

Questions and Answers to the Annual Safety Report

Frequently asked questions regarding the
Development Safety Update Report (DSUR)

	Question	Answer
1	DSUR Start-Stop	
1.1	When to start preparing and where to submit a DSUR?	<p>A DSUR should be prepared after the first authorisation of a clinical trial worldwide (see question 2.1, DIBD (Development International Birth Date)).</p> <p>A copy of the DSUR should be submitted to each concerned European Member State (MS) if a clinical trial is authorised in , this MS for this investigational drug (still using the DIBD).</p> <p>Therefore, the first DSUR can be submitted to a concerned MS earlier than 1 year, but the covered reporting period should not be longer than 1 year.</p>

<p>1.2</p>	<p>When to stop submitting a DSUR?</p>	<p>In Europe an annual safety report is to be submitted throughout the clinical trial (CT) to Member States in whose territory the CT is being conducted (Clinical Trial Directive 2001/20 Article 17(2)).</p> <p>Generally speaking, the submission should stop when the trial ends. However there seems to be 3 different interpretations:</p> <ul style="list-style-type: none"> • The definition of a completed trial for DSUR purposes is given in the <u>ICH E2F</u> glossary: ‘Study for which a <i>final clinical study report is available</i> is a completed clinical trial. For DSUR purposes a trial for which enrolment has begun and a final clinical study report is not available, is considered to be ongoing.’ This would mean a DSUR needs to be submitted to the concerned member states (MS)s until the final clinical study report is completed and its summary submitted to these European MSs. • According to <u>CT1</u> (2.5), the end of CT is to be <i>defined</i> clear and unambiguous <i>in the protocol</i>. In most cases it will be <i>the date of last visit of last patient</i>. • <u>CT-3</u> guidance paragraph 126 reads: ‘The report should only be submitted to the national competent authority and the Ethics Committee <i>if the treatment of subjects is ongoing</i> in that Member State concerned.’ Meaning that DSUR is to be submitted until the end of treatment of the last subject in the MS concerned. <p>In order to harmonise ICH E2F, CT1 and CT3, the interpretation of the ‘treatment of subjects is ongoing’ is that this clinical trial has not ended yet.</p> <p>Therefore, a DSUR should be submitted until the last visit of the last patient in the MS concerned, as specified within the protocol.</p> <p>And a DSUR should only be submitted to the concerned MS(s) on which’s territory the clinical trial has not ended yet, no submission is needed to the concerned MS(s) where the clinical trial ended already.</p> <p>In the case of multiple studies being authorised by the concerned MS within the reporting period, a DSUR must be submitted until the last open CT has come to an end (LVLP) in this concerned MS.</p>
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2	DIBD (Development International Birth Day)	
2.1	What is a DIBD , how is it defined, and what is it used for?	<p>The DIBD is the date of the first authorisation of a clinical trial in any country – worldwide - for the investigational drug, or a designated date linked to the start of a CT in a country without a formal authorisation process.</p> <p>In order to set up harmonisation, it is strongly recommended that the DIBD of a non authorized investigational drug in the EU/EEA is indicated by the sponsor within the DSUR or in the covering letter (see ICH E2F section 3.1.).</p> <p>The DIBD of an authorized drug is the IBD (International Birth Date), the date when the product was first authorised in any country worldwide. For EU/EEA harmonized IBD see HMA web site (http://www.hma.eu).</p> <p>The data lock point (DLP) for a DSUR reporting period is the last day (or the last day of the month, see ICH E2F section 2.2.) before the anniversary of the DIBD.</p>
2.2	Can a DSUR be aligned with the PSUR's (Periodic Safety Update Report) International Birth Day (IBD)?	<p>The dates of a DSUR and PSUR submission can be synchronised by preparing a DSUR based on the PSUR international birthday (IBD). Then the data lock point of the DSUR, the DIBD, is aligned to the one of PSUR, the IBD.</p> <p>However, the first DSUR period should <u>not be longer than 1 year</u>. The DSUR is always submitted on a yearly basis. It is not allowed to change the IBD. (Also see ICH E2F section 2.2.)</p>
2.3	What DIBD should be used for an investigational drug with marketing authorization in the EU/EEA when used in an investigator initiated trial (not by the MAH (marketing authorization holder))?	<p>There are 2 options:</p> <ol style="list-style-type: none"> 1. Use the (harmonised) International Birth Date (IBD) of the investigational medical drug (product), for example as for EU/EEA harmonized IBD published at Heads of Medicines Agencies website (http://www.hma.eu/) 2. If the IBD is not available from these lists, it is possible to use a DIBD, which is the date of the 1st trial authorisation with this investigational medical drug (product) by the sponsor.

<p>2.4</p>	<p>Transitional period: In application of ICH E2F guidance (starting September 2011), how can the DSUR data lock date (the day before anniversary of the DIBD) be aligned to the data lock date of the European Annual Safety Report (ASR) (day before anniversary of the European Birth Date (EBD)) which was required in the previous version of the CT3 guidance?</p>	<p>The DIBD and the European Birth Date (EBD) of the previous annual safety report (ASR) should be aligned in such a way that DSUR periods that are (substantially) longer than 12 month as well as overlapping DUSR periods are avoided.</p> <p>The following are recommendations for the two different scenarios – DIBD before EBD and EBD before DIBD, respectively.</p> <p>1. If the anniversary of the DIBD is earlier than the anniversary of the EBD (e.g. DIBD October and EBD December), only a DSUR should be submitted.</p> <p>In this case the safety report period covered by the DSUR - from start EBD period till end period DIBD -will be shorter than 1 year.</p> <p>2. If the anniversary of the EBD as due date of the European ASR is earlier than the global anniversary of the DIBD (e.g. EBD October and DIBD December):</p> <p>A DSUR should be submitted according to the anniversary of the EBD (in October) and the next DSUR needs to be submitted in accordance with the DIBD anniversary (in December).</p> <p>The following 2 scenarios are exceptional exemptions for the application of ICH E2F, which need to be justified by the sponsor and approved on a case by case basis by all concerned Member States facilitated via CTFG. The request should be send to the concerned MS(s):</p> <p>a) Format Waiver</p> <p>A waiver on the format of the first safety report using the DSUR format is possible with justification by sponsor and harmonised position from all concerned MSs.</p> <p>Therefore in the previous example, if approved the annual safety report submitted in October can be submitted in the old ASR format, but the December one in the new DSUR format. The latter DSUR is covering less than 1 year (October till December same year).</p> <p>b) ASR period adjustment</p> <p>Under certain circumstances a delay of the safety report by up to 3 month, leading to a safety reporting period longer than 1 year, might be exceptionally possible.</p> <p>In the case of approval by all concerned MSs, only one report in the DSUR format will be submitted (e.g. the 'December' report of the previous example).</p>
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3	DSUR for ?	
3.1	Is a DSUR required for a short (less than 1 year) clinical trial?	<p>No. If a clinical trial has been started and ended (CT1 (2.5)) within a time period shorter than 1 year, it will not be subject to annual safety reporting in accordance with current Article 17(2) of CTD 2001/20/EC, even if multiples of such short clinical trials were performed.</p> <p>However, for the latter case of <u>multiple performed short trials</u> for one IMP it is recommended to <u>consider submitting a DSUR</u> to the concerned MSs to be in line with the ICH's objective of comprehensive assessed safety information of one IMP (Investigational Medicinal Product).</p>
3.2	Is a DSUR required for a clinical trial which reached its long-term follow up phase?	<p>Yes, as long as an interventional CT is ongoing (see question 1.2.).</p>
3.3	Is a DSUR required for Phase IV clinical trials, if only such trials are conducted?	<p>Yes, a DSUR is needed. According to the current legislation, it is not possible to grant a waiver for a DSUR for Phase IV trials.</p> <p>For non-commercial sponsor (<u>investigator initiated trials</u>): Member states may accept a simplified document based on the headings of the guidance. Only relevant and available information needs to be filled in for the DSUR. However, the possibility to calculate frequencies of SUSARs (suspected unexpected severe adverse reactions) and SARs (severe adverse reactions) should still be given.</p> <p>CTFG is working on a model example.</p>
3.4	<p>What if a non-commercial sponsor runs several independent CTs with the same investigational drug at different institutes, is one consolidated DSUR needed?</p> <p>Or</p> <p>What if different non-commercial sponsors run independent CTs with non authorized investigational drugs is one consolidated DSUR needed?</p>	<p>Submission of one single DSUR is strongly recommended if the same investigational medical drug (product) is used in the CTs. However, the concerned MSs can accept a trial specific DSUR if this is justified.</p> <p>For investigational medical drug (product) without a marketing authorization it is strongly recommended that the developing or manufacturing company should write a single DSUR.</p> <p>See also ICH E3F section 2.4.2.</p>

<p>3.5</p>	<p>Is a DSUR required for all drugs in the CT, like comparator, placebo, NIMP (Non IMP)?</p>	<p>As given in ICH E2F glossary item 11. (CIOMS VII) an investigational drug is only the experimental medicinal product (IMP) under study or development.</p> <p>As of the CTD Article 2(d) (2001/20) an IMP is the active substance or placebo being tested or used as reference. In addition, Article 17(2) requires a listing of all SARs in the reporting period and a report on subjects' safety in the CT(s) performed.</p> <p>Therefore, a <u>separate</u> DSUR for a comparator, placebo or NIMP is <u>not required</u>.</p> <p>However, <u>relevant safety information</u> of the above mentioned drug types (comparator, NIMP or placebo) should necessarily be addressed in the DSURs of the investigational drugs.</p> <p>Section 2.5 of the ICH E2F on combination therapies and multidrug therapies may also be used for <i>comparators and head to head studies</i>.</p> <p>For multi-therapies or head to head comparisons one DSUR might be acceptable under certain justified conditions, e.g. one study only, also see ICH E2F 2.5.</p> <p>All SARs (serious adverse reactions) of all required drug types (as of above) in the clinical trials are expected in section 7.2 of the DSUR.</p> <p>With regard to format and content please refer to ICH E2F section 2.7 and 3.7 (3.7.1 - 3.7.3). The latter also clearly covers all drug types with regard to the summary tabulations of SAEs (serious adverse events). For IMPs with marketing authorisation the sponsor (in case he is not the MAH) is encouraged to provide relevant safety information to the marketing authorisation holder (MAH).</p> <p>In the case of IMP without a marketing authorisation and a sponsor who is not the IMP developer CTFG recommends to provide relevant safety information to the developing or manufacturing company.</p> <p>The discussion of the question will be continued between the European regulatory bodies to further facilitate annual safety reporting.</p>
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4	RSI (Reference Safety Information)	
4.1	What requires consideration if the RSI is the SmPC ?	Referring to CT1 guidance (section 56) there should be used one SmPC (summary of product characteristics) for the whole clinical trial at least in the EU/EAA. Therefore, the SmPC should be the same in all member states concerned, with an acceptable language.
4.2	Can the IB or SmPC be updated ?	<p>IB and SmPC have 2 <i>objectives</i>:</p> <ol style="list-style-type: none"> 1. Informing stakeholders about state of the art. 2. Being the RSI for expectedness/unexpectedness evaluation of SARs by sponsors, NCAs and ECs. <p>For that effect the RSI in the IB is a clearly-identified section, as described in section 53 of CT3.</p> <p>So, yes, the IB or SmPC can be updated during the DSUR reporting period, especially to inform state of the art. But the RSI in effect at start of the reporting period must remain the RSI throughout the reporting period and forms the basis for expectedness for events in the DSUR reporting period.</p> <p>Updating the RSI (which would require submission of a <i>substantial amendment</i>) during a reporting period is not recommended and may result in MSs requesting continued reporting of certain events of special interest as SUSARs. This is because the RSI for the DSUR and SUSAR reporting may no longer be aligned, resulting in serious events that are no longer reported as SUSARs and therefore not reported to the MSs until the DSUR is submitted, which is not acceptable.</p>
4.3	Is the RSI for DSUR similar to RSI for SUSAR reporting of a clinical trial?	<p>CTFG strongly recommends aligning the RSI of a clinical trial to the RSI of a DSUR, so the basis for expectedness stays unchanged for the reporting period.</p> <p>The RSI during the DSUR reporting period must stay constant (also see question 4.2).</p>
4.4	Can a Development Core Safety Information (DCSI) be used as RSI for a non authorized investigational drug?	A DCSI can only be used as the RSI if it is part of the Investigators Brochure <u>and</u> if the RSI part is only updated according to legislation.

4.5	Can a Company Core Safety Information (CCSI) section of the Company Core Data Sheet (CCDS) be used as RSI for a EU/EEA authorized investigational drug as it is used for PSUR?	A CCSI can only be used as the RSI if it is part of the Investigators Brochure <u>and</u> if the RSI part is only updated according to legislation.
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