Preparation and Submission of Development Safety Update Reports (DSURs)

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Contents

1. BACKGROUND AND PURPOSE 3
2. SCOPE 3
3. PROCEDURE 3
3.1 Preparing the DSUR 3
3.2 Approval and submission of DSUR 5
4. RELATED TEMPLATES 7
5. RELATED DOCUMENTS 7
6. CHANGE HISTORY 7
7. GLOSSARY 8

1. BACKGROUND AND PURPOSE

This SOP describes the process for preparing and submitting Development Safety Update Reports (DSURs) to the MHRA. The DSUR provides the MHRA with the Sponsor's annual evaluation of the safety profile of an Investigational Medicinal Product (IMP).

It is an offence under the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended) (the 'Regulations') to fail to submit a DSUR.

2. SCOPE

This SOP applies to all Clinical Trials (CTIMPs) sponsored by KHP, that are overseen by the KHP-CTO.

3. PROCEDURE

3.1 Preparing the DSUR

Task	Responsibility	Activity
1	Senior Clinical Research Associate	Ensure that the Development International Birth Date (DIBD) for each Investigational Medicinal Product (IMP) is documented and available in the TMF. The DIBD is the date that the first CTA for the Clinical Trial was approved. Determine and document the DSUR reporting period, noting that one of the following approaches must be applied consistently: • **DIBD-anchored reporting period**: The annual DSUR reporting period runs from the DIBD anniversary date to the same calendar date in the following year (i.e. if the DIBD is 25 December 2024, the reporting period is 25 December 2024 to 24 December 2025). • **Month-end reporting period:** The Sponsor may designate the Data Lock Point as the last day of the month preceding the month of the DIBD (i.e. if the DIBD is 25 December 2024, the reporting period is 1 December 2024 to 30 November 2025). Where a Clinical Trial involves multiple IMPs or combination therapy, determine and document the DSUR strategy: • Separate DSURs for each IMP (with reference to combination use), or • A single DSUR covering the fixed or co-administered combination.

		Ensure that the reporting period definition and the DSUR strategy for multi-drug Clinical Trials are formally recorded in the TMF.
2	Clinical Research Associate	Maintain oversight of the DSUR reporting timeline for each applicable Clinical Trial. Ensure that the DSUR is submitted within 60 calendar days of the Data Lock Point. No further DSUR is required once the End of Trial (EoT) notification submission has been acknowledged by the MHRA.
3	Clinical Research Associate	Confirm with the Chief Investigator (CI) whether any Clinical Trial-related publications (including abstracts or interim analyses) have been issued since the previous DSUR submission. Ensure that all relevant correspondence is filed in the TMF.

4	Clinical Research Associate	Compile the information required to prepare the DSUR, including (as applicable):
		• The approved DSUR template (See DSUR template.docx)
		• ICH E2F guidance on Development Safety Update Reports
		• Current and historical versions of the Clinical Trial protocol, including all approved Modifications affecting the protocol since the previous DSUR
		• Reference Safety Information (RSI) applicable during the reporting period, including version history
		• Confirmation of Marketing Authorisation status, where relevant (e.g. manufacturer confirmation or public sources such as the British National Formulary (BNF))
		• Clinical Trial safety data, including:
		  ○ Participant exposure and demographics
		  ○ Serious Adverse Event (SAE) listings
		  ○ Causality and expectedness assessments
		• Copies of any previously submitted DSURs

5	Clinical Research Associate	For Blinded trials, prepare two versions of the draft DSUR using (use **DSUR template.docx** and **Work Instructions for Preparing DSURs.docx**): 1. A full version containing Unblinded safety data for Sponsor-level review and regulatory submission; and 2. A Blinded version that excludes Unblinded treatment allocation, for review by the CI and other individuals who must remain Blinded.

		MHRA guidance for DSURs: Clinical trials for medicines: collection, verification and reporting of safety events - GOV.UK
6	Clinical Research Associate	For Open-Label Trials, prepare one version of the draft DSUR using (use **DSUR template.docx** and **Work Instructions for Preparing DSURs.docx**). MHRA guidance for DSURs: Clinical trials for medicines: collection, verification and reporting of safety events - GOV.UK
7	Clinical Research Associate	Where applicable, confirm whether a risk assessment and proportionality review is required. A review may be required where: • No substantial modification has been submitted in the preceding 12 months; or • The accumulated safety data indicates a potential change in the risk–benefit profile. Conduct the review in accordance with **SOP 22.0 Proportionality and Risk Assessment for Clinical Trials of Investigational Medicinal Products**

3.2 Approval and submission of DSUR

Task	Responsibility	Activity
1	Clinical Research Associate	Circulate the draft DSUR to the Chief Investigator (CI) for review and, where applicable, to the Sponsor-level Medical Assessor. Ensure all correspondence is retained in the TMF
2	Chief Investigator	Review the executive summary to confirm that: • The description and analysis of safety data are accurate and complete; • Any safety-related measures taken during the reporting period are correctly described; and • The conclusions drawn are appropriate. Provide comments or written approval to the CRA. Ensure a copy of the correspondence is filed in the TMF.
3	Sponsor-level Medical Assessor (if separate to	Review the executive summary, with particular focus on: • The evaluation of accumulated safety data; and • The overall benefit–risk assessment.

	the Chief Investigator)	Provide comments or written approval to the CRA, copying the CI. Ensure correspondence is filed in the TMF.
4	Clinical Research Associate	Where required, amend the draft DSUR to address comments received. Re-circulate the amended DSUR to the CI, and where applicable, to the Sponsor-level Medical Assessor, for confirmation of approval. Ensure all correspondence and approved versions are retained in the TMF.
5	Senior Clinical Research Associate	Arrange payment of the applicable MHRA fee for DSUR assessment. See the 'Related Documents' section of this SOP for guidance on: 1. MHRA fees (the fee for DSURs is the fee for 'annual safety reports') 2. The service you use to make payments to the MHRA for DSURs 3. Paying the MHRA online before submitting a DSUR Ensure evidence of payment (e.g. receipt or confirmation email) is filed promptly in the TMF.
6	Clinical Research Associate	Submit the approved DSUR, together with any required accompanying documentation and covering letter, to the MHRA via the appropriate submission route, in accordance with current MHRA guidance. Save a copy of the submission and covering letter in the TMF.
7	Senior Clinical Research Associate	Where the MHRA requests a Serious Adverse Event (SAE) line listing: • Ensure the listing is prepared and submitted to the MHRA within 30 calendar days of the DSUR due date; and • Ensure the line listing and all related correspondence are retained in the TMF.
8	Senior Clinical Research Associate	Upon receipt of the MHRA "case closure" or acknowledgement email (which serves as confirmation of receipt), ensure this is filed in the TMF.
9	Chief Investigator or delegate	Ensure that consideration of the DSUR forms part of the ongoing risk assessment and proportionality review for the trial, in accordance with **SOP 22.0 – Proportionality and Risk**

		Assessment for Clinical Trials of Investigational Medicinal Products.

4. RELATED TEMPLATES

- DSUR template.docx
- Work Instructions for Preparing DSURs.docx

5. RELATED DOCUMENTS

SOPs

SOP 22.0 Proportionality and Risk Assessment for Clinical Trials of Investigational Medicinal Products

Other Documents

MHRA guidance for DSURs
Clinical trials for medicines: collection, verification and reporting of safety events - GOV.UK

MHRA fees (the fee for DSURs is the fee for 'annual safety reports')
https://www.gov.uk/government/publications/mhra-fees/current-mhra-fees#clinical-trials-application-fees

The service you use to make payments to the MHRA for DSURs
https://www.gov.uk/payments/mhra/dsur

Paying the MHRA online before submitting a DSUR
https://assets.publishing.service.gov.uk/media/6846eb635e9253957280617e/User_reference_guide___Paying_online_before_submitting_an_annual_safety_report.pdf

ICH E2F guidance on DSUR contents
https://database.ich.org/sites/default/files/E2F_Guideline.pdf

6. CHANGE HISTORY

CHANGE HISTORY			
Date	Version Number	Change details	Approved by
01 Jan 2010	1.0	Creation	Jackie Powell
24 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
16 Jul 2014	2.1	Correction of administrative error relating to DSUR reporting time, from V1.0 to V2.0 of this document.	Jackie Pullen

31 Oct 2016	3.0	Scheduled review, update to Glossary, clarification of RSI and administrative amendments	Jackie Pullen
19 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
5 Nov 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
14 May 2021	6.0	Amendment to include reporting requirements to Trials under the Type A Notification Scheme	Jackie Pullen
3 Apr 2024	7.0	Updated as per MHRA Inspection finding: Reference Safety Information clarifications and updated procedures added	Ann-Marie Murtagh
31 Aug 2025	8.0	Removed requirements for Annual Progress Reports (APR)	Ann-Marie Murtagh
23 Apr 2026	9.0	Moved SOP to new template ICH GCP E6 (R3) and 2025 clinical trial regulations changes: • Confirm an offence is committed if DSUR is not submitted. • MHRA can request SAE listing after DSUR submission. Sponsor must provide listing within 30 days. • Role of medical assessor where CI is not a GMC licensed doctor.	Ann-Marie Murtagh

7. GLOSSARY

Adverse Event (AE) - Any untoward medical occurrence in a participant who has been administered an IMP, which does not necessarily have a causal relationship with that IMP.

Blinded Trial - A Clinical Trial in which treatment allocation is concealed from one or more parties involved in the Clinical Trial (e.g. participant, investigator, Sponsor staff), in accordance with the protocol and randomisation procedures.

Blinding - A procedure used in a Clinical Trial to withhold information about treatment allocation from one or more parties (e.g. participants, investigators, Sponsor staff) in order to minimise bias in Clinical Trial conduct, assessment, and reporting. '**Blind'** and **'Blinded'** to be construed accordingly.

Chief Investigator (CI) – The overall lead researcher for a Clinical Trial (Outside the UK the term 'Coordinating Investigator', 'Principal Investigator' or 'Investigator' may be used for the

overall lead researcher for a Clinical Trial). Chief Investigators are responsible for the overall conduct of a Clinical Trial.

Clinical Research Associate (CRA) – A staff member employed by the KHP-CTO who conducts monitoring activities for a Clinical Trial, including but not limited to the initiation phase, routine phase, and close down phase.

Clinical Trial of an Investigational Medicinal Product (CTIMP) - Any investigation in human participants (other than a non-interventional trial) intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more medicinal products and/or to identify any adverse reactions to one or more such products and to study absorption, distribution, metabolism and excretion of one or more such products with the object of ascertaining the safety and/or efficacy of those products. Includes clinical trials of ATMPs.

Clinical Trial Authorisation (CTA) – Authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA) to conduct a Clinical Trial. No Clinical Trial can commence in the UK without both a CTA and a favourable ethical opinion. Applications to the MHRA and the Research Ethics Committee (REC) may be made in parallel.

Data Lock Point – A defined point at which data are fixed against further routine change. **For EoT purposes**, it refers to the locking of a Clinical Trial database once data collection and cleaning are complete. **For DSUR purposes**, it refers to the Sponsor-defined annual safety data cut-off.

Development International Birth Date (DIBD) - This is the date that the first CTA for the Clinical Trial was approved.

Development Safety Update Report (DSUR) - A common standard for periodic reporting on drugs under development (including marketed drugs that are under further study).

End of Trial (EoT) – The end of the Clinical Trial as defined in the protocol. The end of the Clinical Trial is typically expressed as a condition-based event, not a predetermined date.

ICH E2F - The International Council for Harmonisation (ICH) Efficacy 2 (2 represents pharmacovigilance) F (F represents the sixth guideline in the 'Efficacy 2' series) guideline that defines the structure, content, and timing of the DSUR for IMPs. It sets out how Sponsors should prepare an annual, cumulative safety evaluation at IMP level, including requirements for the reporting period, Data Lock Point, analysis of AEs and SAEs, assessment of emerging risks, and requirements for an overall benefit–risk evaluation across all ongoing and completed Clinical Trials for each IMP.

Investigational Medicinal Product (IMP) – A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a Clinical Trial. This includes products with marketing authorisation when used in a way different from the approved form, for an unapproved indication, or to gain further information about an approved use.

Investigator Site File (ISF) – The Trial Location-specific set of essential documents held at the Trial Location by the Principal Investigator, demonstrating how the trial was conducted at that particular location and that the investigator complied with the protocol, Sponsor instructions, and GCP.

KHP-CTO Non-Commercial Team - Comprises the Non-Commercial Trials Manager, CRA(s), Clinical Trial Administrator(s), and Training Executive(s).

King's Health Partners (KHP) - King's College London, Guy's and St Thomas' NHS Foundation Trust, King's College Hospital NHS Foundation Trust, and South London and Maudsley NHS Foundation Trust.

King's Health Partners Clinical Trials Office (KHP-CTO) – The department established by King's College London, Guy's and St Thomas' NHS Foundation Trust, King's College Hospital NHS Foundation Trust, and South London and Maudsley NHS Foundation Trust to 1) undertake the set up and financial Management of commercial research hosted by one or more of the KHP Partners, and 2) undertake the regulatory submissions and oversight, as well as monitoring activity for non-commercial research studies sponsored by one of the KHP Partners.

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.

Marketing Authorisation – A regulatory approval granted by the competent authority that permits a medicinal product to be placed on the market, confirming that its quality, safety, and efficacy have been adequately demonstrated.

Medical Assessor - A medically qualified individual responsible for providing clinical judgement on individual safety reports arising during a Clinical Trial. The assessor may be involved in the Clinical Trial in another role (i.e. as a CI, PI, Sponsor Team member or Trial Location Team member), or their sole involvement may be as the assessor. At Trial Location-level, assessment of safety events involves initial clinical evaluation and causality assessment for participants at the Trial Location. At Sponsor-level, assessment involves reviewing serious safety events across all Trial Locations, confirming seriousness, causality, and expectedness using the RSI, and supporting regulatory determinations such as SAR and SUSAR reporting.

Medicines & Healthcare products Regulatory Agency (MHRA) – The UK government agency responsible for regulating medicines, medical devices, and Clinical Trials. In the context of Clinical Trials, the MHRA i) acts as the licensing authority for Clinical Trials, ii) reviews the scientific, quality, and safety aspects of a Clinical Trial application, iii) issues CTAs, iv) oversees GCP and GMP inspections, v) monitors pharmacovigilance and safety reporting, and vi) enforces compliance with UK medicines legislation.

Modification - Any change to a Clinical Trial after initial approval that affects the information or conditions on which the Clinical Trial was authorised. Includes minor modifications, Modifications of an Important Detail (MOIDs), Route A and Route B substantial modifications.

Non-Commercial Trials Manager (NCTM) – The most senior member of the KHP-CTO Non-Commercial Team.

Open-Label Trial - a Clinical Trial that is not designed to be Blinded, meaning that the participant, investigator, and trial staff are aware of the treatment being administered.

Partner Trusts – Guy's and St Thomas' NHS Foundation Trust, King's College Hospital NHS Foundation Trust, and South London and Maudsley NHS Foundation Trust.

Principal Investigator (PI) – The individual at a Trial Location who has primary responsibility for the conduct of the Clinical Trial at that Trial Location.

Reference Safety Information (RSI) – The authoritative document used to determine the expectedness of SARs occurring during a Clinical Trial. It defines which SARs are considered expected for the IMP, based on the safety information available at the time, and is used by the Sponsor to assess whether a SAR qualifies as a SUSAR. If the IMP has a Marketing Authorisation, the SmPC will be used as the RSI. If the IMP does not have a Marketing Authorisation, the IB will be used as the RSI.

Regulations – The Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended).

Research Ethics Committee (REC) – A national independent body 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 Clinical Trial, and to provide public assurance of that protection by, among other things, expressing an opinion on the Clinical Trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform Clinical Trial participants and obtain their informed consent.

Senior Clinical Research Associate (sCRA) – A staff member employed by the KHP-CTO to undertake advanced CRA duties, including the line management of CRAs.

Serious Adverse Event (SAE) - An Adverse Event that results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or consists of a congenital anomaly or birth defect.

Sponsor - The person or body who takes on ultimate responsibility for the initiation, management and financing (or arranging of the financing) of a Clinical Trial. The Regulations allow for two or more persons or bodies to take on responsibility for Sponsor functions.

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

Suspected Unexpected Serious Adverse Reaction (SUSAR) - A Serious Adverse Reaction to an IMP that is unexpected, meaning that the nature or severity of the reaction is not consistent with the applicable product information according to the RSI.

Trial Master File (TMF) - A standard filing system which contains all essential documents which individually and collectively permits the evaluation of the conduct of a Clinical Trial and the quality of the data produced. 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 Records.

Unblinding - A procedure used in a Clinical Trial in which treatment allocation is revealed for an individual participant or, in rare cases, for the Clinical Trial as a whole. Unblinding may occur in accordance with the protocol (e.g. at EoT), or prematurely, where necessary to protect participant safety or to meet regulatory reporting requirements. '**Unblind'** and '**Unblinded'** to be construed accordingly.