CTR training Day 2 -- QnA

Safety reporting and assessment

Summary of results

1) The final report is due 1 year after the end of a trial. Is this the last end date in all countries or the last date in a given country? The summary of results is due within 1 year after the end of the trial in all EU countries (see CTR Article 37(4) for further information). It could be deferred to the global end if scientifically justified.

Ethics Committees and safety

2) Will ethics committees receive SUSARs/ASR? And if so, how?
   Ethics committees will access ASRs directly through CTIS (by role permission in CTIS as assigned and in alignment with national law); It has to be clarified by COM/EMA if ethics committees will have access to SUSARs via EVDAS. There will be no direct submission of ASRs and SUSARs from the sponsor to ethics committees.
3) The ethics committee (EC) receive the annual safety reports. See question above. Could EC participate in the saMS tasks? It is a national decision as to whether Ethics committees are involved in saMS tasks.

Legal basis of saMS and national responsibilities for safety assessment

1) Is the framework for saMS assessment on basis of active substance, and uncoupling this from benefit/risk assessment for an individual trial robust and aligned with the primary legislation where the premise for the cooperation relates to a single clinical trial?
   The CTR and Implementing Regulation (IR) will provide the legal basis for the saMS for the assessment of SUSARs and ASRs linked to an active substance. Member State best practice guidance will provide the basis for the saMS involvement and responsibility for the assessment of other safety notifications and information when linked to an active substance and asked for by RMS/MSC. When it is possible, to support oversight and avoid redundant assessments, saMS will be on the basis of an active substance as in pharmacovigilance, while due to tight cooperation with RMS and MSCs the link to individual CT benefit risk is maintained. This approach also takes into account the relevant guidance on the development of safety update reports (ICH E2F). Clinical trials are national authorisations under Directive and CTR. Under the Directive, MS are required to assess the risk of an IMP on participants' safety and take corrective measures and/or risk mitigating actions to protect the safety of subjects, if necessary (CT-3).

2) Is the transfer of the assessment responsibility to the saMS under the draft Implementing Regulation, legally appropriate, given that a CT is a national authorisation? MSC will maintain responsibility and overview of safety for clinical trials in their territory by being involved in all ASRs, other safety notifications and information and SUSAR signal cases, with the option to comment and raise queries on the saMS assessments. In addition, a MSC can take action by themselves for a CT in their territory anytime, irrespective of saMS recommendations, and outside of coordinated assessments, however coordinated action is strongly preferable.

Member States concerned may continue their national safety assessment activities in trials that they have authorised and where they are not a safety assessing Member State.

saMS

4) What about a CT with several IMPs? Does it mean that 5 IMP=5 saMS? Are alternative options considered? A CT with multiple IMPs means multiple saMS, yes. An exception might be a single ASR for a multitherapy trial where the RMS may assess the ASR with support of multiple saMSs, if necessary.
5) How is a saMS selected? Is it one of the MSCs? What qualifications are needed? Any Member State can volunteer for the role of saMS. If there are no volunteers, the role of saMS will be determined from Member States concerned based on a fair workshare algorithm. If more than one MS volunteers, the RMS for the trial will select between them based on expertise and knowledge regarding the IMP or fair workshare (the MSC with the smallest workload as saMS will be selected). As an exception, the MS volunteering with experiences with this active substance or class will qualify for being saMS
6) Is it feasible for the saMS to be responsible for safety and substantial modifications for multiple trials with various indications, and multiple sponsors, when ASRs etc are on different timelines? saMS may be asked for input with regard to the safety profile of an active substance for a substantial modification (in particular when the SM contains changes to the RSI), however assessment is the responsibility of the RMS/MSC. An ASR is submitted per development compound /IMP = active substance and there is usually only one per active substance (In a few cases there could be more than one ASR if in combination or in another indication with a totally different safety profile). For authorised active substances, further ASRs may be submitted by different sponsors. However, as the saMS is the expert for the safety profile of the active substance, it will be much easier to assess this too than another MS not as familiar with the active substance. Therefore, the saMS are encouraged to volunteer for same active substance by different sponsors.
7) What about roll over CT with patients from multiple trials? If this new CT treats patients with a different active substance it would be a different saMS responsible for safety assessment, if it was an extension trial with the same active substance, it would be the same saMS, also in case of long term follow up

ASR

8) The ASR is often by CT for non commercial CTs, not occasionally This is the only exception to saMS assessing the ASR, in this case the RMS will assess the ASR and may ask for the support of the saMSs of the active substances, if necessary. Different Member States have different levels of non-commercial CTs and ASRs per CT.
9) If a MS is currently assessing the ASR in the workshare pilot of CTFG, if the CTR goes live will this MS be responsible for the active substance as saMS if a CT with this substance is submitted in CTIS or transferred? With (any) submission to CTIS the saMS selection should be triggered by RMS. The workshare pilot for the ASR as performed currently is different to saMS role within CTR. Therefore, a MS that assessed an ASR in this pilot does not automatically become the saMS under the regulation. However this MS is invited and encouraged to volunteer for this responsibility – as it definitively has some experiences with the active substance

Assessment Reports

10) In all the Assessment Reports, be it of Part I, II or Safety, there are too many tick boxes to be checked. In assessment reports, tick boxes are supplemented with text fields, such it is up to the assessor to specify, that way all MSC can follow the assessment and conclusion. Assessment reports have been designed to be clear and easy to use for the assessor, while also providing as much relevant information as possible to allow MSCs to be reassured that the saMS has thoroughly assessed the documents/information and to be adequately informed of any safety issues, without having to perform a full assessment themselves. In addition, flexibility is given depending on the case /results of assessment. Assessment report templates will be developed by CTFG and shared with all EU/EEA MS.
11) Too time consuming, without any added value. They could be replaced by a statement by the assessors that they took care of all the needed aspects in their evaluation. Please see response to previous question.

SUSARs

1) SUSAR re-routing, please explain? How will the SUSAR information be presented in re-routing to ethics? There will be no direct reporting of SUSARs from sponsors to NCAs or ethics committees under the CTR. NCAs will access SUSARs directly through EudraVigilance, NCAs may also request that SUSARs areSUSARs will be re-routed to them from EudraVigilance. Re-routing requirements are being developed by the EMA. NCAs will be able to set SUSAR re-routing rules themselves if they wish opt-in or opt-out to receive copies of the SUSARs submitted to EudraVigilance. The rerouting options that will be made available are described in the EU ICSR implementation guide[1] see section I.C.2.2.2 Retransmission rules for Clinical Trial SUSAR ICSRs for further information[2]. Ethics committees would need to have their own pharmacovigilance IT system in order to be able to process the rerouted E2B(R3) SUSAR XML files and send back acknowledgement messages to confirm receipt
2) What about the responsibility of the investigators when there is a conflict with the Sponsor regarding the definition of a SUSAR? Reporting rules for SUSARs will not change under the CTR. The investigator will remain responsible for determining seriousness and for assigning causality. The sponsor will remain responsible for also assigning causality, and determining expectedness. Investigator causality cannot be downgraded, however an assessment of an AE can be upgraded.
3) Brief documentation of assessment each SUSAR. Can you elaborate on workload? Documentation of each SUSAR will be a quick and easy process if there is no signal/no issue detected. CTFG are currently in discussions with the EMA to develop a tool for the screening of SUSARs, ideally the output document received from the EMA will have a field for the assessor to add a short comment in. If an issue or potential issue is identified there will be a more detailed review and template assessment report to be completed. The latter template is in discussion.
4) Also, very concerned about the burden on saMS to review SUSARs on weekly basis, and assessment of 'other safety notifications'. Is this feasible? Overall, an increased workload is expected where a MS has the role of saMS, and this will be offset by a reduced workload where a MS is not saMS (for example due to not having to do a full assessment or write an

[1] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-union-individual-case-safety-report-icsr-implementation-guide_en.pdf
[2] with further questions related to re-routing, please contact EMA helpdesk: https://servicedesk.ema.europa.eu/jira/servicedesk/customer/portals

assessment report). Review of SUSARs is performed today, as a current national duty. However, some additional workload is also expected for assessment of SUSARs from third countries. CTFG are also looking into IT support by EMA PV (eRMR) and developing best practice guidance on risk based assessment, further training will be planned and provided later on.

Auxiliary Medicinal Products (AxMPs)

1) Could you please elaborate a bit on the AxMP reported similar to IMP? Authorised AxMPs will follow the safety reporting rules under Article 46 in the CTR (referring to Chapter 3 of Directive 2001/83/EC). Recommendations for the safety reporting of unauthorised AxMPs cancan be found here: Q7.46 and Q.7.47 of the Q+A document: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf and the AxMP guidance: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017_06_28_recommendation_on_axmps.pdf

Other safety notifications *(Temporary halt or early termination by the sponsor for reasons of subject safety, Art 38; Other reporting obligations relevant for subject safety, Art 53; Urgent safety measures, Art 54)*

1) Who will determine if saMS or RMS should be in charge of the assessment of a safety notification? CTFG? While the MSC itself is always responsible, it is best practice that where multiple MS are involved, the RMS should review the notification. If the notification is linked to a specific trial and not to an active substance the RMS should lead the assessment. However if the RMS thinks the issue is linked to an active substance they should ask the relevant saMS to assess if necessary. Exact details are still under discussion and will be included in the guidance on safety by CTFG. A national only issue (eg part II) may only be notified to MSC and not be subject to a coordinated workshare assessment. At the same time, MSC can decide to ask help from the RMS or saMS where necessary

RSI

2) Is it correct to report in the RSI table fatal SARs listed in SmPC but consider them as unexpected ? Answer: If a fatal SAR is considered unexpected it should be noted 'not applicable' for the frequency. The RSI should include expected SARs only. The information on fatal SARs should be provided elsewhere in the IB. For further information see Q7.9 of the Q+A document: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf
3) How do you deal on the fact that many SMPC do not mention whether AR have been observed as serious if the sponsor refers to the SMPC in a clinical trial with a product with marketing authorization? Answer: SmPC section 4.8 indeed includes both serious and non-serious ARs, we accept this limitation, if the use of SmPC is justified (for e.g similar safety profile is expected to the licenced indication). SmPC 4.8 is often used by a non-commercial sponsor, who do not have access to the IB/RSI. For further information see Q7.8 of the Q+A document: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf

IB

4) If a sponsor is repeatedly warned that it is not complying with the regulations to update the IB properly, what steps would be taken to compel it to do so? Answer: If a sponsor does not comply, you can establish a corrective measure under Article 77 of the CTR. If they repeatedly do not follow, you can for example trigger an inspection or halt the trial. Other MSC should also be informed (if not already) for joint action in EU/EEA (currently via CTFG, in future by exchange with MSC on CM).

Others

1) Could you please elaborate more in detail the assessment of progression in oncology trials. Answer: Disease progression in oncology trials is an SAE and usually disease related, however keep in mind that any SAE should be assessed by the investigator and if deemed related to the IMP because for e.g. of a high severity in comparison to what is expected for this population, it should be reported as a SUSAR. Ideally there should be an IDMB to look at disease progression, especially to make sure that there is no lack of efficacy in an oncology trial
2) For non-commercial investigators, also applies In general, the same rules apply to all sponsors, regardless of whether or not they are commercial or non-commercial sponsors

Preparedness, MS aspects

1. Ok, but how do we recognise our country?

the traffic light/heatmap tables are without any information about MS, and also such way randomised that you can't identify the country. The white lines - no answer or MS not responded within last half year....

2. how is organised the follow up activities of the clinical trials in the ethics committee? is there a cooperation with the NCA?

The CTR does not foresee any selection of ethics committee by the sponsor, and CTIS will not accommodate for this. EC selection is a Member State responsibility.

3. As EC members in France/BE are all volunteers, it means that they do not receive any fee??

There is a small or no financial compensation for members in FR. In Belgium no fee at all.

GCP/GMP aspects

1. What will happen with annex 13? will this be replaced with the CTR or other regulation. Annex 13 contains all GMP for IMP. What will happen with rules not related to labelling. Are they all covered by the CTR as well?

There will a new Regulation and new guidance, which will be implemented together with the CTR. :
a) Commission Delegated Regulation (EU) 2017/1569 of 23 May 2017 supplementing Regulation (EU) No 536/2014 of the European Parliament and of the Council by specifying principles of and guidelines

for good manufacturing practice for investigational medicinal products for human use and arrangements for inspections;

b) Detailed Commission guidelines on good manufacturing practice for investigational medicinal products for human use, pursuant to the second subparagraph of Article 63(1) of Regulation (EU) No 536/2014.

2. Is there any chance that some GCP 'flexibility' accepted during the Covid period could remain valid in the post-Covid era? e.g. study treatments sent at home (for self-admin or by visiting research nurse), biospecimen collection at home or at family doctor's practice or at local lab, some exams by telemedicine or visiting research nurse (incl participant safety), more extensive remote monitoring, etc. In the end, these are all common aspects of decentralised or virtual trials that will become more common in the future.

3. Labelling can take a long time to agree with the sponsor. What to do if the labels do not comply but ALL other documentation (IMPD/clinical etc.) is in order?
Appropriate labelling is one of the requirements of the legislation. Therefore, labels should be compliant with the Regulation (and currently with Annex 13 of GMP), as the other documents. If labels are not compliant, a GNA/question/objection should be raised to the Sponsor. (see ANNEX I- Section J. CONTENT OF THE LABELLING OF THE INVESTIGATIONAL MEDICINAL PRODUCTS: 58. A description of the content of the labelling of the investigational medicinal product in accordance with Annex VI shall be provided.)

4. Can you elaborate what is required for IMPS manufactured outside of the EU where no MRA is available (full Third Country production)?
The Sponsor should identify the site(s) responsible for importing and releasing the IMP(s) into EU. Such site(s) should hold a valid Manufacturing and Importation Authorization issued by an European Competent Authority. A QP declaration should be issued to certify that all activities outside EU are carried out with quality standards at least equivalent to EU GMP (see also Annex I of the CTR- Section F(33) and Q&A 8.4). Details on batch release of IMPs manufactured in a 3rd Country are also available in paragraph 8. RELEASE OF BATCHES of Detailed Commission guidelines on good manufacturing practice for investigational medicinal products for human use, pursuant to the second subparagraph of Article 63(1) of Regulation (EU) No 536/2014

5. For GCP, there were only the questions related to SB, their assessment and status, this was answered in the chat by Ernesto and Elke this is under construction/progress in work. – We could make a short note on this in the post-meeting Q&A.

6. Is a site located in Northen Ireland allowed to perform batch release and QP certification in EU for clinical trials?

If an investigational medicinal product is shipped from Great Britain to Northern Ireland and then to the EU, it is regarded as an imported investigational medicinal product and therefore the batch release for this product needs to be certified by a QP in the EU (or NI) according to Article 13(2) of Directive 2001/20/EC.

If (part of) the IMP is manufactured in GB and imported from GB to NI by a MIA holder in NI and its batch release is certified by a QP in NI, it can be used in the rest of the EU.

Please note that certain flexibilities are in place for importing IMPs from GB to NI, IE, MT and CY provided that the IMP is not made available in any other EU Member States: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52021XC0125(01)&from=EN

Transparency, publication

1. Will you come back to publication of inspection reports?
2. To which degree the sponsor will be allowed to redact any information e.g. if they (or their vendors) can try to obstruct publication if there is something in the report which is not
3. Regarding the publication of data on the EU portal: if a product is not on the market then which data may be use in completing the evaluation reports? Will these reports be published immediately after the approval of the study?
4. Will reports of inspections by third countries only be available in CTIS in a redacted format?
5. What happens if a trial is a combination of category 1 and 2 trials?

GDPR/CTR

1. Can you please give the reference to the provision saying that the consent under GDPR does not have to be given in writing?
   Please see recital 32 of GDPR that states: "Consent should be given by a clear affirmative act establishing a freely given, specific, informed and unambiguous indication of the data subject's agreement to the processing of personal data relating to him or her, such as by a written statement, including by electronic means, or **an oral statement**. This could include ticking a box when visiting an internet website, choosing technical settings for information society services or **another statement or conduct** which clearly indicates in this context the data subject's acceptance of the proposed processing of his or her personal data." (emphasis added).
2. If subject withdraws consent under GDPR, can the sponsor still process/collect safety data for regulatory purposes?
   If that means that the processing is necessary for compliance with a legal obligation to which the sponsor is subject, then yes.
3. Is it possible that the participant withdraws consent from trial under CTR but the sponsor still processes the data collected until then?
   If, after a participant withdrew his/her consent from a trial under CTR, the sponsor still needs to process participant's personal data for regulatory purposes, then it can do so (as the processing is necessary for compliance with a legal obligation to which the controller is subject).
4. Is a controller the so-called DPO?
   No, a controller is natural or legal person, public authority, agency or other body which, alone or jointly with others, determines the purposes and means of the processing of personal data. A DPO (Data Protection Officer) is a person with expert knowledge of data protection law and practices that should assist the controller to monitor internal compliance with GDPR.
5. Is the health care institution/hospital/trial site the exclusive controller of the medical charts of the subjects?

If the health care institution/hospital/trial site determines the purposes and means of a processing of personal data, it becomes the controller for that particular processing. It also means that it becomes responsible that the data are collected for specified, explicit and legitimate purposes and not further processed in a manner that is incompatible with those purposes; further processing for archiving purposes in the public interest, scientific or historical research purposes or statistical purposes shall, in accordance with Article 89(1) of GDPR, not be considered to be incompatible with the initial purposes.

6. Joint controllers where there are two sponsors?
   Only if both together determine the purposes and the means of the processing of personal data (i.e. in practice it usually means if they are both involved in the planning of the clinical trial).
7. What if you can use big data (e.g. gene sequencing results) to identify subjects in clinical trials? Would that (indirectly identifying persons) be a violation of GDPR?
   The mere fact that you can (possibly) identify a data subject is not a violation of GDPR. It however means that any information relating to the individual must be treated as personal data and therefore GDPR (and possibly applicable national laws) applies.
8. Two research institutions are joint controllers if they work on the same project but the means are different?
   If both together determine the purposes and the means of the processing of personal data, they are joint controllers.
9. When the legal basis for data processing is consent, how and by whom this consent and/or the GDPR process is assessed?
   According to Article 7 of GDPR, the controller must be able to demonstrate that the data subject has consented to processing of his or her personal data. In general, the controller is responsible for, and must be able to demonstrate compliance with, the compliance with principles relating to processing of personal data (Article 5 of GDPR).

MS preparedness to use CTIS

Additional information:

LINK to CTIS training programme page including many materials on CTIS MS and sponsor workspaces: elearnings, videoclips, infographics, quick guides, FAQs: https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trial-regulation/clinical-trials-information-system-ctis-training-programme

EMA is developing a training catalogue - an elearning training programme , already available at the EMA website. This traininh allows to train at any moment a new end user or chech/remind functionalities.

https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trial-regulation/clinical-trials-information-system-ctis-training-programme

Latest CTIS training module added a week ago is nr 12 - Data protectionhttps://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trial-regulation/clinical-trials-information-system-ctis-training-programme

MS mAster Trainer programme is ongoing since Dec 2020: each MS has 2 nominated Master Trainers covering both ethics committees and NCA. So far 4 modules have been disseminated to all, and 2 more to half the group: work is going well and Master Trainers are learning the system well, we can see fom the feedback they give

Transition

1. Would it be possible to elaborate more on the transitional period (art. 98)? If an ongoing trial, approved under Directive, has not yet concluded 3 years after implementing the Regulation, what needs to be done (by the sponsor)? Submit the dossier for approval according to Regulation? And if so, is a full review applicable according to the CTR or not?

Was answered during the presentation. See also QnA chapter 11 on transitional measures

2. Until when it will be possible to submit an application under VHP?

Until around November (to allow sufficient time for completing full assessment process before the application date of the CTR)