Preparation and Submission of Development Safety Update Reports (DSURs)

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Owner	King's Health Partners Clinical Trials Office
Originally Prepared by	Jackie Pullen
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Approved by	Ann-Marie Murtagh, Director KHP-CTO
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Relevant regulations/legislation/guidelines	Statutory Instrument 2004 no 1031 Statutory Instrument 2006 no 1928 *(as amended from time to time)*

CHANGE HISTORY			
Date	Version	Change details	Approved by
24th Jun 2013	2.0	Amended to reflect re-branding of JCTO to KHP-CTO and to state that KHP-CTO will be responsible for submission of DSUR to REC.	Jackie Powell
16th Jul 2014	2.1	Correction of administrative error relating to DSUR reporting time, from V1.0 to V2.0 of this document.	Jackie Pullen
31st Oct 2016	3.0	Scheduled review, update to Glossary, clarification of RSI and administrative amendments	Jackie Pullen

19th Apr 2018	4.0	A section has been added regarding the process if no patients have been enrolled onto the trial. 4.1 updated for multinational trials. Updated glossary terms for Reference Safety Information. Addition of MedDRA to glossary.	Jackie Pullen
5th November 2018	5.0	Minor amendment to include trials managed by KHP-CTO Amendment to describe how the SAE line listing will be produced	Jackie Pullen
14th May 2021	6.0	Amendment to include reporting requirements to Trials under the Type A Notification Scheme	Jackie Pullen
3rd April 2024	7.0	Updated as per MHRA Inspection finding: Reference Safety Information clarifications and update procedures added	Ann-Marie Murtagh
22 October 2025	8.0	Removed requirements for Annual Progress Reports (APR)	Ann-Marie Murtagh

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1.0 PURPOSE

This SOP describes the standardised process for preparing and submitting Development Safety Update Reports (DSURs) to regulatory authorities and Research Ethics Committees (RECs) for clinical trials sponsored by King's Health Partners (KHP) organisations or managed by KHP-CTO. The DSUR provides a comprehensive, annual evaluation of the safety profile of an investigational medicinal product (IMP) under investigation, meeting regulatory requirements in ICH regions.

2.0 SCOPE

Applies to all CTIMPs sponsored by one or more KHP organisations or where KHP-CTO undertakes sponsor responsibilities

3.0 DEFINITIONS

Full glossary provided in APPENDIX 1. Key definitions include:

Term	Definition
DSUR	A common standard for periodic reporting on drugs under development (including marketed drugs that are under further study) among the ICH regions. In the EU it replaces the annual safety report.
DIBD	Development International Birth Date — date of the first authorisation to conduct a clinical trial of a specific investigational medicinal product in any country worldwide.
IMP	Investigational Medicinal Product - pharmaceutical form of an active substance or placebo being tested, or used as a reference in a clinical trial
RSI	Reference Safety Information — defines which reactions are expected for the Investigational Medicinal Product (IMP) being administered to subjects participating in a clinical trial.
Licensing Authority	The government body responsible for the grant, renewal, variation, suspension and revocation of licences, authorisations, certificates, designations, opinions] and registrations under the Clinical Trial Regulations. The Medicines and Healthcare Products Regulatory Agency is the licensing authority for the UK.

4.0 PROCEDURE

4.1 Reporting Timelines

- The DIBD is used to determine the start of the annual reporting period for the DSUR.
- The start of the annual period for the DSUR is the month and date of the DIBD.
- The data lock point of the DSUR will be the last day of this one-year reporting period. The Sponsor can designate this as the last day of the month prior to the month of the DIBD.
- For multinational trials, the DIDB date is the sponsor's first authorisation to conduct a clinical trial in any country worldwide. The start of the annual period for the DSUR is the month and date of the DIBD.
- Submission deadline: within 60 calendar days after DLP to all relevant licensing authorities and RECs.
- DSUR submission continues annually until End of Trial Notification is acknowledged.

4.2 DSUR and IMPs

- DSURs are generally IMP-specific.
- Rationale for combined or separate DSURs must be documented.
- All Serious Adverse Reactions (SARs) — including those involving comparators, placebos, or non-IMPs — must be included, with processes designed to ensure proportionality, traceability, and data integrity

The following table provides examples of strategies for preparation of DSURs for multi-drug therapies. (*See section 4.2*):-

Table 1

Multi-drug therapy used in clinical trial(s)	DSUR
Investigational drug (A) + marketed drug(s) (X, Y, Z)	Either a single DSUR focusing on (A+X+Y+Z) or A single DSUR focusing on (A) including data on the multi-drug therapy
Two investigational drugs (A) + (B)	Either a single DSUR focusing on (A + B) or Two separate DSURs (A) and (B), each including data on the multi-drug therapy

Two (or more) marketed drugs as an investigational drug combination (X, Y, Z)	A single DSUR focusing on the multi-drug therapy

4.2.1 Unlicensed IMPs

- Where an unlicensed IMP is being developed by one or more Partner Organisations, one DSUR will be submitted annually for the IMP.
- This DSUR will cover IMP and safety data from all trials being conducted within the reporting period.
- In these instances, cumulative safety information should be included in the DSUR for any previous studies of the same product.

4.3 Reference Safety Information

- The expectedness of an adverse reaction is determined in the reference safety information (RSI).
- RSI must be agreed during trial setup and approved by the licensing authority.
- The same RSI is used for the entire DSUR reporting period for SAE line listings.
- RSI changes are substantial amendments requiring approval before implementation.
- Significant safety updates should be submitted immediately; minor updates may align with the next DSUR cycle.

4.4 Responsibilities

- Sponsor: Overall responsibility for DSUR content and submission.
- Quality Manager (or delegate): Oversees preparation, selects reporting strategy, signs DSUR.
- CRA: Collates pharmacovigilance data, prepares draft DSUR, ensures timely submission.
- CI: Reviews and approves DSUR content.
- CTA: Monitors upcoming DIBDs, coordinates timelines.
- The recommended format and content of the DSUR, including table of contents, section numbering, and content of each section, can be found in section *5.1 Related Templates*. For each heading where information is available, the information should be presented concisely; when no information is available or a DSUR section is not applicable, this should be stated.

4.5 Special Cases

- No Patients Recruited: Submit 'No Patients Recruited' letter in place of DSUR.
- Type A Notification Scheme Trials: Full DSUR required.

4.6 Submission

- Submit DSUR or No Patients Recruited letter to licensing authority and REC (with standard cover page) no later than 60 days after the Data Lock Point.
- DSURs for trials using combined review will be submitted within IRAS and do not need to be reported separately to the REC.
- File approved DSUR in Trial Master File (TMF) and Sponsor File

5.0 RELATED TEMPLATES

5.1 KHP-CTO DSUR Guidance Template

5.2 REC safety report submission cover page

5.3 No Patients Recruited Letter Template

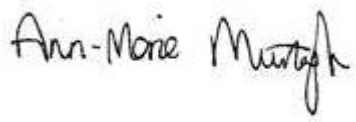
6.0 RELATED DOCUMENTS

6.1 EMA: ICH guideline E2F on development safety update report

6.2 European 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 Guidance 2011/C/172/01')

6.3 Clinical Trial Facilitation Group (CTFG) - Q&A document - Reference Safety Information

7.0 APPROVAL AND SIGNATURE



Ann-Marie Murtagh
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Date: 22//10/2025

Appendix 1

GLOSSARY

Adverse Event (AE) - 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.

Blinding - The practice of keeping the trial participants, care providers, those collecting data, and sometimes even those analysing data unaware of which intervention is being administered to which participant. Blinding is intended to prevent bias on the part of study personnel.

Chief Investigator (CI) –The overall lead researcher for a research project (Outside the UK the term Coordinating Investigator or Investigator may be used). In addition to their responsibilities if they are members of a research team, chief investigators are responsible for the overall conduct of a research project

Clinical Research Associates (CRAs) – A professional who organises and monitors clinical trials to assess the safety and effectiveness of new or existing drugs, medical devices, or treatments. CRAs play a vital role in ensuring that clinical trials are conducted ethically, safely, and in accordance with established protocols and regulations. CTO CRA's monitor compliance, for clinical trials where regulatory oversight has been delegated to the KHP CTO.

Clinical Trial of an Investigational Medicinal Product (CTIMP) - a type of clinical trial that investigates the safety and efficacy of a drug or other medicinal product that is not yet authorised for general use. It can also involve studying how the drug is absorbed, distributed, metabolised, and excreted, or identifying any adverse reactions.

Development Safety Update Report (DSUR) - A common standard for periodic reporting on drugs under development (including marketed drugs that are under further study) among the ICH regions. In the EU it replaces the annual safety report.

Development International Birth Date (DIBD) - Date of the Sponsor's first authorisation for conducting an interventional clinical trial in any country.

Data Lock Point – Day prior to the DIBD. The Sponsor can designate this as the last day of the month prior to the month of the DIBD.

Investigational Medicinal Product (IMP) - means a pharmaceutical form of an active substance or placebo being tested, or used as a reference in a clinical trial. This includes a medicinal product which has a marketing authorisation but is, for the purposes of the trial –

1. used or assembled (formulated or packaged) in a way different from the form of the product authorised under the authorisation,
2. used for an indication not included in the summary of product characteristics under the authorisation for that product, or used to gain further information about the form of that product as authorised under the authorisation.

King's Health Partners (KHP) - King's Health Partners brings together research, education and clinical practice across three NHS Foundation Trusts - Guy's and St Thomas', King's College Hospital and South London and Maudsley - and a world-leading university, King's College London.

King's Health Partners Clinical Trials Office (KHP-CTO) - Established in 2006 by King's College London, Guy's & St Thomas' NHS Foundation Trust, South London and Maudsley NHS Foundation Trust and King's College Hospital NHS Foundation Trust to provide a streamlined approach for all aspects of trial administration. The King's Health Partners CTO has two sections: the Commercial Team which provides a single interface for those wishing to conduct trials sponsored by the pharmaceutical industries and the Quality Team that supports investigators at King's Health Partners institutions who undertake CTiMP trials where King's Health Partners are the sponsor or co-sponsor

KHP-CTO Quality Team - Comprises the Quality Manager, Clinical Research Associate(s), Clinical Trial Administrator(s), Systems Executive and Training Executive (s)

Licensing Authority – the government body responsible for the grant, renewal, variation, suspension and revocation of licences, authorisations, certificates, designations, opinions] and registrations under the Clinical Trial Regulations. The Medicines and Healthcare Products Regulatory Agency is the licensing authority for the UK.

MedSciNet's Active Trial Tracking System (MATTS) –The electronic Clinical Trial Portfolio Management System used by the KHP CTO.

Medical Dictionary for Regulatory Activities (MedDRA) - A clinically validated international medical terminology dictionary (and thesaurus) used by regulatory authorities for the purposes of adverse event classification.

Medicines & Healthcare products Regulatory Agency (MHRA) - the UK's regulatory body responsible for ensuring the safety and effectiveness of medicines, medical devices, and blood components for transfusion. It operates as an executive agency sponsored by the Department of Health and Social Care.

Principal Investigator (PI) - the individual primarily responsible for the conduct of a research study at a specific research site

Quality Assurance (QA) - Systems and processes established to ensure that a trial is performed, and the data are generated in compliance with GCP.

Reference Safety Information (RSI) - Defines which reactions are expected for the Investigational Medicinal Product (IMP) being administered to trial participants participating in a clinical trial.

Research Ethics Committee (REC) – An independent body, consisting of healthcare professionals and non-medical members, whose responsibility is to protect the rights, safety and well-being of human trial participants involved in a trial and to provide public assurance of that protection by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial participants and obtain their informed consent.

Standard Operating Procedures (SOPs) - detailed, written instructions to achieve uniformity of the performance of a specific function, SOPs are the basis against which Quality Systems and Processes are conducted and monitored.

Trial Master File (TMF) - a standard filing system which allows the effective storage and location of essential documents, that is the large volume of regulatory documents and approvals needed for clinical research. The filing system can be in the form of a single project file or a number of files/filing cabinets, depending on what is deemed most appropriate for a particular clinical trial given its size and complexity. The regulatory documents and approvals within the TMF will be maintained alongside case report forms and source documentation.

The Regulations - The Medicines for Human Use (Clinical Trial) Regulations 2004 which transposed the EU Clinical Trials Directive into UK legislation, as Statutory Instrument 2004 no 1031**.** An amendment to implement Directive 2005/28/EC was made to the Regulations as Statutory Instrument 2006 no 1928. As amended from time to time.