experience
12. Non-clinical Data
13. Literature
14. Other DSURs

15. Lack of Efficacy
16. Region-Specific Information
17. Late-Breaking Information
18. Overall Safety Assessment
    - 18.1. Evaluation of the Risks
    - 18.2 Benefit-risk Considerations
19. Summary of Important Risks
20. Conclusions

Appendices to the DSUR:

1. Investigator's Brochure
2. Cumulative Table of Important Regulatory Advice
3. Status of Ongoing and Completed Clinical Trials
4. Cumulative Summary Tabulations of Demographic Data
5. Line Listing of Serious Adverse Reactions*
6. Cumulative Summary Tabulations of Serious Adverse Events
7. Scientific Abstracts (if relevant)
8. Regional Specific Information

5.6 Reference Safety Information

The Reference Safety Information (RSI) is contained within the approved Investigator Brochure (IB) or Summary of Product Characteristics (SmPC) in place at the start of DSUR reporting period.

The RSI in effect at the start of the DSUR reporting period serves as RSI during the reporting period. A pdf of the SmPC or IB is be added as an appendix to the DSUR.

If there are changes to the RSI during the reporting period these should be listed in the report. Any change to the RSI within an IB or SmPC is considered a substantial amendment. The substantial amendment must be approved before the new RSI can be implemented.

5.7 Preparation and Submission of the DSUR

See also: Guideline 55.002A: PV Office - Creation and submission of Development Safety Update Reports

A template for the DSUR for CTIMPS sponsored by NHS GGC or co-sponsored with the University of Glasgow is available (Form 55.002A). This template should be used for the preparation of the DSUR for all sponsored/co-sponsored trials (where the preparation of the report has not been delegated to another organisation). The PV Manager will liaise with the CI (or designee) and other colleagues as appropriate (e.g. Clinical Trials pharmacist, R&D Coordinator, study data manager) and coordinate the process for the preparation and submission of the DSUR.

- The anniversary of the CTA data will be the data lock point for the report
- On (or as soon as possible after) this date the PV office will collate the information for the report (e.g. study details, IMP details, listings of SAEs and SARs)
- A draft report will be created using the GCTU DSUR template
- The draft report will be forwarded to the Chief Investigator
- The Chief Investigator or designee will review the information in the draft report and will complete the required sections.
- Once the report is finalised and signed, a copy will be returned to the PV Manager
- The PV Manager will submit the report on behalf of the CI to the MHRA and the Ethics Committee with the required documentation.
- The PV Manager will forward a copy of the report and the associated documentation to the CI and Sponsor's representative.

6. Referenced documents

1. The Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended) - SI. 2004 No. 1031

2. ICH guideline E2F: Note for guidance on development safety update reports

http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/development-safety-update-report.html (Accessed03/06/2015)

3. Communication from the Commission — Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3') (2011/C 172/01)
http://ec.europa.eu/health/files/eudralex/vol-10/2011_c172_01/2011_c172_01_en.pdf (Accessed03/06/2015)

4. Medicines and Healthcare products Regulatory Agency (MHRA). Clinical trials for medicines: Submit development safety update reports (DSURs)
https://www.gov.uk/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#l9
(Accessed 03/06/2015)

5. THE RULES GOVERNING MEDICINAL PRODUCTS IN THE EUROPEAN UNION VOLUME 10 - GUIDANCE DOCUMENTS APPLYING TO CLINICAL TRIALS QUESTIONS & ANSWERS VERSION 10.0 (APRIL 2012)
http://ec.europa.eu/health/files/eudralex/vol-10/ctqa_v10.pdf (Accessed 03/06/2015)

7. Related documents

Form 55.002A: Development Safety Update Report (DSUR) Template
Guideline 55.002A: PV Office - Creation and submission of Development Safety Update Reports

8. Document History

Version	Date	Description
1.0	22/11/07	Release of Version 1 (for review)
1.1	19/05/08	Released to staff
1.2	18/06/09	Addition of Annual Safety Report Template as Appendix 1
1.3	12/10/10	Annual Safety Report template updated Addition of reference to guideline 18.003 Document template updated
2.0	15/05/13	Title amended Amended to reflect requirements of Development Safety Update Report Annual Safety Report template replaced with DSUR Template
3.0	15/12/15	Update to new SOP template. Change to Staff Category and Scope. Addition of section regarding DSURs for trials with the same IMP and for blinded trials. Minor changes to section 5.7. References updated
4.0	15/07/2016	Reviewed and released as part of SOPs reorganisation process. SOP category changed and SOP renumbered (previously 18.003). 'Prepared by' changed to Caroline Watson, Approved by' and 'Released by' changed to Julie Brittenden. References to other documents updated to reflect new structure. No changes to content.
5.0	09/10/19	Minor changes relating to change in PV office organization. DSUR prepared by PV Manager rather than PV office. Removed DSUR Checklist.