Preparation and Submission of Development Safety Update Reports (DSURs)

Policy Details	
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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

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1.0 GLOSSARY

Adverse Event (AE) - Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Blinding - A procedure in which one or more parties involved in the conduct of a clinical trial are unaware of the treatment assignment(s).

Chief Investigator (CI) - A Registered Physician, Dentist, Pharmacist or Registered Nurse who has overall responsibility for the conduct of the trial.

Clinical Research Associates (CRAs) – Part of the KHP-CTO Quality Team. Ensure compliance with the Regulations, GCP and SOPs, by monitoring clinical trials.

Clinical Trial - Any investigation in human subjects, other than a non-interventional trial, intended to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal product or to identify any adverse reactions to one or more such products and to study absorption, distribution, metabolism and excretion in one of more such products with the object of ascertaining the safety or efficacy of those products.

Competent Authority (CA) – Regulatory Agency responsible for regulating clinical trials within an EU Member state.

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.

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 Academic Health Science Centre is a pioneering collaboration between one of the King's College London (University) and three of London's most successful NHS Foundation Trusts – Guy's & St Thomas'. King's College Hospital and the South London & Maudsley.

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.

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

MATTS – MedSciNet's Active Trial Tracking System. An electronic Clinical Trial Portfolio Management System.

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) - UK Competent Authority responsible for regulation of clinical trials.

Principal Investigator (PI) - A Registered Physician, Dentist, Pharmacist or Registered Nurse who has responsibility for the conduct of the trial at a host 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 subjects participating in a clinical trial..

Research Ethics Committee (REC) – An independent body in a Member State, consisting of healthcare professionals and non-medical members, whose responsibility is to protect the rights, safety and well-being of human subjects 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 subjects 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 - Statutory Instrument 2004/1031 – the Medicines for Human Use (Clinical Trials) Regulations 2004 which transposed the European Union Directive 2001/20/EC for Clinical Trials into UK law effective from the 1st May 2004 and any amendments that may arise.

2.0 BACKGROUND AND PURPOSE

The purpose of this SOP is to describe the process for preparing and submitting DSURs to regulatory competent authorities and RECs for clinical trials sponsored by one or more King's Health Partners Organisations, or clinical trials where the sponsor responsibilities are managed by the KHP-CTO.

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 ICH regions. US and EU regulators consider that the DSUR, submitted annually, would meet national and regional requirements currently met by the US IND Annual Report and the EU Annual Safety Report, respectively, and will therefore take the place of these existing reports.

The main objective of a DSUR is to present a comprehensive, thoughtful annual review and evaluation of pertinent safety information collected during the reporting period related to a drug under investigation, whether or not it is marketed, by:

(1) Examining whether the information obtained by the sponsor during the reporting period is in accord with previous knowledge of the investigational drug's safety.

(2) Describing new safety issues that could have an impact on the protection of clinical trial subjects.

(3) Summarising the current understanding and management of identified and potential risks; and

(4) Providing an update on the status of the clinical investigation/development programme and trial results.

3.0 SCOPE

All clinical trials sponsored by one or more King's Health Partners Organisations, or clinical trials where the sponsor responsibilities are managed by the KHP-CTO, i.e. End of Trial Notification has not been submitted to the regulatory competent authority, after the 1st September 2011.

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.

The DSUR will be submitted to all applicable regulatory competent authorities in countries where the trial is being conducted and approving RECs no later than 60 calendar days after the DSUR data lock point.

A DSUR must be submitted during every 12-month reporting period until the End of Trial Notification has been submitted to the competent authority of the member state where the trial is being conducted.

4.2 DSUR and IMPs

The purpose of the DSUR is to be IMP specific however, this may not always be the case as the King's Health Partner Organisations acting as Sponsor will not be the Marketing Authorisation holder of the IMP. For UK trials the MHRA have agreed that non-commercial organisations who are not developing the drug may submit separate reports.

The rationale for separate DSURs should be provided in each report.

A separate DSUR for a comparator, placebo or non-IMP is **not** required. However, all SARs must be listed in the DSUR including those relating to comparators, placebos and non-IMPs.

4.2.1 Products with a Marketing Authorisation

4.2.1.1 Single IMP, Single Therapeutic Area, Multiple Trials

In general, a single DSUR will be prepared for each IMP under investigation in clinical trials; however, if a single IMP is being investigated within the same disease area in multiple trials, one DSUR will cover all trials and the DIBD will be the *first* CTA authorisation of these trials.

4.2.1.2 Single IMP, Multiple Therapeutic Areas, Multiple Trials

One DSUR for an IMP that is being investigated in multiple trials with different patient populations and in different therapeutic areas may be produced and submitted or an individual DSUR may be submitted for each trial.

4.2.1.3 Combination Products

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.

For trials involving multi-drug therapy, i.e., combinations of drugs that are not fixed, the sponsor can prepare either:

(1) A DSUR for the multi-drug therapy, or

(2) DSUR(s) for one or more of the individual components; in this case information on the multi-drug therapy trials can be included in the DSURs of one or all of the components.

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

4.2.2 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).

During trial set-up the Reference Safety Information (RSI) is to be determined by the CI and approved by the Competent Authority (MHRA for UK); this could be presented either as information in the Protocol, in the Investigator's Brochure or in the Summary of Product Characteristics (SmPC). The Reference Safety Information will be defined in the Trial Protocol.

If the RSI is contained within the IB, the IB should contain a clearly identified section to this effect. This section should include information (e.g.in table form) on the frequency, severity and nature of the expected serious adverse reactions (please see KHP-CTO SOP 10.0 CREATION & MAINTENANCE OF INVESTIGATOR BROCHURE).

Where trials are being conducted in more than one country, and the IMP marketing authorisations have resulted in different SmPCs, the Sponsor should select the most appropriate SmPC, with reference to the subject safety, as RSI. A single DSUR should be produced for the trial as a whole and submitted to all Competent Authorities where the trial is running (if applicable as per the in-country guidelines).

Usually, a single document should serve as the RSI. However, in certain circumstances, it might be appropriate to use more than one reference document to support the DSUR (e.g., for a DSUR providing information on an investigational drug used in combination and as monotherapy).

The RSI in effect at the start of the reporting period must be used to determine whether the information received during the reporting period remains consistent with previous knowledge of the safety profile of the investigational drug. Section 7.1 of the DSUR should clearly indicate the version number and date of the IB or SmPC used for this purpose.

The RSI for any IMP involved in a clinical trial must stay consistent during each DSUR reporting period for the purpose of SAE line listing in the DSUR. The RSI may change during the conduct of a clinical trial. This is a substantial amendment that should be submitted to the regulatory competent authority for approval. For the purpose of SUSAR reporting, the version of the RSI at the moment of occurrence of the SUSAR should be used to assess expectedness. Thus, a change of the RSI impacts on the number of adverse reactions to be reported as SUSARs.

If the RSI information in the IB or SmPC has been revised during the reporting period, the Sponsor should provide a copy of the current (used for that reporting period) and, if applicable, the new (to be used for the next reporting period) version of the IB or SmPC as an attachment to the DSUR, listing any significant safety-related changes in the relevant section of the DSUR. The RSI in effect at the start of the reporting period serves as the RSI during the reporting period for SAE line listings in the DSUR.

If there are any changes to the RSI the updated RSI must be submitted to the regulatory competent authority for approval before it can be used for the purposes of expedited reporting. If an update to the RSI occurs mid DSUR period, and after a risk assessment the changes to the RSI are deemed minimal or not relevant to the study population, the submission to the competent authority can be delayed to be in line with the next DSUR submission.

If updates are important to patient safety, submit a substantial amendment immediately, but state the RSI will not be implemented until start of next reporting period.

4.4 Responsibility for Preparation & Submission of DSUR

4.4.1 Responsibility

The trial Sponsor is considered responsible for the preparation, content and submission of a DSUR.

4.4.2 Preparation

The KHP-CTO Quality Manager (or delegate), in conjunction with the relevant CI's involved in the use of an IMP will select the most appropriate option *(as detailed in Table 1)* for their trial(s) and drug(s) under investigation.

At the beginning of each calendar month, the KHP-CTO Clinical Trial Administrator (CTA) (or delegate), will alert the Quality Manager and trial CRA(s) to which DIBDs will occur in that month. The PV data for the DSUR will be collated by the KHP-CTO CRA from the Pharmacovigilance database after the Data Lock Point has occurred. The DSUR will be reviewed and approved by the Chief Investigator(s).

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.

The final DSUR will be signed by the Quality Manager (or delegate).

For Trials under the Type A notification scheme a short-format DSUR may be submitted as an alternative to producing a full DSUR (see related templates 5.4). This will be in the format of Health Research Authority Annual Progress Report. The cover letter will indicate that this is an Annual Progress Report (APR) in lieu of a full DSUR and will include the EudraCT number and CTA reference number. A list of all serious adverse reactions will be included in section 6 of the APR.

4.4.3 No Patients Recruited Letter

If a trial has received a Clinical Trial Authorisation (CTA) approval and no patients have been enrolled on to the trial at the time of the data lock point, a 'no patients recruited letter' will be completed and submitted in place of the DSUR. The letter will be signed by the Quality Manager (or delegate).

4.4.4 Submission

The final signed DSUR, short-format DSUR or "No Patients Recruited Letter" will be submitted to the regulatory competent authority by the KHP-CTO CRA or delegate, as per their requirements, no later than 60 days after the Data Lock Point.

The KHP-CTO CRA or delegate will submit a copy to the approving REC(s), with the REC standard cover page (see related templates 5.2).

A copy of the DSUR will be filed in the trial TMF and in the Sponsor File.

5.0 RELATED TEMPLATES

5.1 DSUR Guidance Template

5.2 REC safety report submission cover page

5.3 No Patients Recruited Letter Template

5.4Health Research Authority Annual Progress Report Template

6.0 RELATED DOCUMENTS

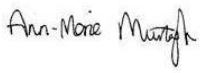
6.1 ICH guideline E2F - Note for guidance on DSURs

6.2 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 https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2017_11_CTFG_Question_and_Answer_on_Reference_Safety_Information_2017.pdf

6.4 KHP-CTO Work Instructions for DSUR preparation

7.0 APPROVAL AND SIGNATURE



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Ann-Marie Murtagh Date
Interim Director
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