EUFEMED Innovation Club Workshop: 18 November 2022

Reporting Obligations Under the New Clinical Trials Regulation

Summary

The new clinical trials regulation (CTR) is replacing the old clinical trials directive (CTD), and the text of the CTR now has to be implemented in national legislation. This means that all clinical trials in Europe will be done in the same way in future. The CTR intensifies the obligations for sponsors in relation to both trial management and results reporting.

The meeting was opened with an overview of reporting obligations for running trials under the new CTR given by Ingrid Klingmann of Pharmaplex bv, Belgium. The meeting continued with a session focusing on Sponsor reporting obligations for clinical trial results presented by Kerstin Breithaupt-Grögler of kbr, Germany. The round table discussion involved Jelle Klein (Belgium) and Thomas Smith (United Kingdom [UK]), with Izaak den Daas as moderator.

Session moderator: Izaak den Daas, Director Patient Studies, QPS Netherlands BV

Expert panel:

- Kerstin Breithaupt-Grögler, Specialist in Clinical Pharmacology, kbr, Germany
- Jelle Klein, Medical Director, SGS, Belgium
- Ingrid Klingmann, Managing Director, Pharmaplex bv, Belgium
- Thomas Smith, Independent Patient Consultant, UK; Fellow of European Patients' Academy on Therapeutic Innovation (EUPATI)

Introduction

This meeting was introduced by EUFEMED's President, Dr Tim Hardman, and the moderator was Izaak den Daas. This webinar was the third in the series on the new CTR coming into effect in 2023. The topic of this webinar was on reporting obligations under the CTR, with a particular focus on suspected unexpected serious adverse events (SUSARs), serious breaches, the summary of trial results and the lay summary of trial results. After introducing the various participants, discussions began with a presentation of the reporting obligations for running trials under the CTR.

Reporting obligations for running trials under the new CTR

Speaker: Ingrid Klingmann (Pharmaplex)

Background

On the intentions of the CTR concerning transparency, the topic of transparency was raised primarily by the European Parliament, which wanted to strengthen aspects of transparency and the ability of the regulation to achieve this.

Reporting requirements

Recital 25 of the CTR states: "In order to increase transparency in the area of clinical trials, data from a clinical trial should be submitted in support of a clinical trial application, if that clinical trial has been recorded in a publicly accessible and free of charge database". Some databases that would fulfil these requirements are then listed. It states that "Specific provision should be made for data from clinical trials started before the date of application of this Regulation". The intention is to make sure that under the CTR, the trials that were started earlier also fall under these requirements.

Recital 37 explains another important aspect, that this regulation allows patients "to assess possibilities to participate in a clinical trial", and allows for "effective supervision of a clinical trial by the member state concerned". Patients can search for trials and see which trials exist, which trials are open for recruitment, where they stand and whether there is still a chance that they can join. Patients can also discover where the trial is being performed, and whether there is a site in their country or region. Enabling this was an important intention of the CTR. It also intends to ensure seamless and reliable supervision by the member states involved. There is now a request to clearly define and announce the start of the trial and the end of the trial, but also the end of recruitment, which is very important, especially for patients. Additionally, the results have to be made available within a year after the end of the clinical trial. This has created a lot of additional workload and complexity (see the presentation by Kerstin Breithaupt-Grögler for more details). This is a significant task for sponsors to achieve.

Start of the clinical trial

In Recital 38, the first act of recruitment is more clearly defined. The first act of recruitment is now at the start of the trial, and the recruitment strategy has to be described in the protocol. Therefore, it is necessary to discern, especially in early phase trials, how to deal with this in the most efficient way in practical terms. The definition related to the start of the trial (Definition 25) states this is "the first act of recruitment of a potential subject for a specific clinical trial, unless defined differently in the protocol". There is scope to describe in

the protocol how exactly recruitment is going to be done and what is meant by the start of the trial.

The text of the regulation, Article 36, deals with these reporting obligations. It makes clear that "The sponsor shall notify each member state involved of the start of a clinical trial" in that country. Therefore, in multinational trials, a national announcement has to be done through the European Union (EU) portal (Clinical Trials Information System; CTIS) for each country involved, and this needs to be done within 15 days from the start of the trial, i.e., the first act of recruitment. There is also a requirement to notify in CTIS the first visit of the first subject in each country within 15 days, and the end of recruitment in each member state within 15 days after the end of subject recruitment. In a situation where a trial is put on hold and is subsequently restarted, there is also a requirement to report this within 15 days after the restart.

End of the clinical trial

The end of the trial is defined in Definition 26 of the regulation as "the last visit of the last subject, or at a later point in time as defined in the protocol". So, there is some flexibility in case a special situation needs to be described and enabled. Article 37 states that the end of the trial has to be presented in the portal within 15 days for each member state, for the EU as a whole, and in a global trial, for all countries that were active in the trial.

Temporary halt of the clinical trial

Special conditions are explained for temporary halts, which have to be kept in mind. A sponsor can halt a study and if such a halt occurs, it has to be notified within 15 days. And if the study is then resumed for whatever reason, then that also needs to be notified within 15 days. If this halt is because of a change in the benefit-risk balance, so if there is a safety issue, again this halt needs to be communicated without undue delay but not later than 15 days; however, the restart of such a trial requires a substantial modification and an approval. And therefore, in this case the trial cannot simply be restarted, but formal approval has to be obtained through the substantial modification. This is certainly going to mean additional workload for sponsors to ensure these regular updates in CTIS.

Safety reporting

One potentially significant improvement is in the area of safety reporting (CTR Articles 40 to 44). Under the CTD, SUSAR reporting to the competent authority and ethics committee was required in each country where the study was taking place. However, conditions were variable and, in some countries, the ethics committee no longer wanted to get this information on a one-on-one basis, but only in a consolidated way, for example, every 3 months or every 6 months. Thus, it was necessary to know exactly what the reporting

requirements were, country by country. And because the CTD is continuing to be a valid regulatory framework for clinical trials that started under the CTD, this reporting will have to continue until the end of the transition period, which is 2025.

However, in the meantime, the EudraVigilance database has finally become fully functional, and therefore there is an agreement that practically all SUSARs have to go into this database. This also applies to studies that are being run under the CTD. This system will now provide SUSAR information to competent authorities and ethics committees of all the countries involved through CTIS, because EudraVigilance is part of CTIS. The timelines for SUSAR reporting remain unchanged: 7 days after a life-threatening or deadly event and 15 days for all other events. But what is now requested from the sponsor is the reporting of all SUSARs wherever in the world they occurred, and also after a subject has left the study, but only in EudraVigilance. So, in addition, later SUSARs that occur after the patient has left the study anywhere in the world have to be entered into EudraVigilance in future.

What also remains is the annual safety report in the Development Safety Update Report format and here the requirements remain unchanged, it also now goes into CTIS. The SUSARs and annual safety reports will be jointly assessed, and this is something important to know. These will be jointly assessed under the leadership of one of the concerned member states, but this must not be the reporting member state. So, the authorization of the trial can be coordinated by one country's competent authority, but the safety information is coordinated in the assessment of these events by another of the involved competent authorities. Where national legislation defines that ethics committees also get access to this information, then this will occur via the system. But otherwise, there will be countries whose ethics committees are cut off from this type of information.

There are also annexes in the CTR, and Annex III covers safety reporting obligations. It makes clear that medication errors, pregnancies and use outside the protocol also need to be reported like adverse reactions. The expectedness definition remains the same; it is the sponsor who has to verify versus the Reference Safety Information in the Investigator's Brochure or the summary of product characteristics to see whether the event was expected or not. It is important to note that the cover letter needs to reference the location of the Reference Safety Information, and that unblinding of serious adverse reactions before potential reporting as a SUSAR should be done by a staff member that is not involved in the clinical trial. That is the same as before, but if something like this occurs it also needs to be clearly reported to the Data and Safety Monitoring Board and the European Medicines Agency (EMA). So there will hopefully be a big reduction in complexity and need for resources. This all now goes into EudraVigilance once and is then assessed and coordinated within CTIS and within the coordinated assessment procedure.

Serious breaches

For serious breaches, there will definitely be changes in what has to be done and what is going to be checked in audits and inspections. Therefore, it is very important to discuss this, because it is the same for early phase trials as it is for later phase trials. In December 2021, an EU guideline was released in the context of the CTR legislation, which can be found in EudraLex Volume 10 (https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-notification-serious-breaches-regulation-eu-no-536/2014-clinical-trial-protocol_en.pdf). This is a guideline that was originally developed by Medicines and Healthcare products Regulatory Agency (MHRA) in the UK; these EU Commission guidelines are usually under the leadership of one of the member states and are then assessed and agreed and released by all of them, but one is in the lead. And in this case, it was the MHRA, but when Brexit occurred, they had to separate from this whole regulatory framework. The MHRA has a very similar guideline on this topic now, so for serious breaches, conditions are practically the same on the continent and in the UK.

The appendices in this guideline are interesting; Appendix I gives examples of serious breaches, and Appendix II covers points to consider for sponsors in relation to the assessment of a breach (what the sponsor should do). Appendix III a is a template form for reporting a serious breach (as it appears in CTIS). Appendix III b is information that needs to be submitted together with a notification of a serious breach.

The definition of a serious breach is any deviation of the approved protocol version or the CTR that is likely to affect the safety or rights of trial participants and/or data reliability and robustness to a significant degree in a clinical trial. That is quite general, and the question is, how is this going to be interpreted? What people also need to be aware of is that the sponsor has to identify which is the affected member state and whether the member state is directly affected by the serious breach. For example, the member state where the sponsor is based (as they have the overall responsibility), and/or the member state where patients are affected by the breach, or it could be the member state where the breach occurred, so for example, in an Interactive Response Technology provider, or in a lab, or anywhere else where study activities are performed outside the countries where the patients are enrolled.

Examples are as follows:

- Consent: patient information leaflet and informed consent updated, but at one trial site, this was not relayed to the patients until approximately 2-3 months after approval. In this case, if there was a systematic or persistent problem and/or if it had a significant impact on the safety and rights of a trial subject, then it had to be considered a serious breach

- Access to data: the investigator would not allow sponsor/Clinical Research Organisation (CRO) access to the trial participants' notes. This is a serious breach
- Loss of trial data: this is a serious breach as it is likely to affect the safety and rights of a trial subject. Clinical Trial sponsors and vendors should have agreements in place addressing business continuity, and ensuring that clinical trials data are retrievable at any point in time
- Randomisation errors
- Privacy: the sponsor contracted CRO to build an electronic case report form. The electronic case report form contained patient identifiable information, and both the sponsor and CRO had access to all this information. This is also a serious breach
- In an investigator-initiated trial, there was a case where the names and addresses of trial subjects of other investigator sites had been handled by one of the other sites, which was in response to the investigator, and this was also considered a serious breach because it was likely to affect a significant degree the rights of the trial subjects

There is a quite long list of examples that should help to understand whether something is to be considered a serious breach or not, but it is not always clear. There can be differences between the judgement of the site (the clinical trial unit) and the sponsor, and therefore, there are quite detailed descriptions on how the reporting has to occur.

Reporting of serious breaches

When the sponsor has reasonable grounds based on evidence to believe that a serious breach has occurred, the first information on the breach is expected to be reported within 7 days. The breach has to be investigated and action taken; this occurs in parallel with the notification, or even after the notification. If it really is something serious, it has to be reported right away with further investigation in parallel. Serious breaches to the regulation or the protocol have to be notified by the sponsor through CTIS within 7 days after the sponsor has become aware of the breach. In other cases, some degree of investigation and assessment may be required by the sponsor prior to the notification just to have an idea what happened and whether anything happened at all. It is an obligation of the sponsor to make a judgement on how quickly they can notify this serious breach in a meaningful way in CTIS. There is some flexibility, but on the other hand, in case of an inspection, the sponsor will have to justify what has been done.

The reporting should officially go to the most affected member states. A decision tree is provided in the guideline, which a sponsor can follow to find out what they should report to whom. If the clinical trial is authorised in only one member state, which is mostly the case in early phase trials, the member state in which the clinical trial is authorised is the most affected member state. But if there is more than one country, the situation is different. If the serious breach affects only one member state, then this is the most affected one, and if

not, then we have to see if the serious breach occurred in a specific member state, for example, outside of where the patients were recruited. The decision tree details to whom this serious breach has to be reported.

Sponsor obligations for serious breaches

The sponsor is expected to do a thorough root cause analysis to identify the cause of the serious breach and to assess the impact of the breach on the reliability and robustness of the data, as well as the impact on trial participants' safety and/or rights. This assessment needs to be properly documented, along with the appropriateness of the decision and of the actions taken, because it might trigger an inspection. It is very important to have good documentation of what occurred. If it is not properly documented, there might be a problem resulting either in an acute inspection if it is very significant issue, or an inspection after the end of the trial. The question of relationship with the CRO is also described in this guideline, and it is clearly recognised that there can be differences of opinions and disagreements. But if there are such disagreements between a service provider and the sponsor resulting in no notification of the serious breach, then the classification and assessment of the breach needs to be presented, along with the nature of the assessment by both parties. The related communication between the sponsor and delegated party needs to be clearly and transparently documented, so that the situation is clearly defined, and the sponsor must make sure that this situation can be verified afterwards and potential problems then identified.

In conclusion, serious breaches will now require attention during clinical trials in all phases, and people need to be fully aware of the need to understand what constitutes a serious breach, what needs to be done internally, and how the reporting works. Reading the guideline is recommended. It is not very long, but it is very helpful. Teams need to be fully aware of this too, because this topic was not present at this level of intensity before the CTR.

Sponsor reporting obligations for clinical trial results

Speaker: Kerstin Breithaupt-Grögler (kbr)

Recital 37 of the CTR requires the results of the clinical trial to be reported within 1 year of the end of the trial. The sponsor has to submit a summary of the clinical trial results to the EU database, which is done via CTIS.

Integrated clinical study report

The content of the clinical study report is something that has been done in the same way for the last 20 years, applying good quality based on the International Council for

Harmonisation (ICH) E3 guideline on the reporting of clinical trial results. The full clinical study report is also called an integrated report, because it compiles all of the information on planning and conduct as well as compiling the raw data, the analysed data and the statistical analysis, and it also discusses the results and puts them into further context.

Clinical trial report content

Looking into this content in more detail, the ICH E3 guideline clearly guides us through the list of contents concerning general information and methodology, then concerning results and discussion. Coming back to the other requirements set up in the EU CTR, this calls for the presentation of the scientific results summary via CTIS, and it may be possible to use the synopsis of the full clinical trial report. It is not requested that the scientific results summary be presented in the same format as the synopsis, which we know has standardised format to enable comparison across trials, practically worldwide, and is the established standard, but it could be a means of complying with this reporting requirement.

There is also a section where changes in conduct and analysis are reported. These are changes between the planned and actual methods. This could also be a place where serious breaches could be reported. This is because the reporting obligation is not only within CTIS to other member states, in order to enable other countries to adapt their risk-benefit evaluation for a specific trial if necessary, but also at the end of the trial, when the sponsor has to come up with a full evaluation of the amount and the type of serious breaches that were observed in a clinical trial and that need to be reported in the clinical trial report. Depending which types of serious breaches have been seen, they will lead to withdrawal of patients or to specific patient data that cannot be included in the overall evaluation because patients cannot be included into the protocol analysis. The results section covering the details of the study patients may also be a place where a sponsor could report serious breaches.

The results section of the full clinical trial report also covers efficacy and safety results and discussion, as well as a section for all the raw data, the statistical analysis and all further essential documents related to the clinical trial.

Summary of the results of the clinical trial

Another new guidance for the summary of clinical trial results that has to be provided within CTIS is Annex IV of the CTR. It provides some hints on what the content of the results summary should be. It should identify the trial, identify and report on subject disposition on baseline characteristics, the endpoints that were assessed and the outcome of these endpoints, the method of assessing adverse events, which adverse events were observed, and any important additional information.

Lay summary

Another type of report that has to be prepared, in addition to the clinical trial report and the summary of trial results, is the lay summary. This is a summary of clinical trial results in a format understandable for laypersons. It aims to increase transparency and trust in clinical research as addressed by Ingrid Klingmann, who shared with us the principles of why the CTR took up specific aspects. This lay summary is targeted at the general public and interested patients, as well as trial participants. This specific information is not only intended for those who were involved in a trial and who know a lot about the specific trial from their informed consent form, it is also targeted at other patients in that indication, or just the general public that might be interested in research.

It is mandatory to write a lay summary for all types of clinical trials, including early phase clinical trials, i.e., phase 1 trials without therapeutic intent. There is some information in Annex V of the EU CTR on what needs to be reported, but only basic information on 10 elements that have to be covered. The summary should identify the trial sponsor and address the following questions:

1. Why was the trial done?
2. What were the populations?
3. How were the subjects characterised?
4. Which products were used?
5. What were the safety reactions and their frequency?
6. What were the overall results?
7. Are there any comments on how the results can be seen in the context of results from other trials?
8. Where can I find more information if the content of lay summary is not enough for me?

Guidance documents for content and development of lay summaries

As there was no guidance on what should be contained in these 10 elements, additional recommendations have been set up in recent years. The first is from an EU expert group that worked on the content of the 10 elements but also described some principles of numeracy and literacy concerning lay language. There is also a question and answers document on the EU CTR, which is now applicable. In addition, a large group of stakeholders from different companies, persons and institutions involved in clinical research have been working together for 2 or 3 years to set up Good Lay Summary Practice (GLSP).

Good Lay Summary Practice

Ingrid Klingmann was one of those who started this initiative, and also brought it to the conclusion that the EMA could endorse the GLSP guidelines. They can be found in the EMA

framework within EudraLex. A brief summary of the content of the GLSP recommendations is presented below. First of all, it is necessary to know the setup of lay summaries: this is a process that needs planning and starts with the planning of the clinical trial, through the development of the lay summary. Translation is necessary because the lay summary should be available in all the languages in which the trial actually took place for all trial participants to be able to understand it. Regarding dissemination, the EU CTR requires the lay summary to be uploaded in CTIS.

The CTIS system has one open end where the general public can look into all that is posted, but this is a complicated way to find the information, and other means of dissemination might be worthwhile. The GLSP guidelines also explain which competencies are required: lay summaries have to be correct and have to reflect the scientific output of the trial, and thus have to be aligned with the summary of trial results and with the full clinical trial report. However, they have to present this in very different language—in lay language—and other principles of numeracy and literacy have to be applied. Thus, different knowledge might be required for people who engage in lay summaries. This can be looked up in GLSP.

Another element of GLSP provides further description regarding the results of the clinical trial and what to add to the lay summary. The primary endpoint has to be described and in addition, the writer must make sure that no cherry picking takes place when choosing secondary endpoints that may be helpful for patients to base their questions to the treating physicians on. Are there patient related outcomes that are reportable? Or does the summary just report the secondary objectives based on what is positive for the compound and not what is negative for the compound? There are a lot of discussions and questions and it is not easy to determine what (apart from the primary endpoint) should be added to the description and reporting of the clinical trial results.

A further GLSP element contains provisions regarding the adverse reactions that need to be reported. This can be difficult because the categories are different from the usual evaluation categories reported in the clinical trial report. Within this context, the focus of the general public might be different from the sponsor focus on these categories. In a clinical trial report, every serious adverse event is also an adverse event, but this might not be compliant with the categories called for by the lay summary. This is because the lay summary has to differentiate between serious adverse events and non-serious ones. In addition, the most common adverse events should be presented first. There is no clear definition what a common adverse event is and what it is not.

Layout and design are also described in GLSP, and readability for a layperson may very much depend on the layout and the design that is chosen. It may be necessary to implement user testing too. As each sponsor will produce more than one lay summary in the future, they should try to establish a new routine, and standardise the stakeholder review of a document

before it is uploaded to the sponsor website or to CTIS. Translation is a big question and an English master version is always needed. The translation procedure has to reflect cultural differences without losing the context in which the sponsor wishes to place the lay summary.

Guidance is also given regarding some aspects of dissemination: it has to be clear that dissemination is done in a non-promotional manner. Dissemination of the summary by methods other than CTIS may require clear cut evaluation of what is possible in a specific country. There may be national laws requiring further ethical considerations if it is disseminated directly by an investigator, for example, and whether a sponsor would need a separate website, apart from their own website, which could be regarded as being a promotional one.

The GLSP guidelines are one source of information for this new type of report—lay summaries. The GLSP Network website provides additional information and updates on further developments (https://glsp.network/).

Timelines

For the sponsor, the timelines provided in the EU CTR are tight. For patients, these timelines might seem long. The usual timeline is 12 months after the end of the trial; the summary of the clinical trial report as well as the lay summary should be available in CTIS. For paediatric trials, the timeline is shorter, as it is only 6 months for phase 1 trials without therapeutic intent. An extension of timelines may be requested by the sponsor for up to 30 months after the end of the trial. In early phase and exploratory clinical trials, the end of trial could be defined in the clinical trial protocol as the last subject last visit or last finding. Or when complex analytical methods have to be established (especially when in addition to pharmacokinetics [PK], pharmacodynamic exploratory biomarkers are assessed, for which validated methods may not be in place), and it may take at least 6 months to obtain all the data from biological assays, the end of trial could potentially be defined as database lock. In this case a clear rationale has to be provided for defining end of trial as database lock in the clinical trial protocol.

Deferral of publication

Sponsors have the option to defer publication of specific data/documents to protect commercially confidential information. Patients really want to have access to trial results so that they can find opportunities to engage as trial participants, ask their treating physicians further questions, enable discussion of results early on, and have access to innovative treatments as soon as possible. Thus, transparency is really important for patients. On the other hand, from the sponsor's perspective it can be complex to clear data, achieve database lock, perform all the evaluations, and then put the results (which might be from an

early phase clinical trial and might contain commercially confidential information) into a publicly accessible database. This is why the EMA planned that deferral rules can apply depending on the trial category, and depending on the type of data that are being published. Further information can be found in a draft guidance document on protection of personal data and commercially confidential information (EMA/212507/2021).

Regardless of which type of deferral is being requested, when input is provided to CTIS and all the documents in a clinical trial authorisation application are included, two versions of documents have to be provided, one intended for publication and the other not for publication. In the document intended for publication, redaction (blacking out text) may be used so that certain data are not legible. But this should be done with the utmost reluctance because otherwise, the clear intention of EMA to increase transparency could be weakened. The sponsor may ask for deferral, but the assessment report produced by the competent authorities states whether this deferral will be accepted or not.

Deferral rules for confidential information

Different rules apply for different types of data. Early phase clinical trials without therapeutic intent such as PK/pharmacodynamic trials, bioequivalence trials or first-in-human trials usually fall into Category 1, but only if there is no therapeutic intent. In some cases, for example with a new therapeutic oncology treatment, the first trial may be conducted in patients. And if there is an intention for treatment with specific complex compounds that are only given once, for example, the trial would not fall within this category. The main characteristics regarding the sponsor and some aspects of notifications the sponsor receives can be deferred until the final summary of results is added into CTIS. The more detailed information in the subject information sheet, the clinical trial protocol, the Investigational Medicinal Product Dossier, the Investigator's Brochure, or the responses to a request for further information from the authorities can be deferred for a longer time period, up to 7 years after the end of the trial. This may be around the time when a marketing authorisation is obtained. Thus, the information provided in all of these documents would no longer be commercially confidential. Clinical trial summaries for an intermediate data analysis and for the final analysis, as well as the lay summary, can be deferred for a maximum of 30 months if requested by the sponsor and if the competent authority accepts the reasons provided for the deferral.

Information that should not be considered commercially confidential

The draft guidance document on protection of personal data and commercially confidential information also defines information that should not be considered commercially confidential, and should always be made publicly available. This is to ensure increased transparency, help patients to find the information they need for their individual treatment

schedule, help them decide whether to participate in a trial in order to have quick access to innovative treatment, or help them prepare for further discussions with their treating doctor.

Information that cannot be considered commercially confidential includes information that is already in the public domain, information that does not bear innovative features, and information that would not qualify as commercially confidential, e.g., general administrative information, some aspects of quality related information, and non-clinical and clinical information. Sponsors requesting deferral should inform themselves, and can find some guidance in this document. Sponsors should be aware that it must be possible for the public to understand the development of a new compound. Withholding all the information is not helpful, as this is not compatible with the drive for increased transparency and trust in research.

Trust in research is essential. This has been illustrated throughout the pandemic when many people unfortunately did not get vaccinated because they did not have enough trust in clinical research. This is something that should be avoided, so building up transparency and trust helps clinical researchers to really address the needs of the public.

Following the presentation by Kerstin, the audience were encouraged to ask any questions.

Izaak den Daas: (Question from an audience member) The first act of advertisement is considered the start of the trial. How will phase 1 units handle this when they recruit volunteers from the existing volunteer database? Starting recruitment before the start of the trial is probably a very interesting issue now. Jelle, as a representative of a phase 1 CRO, can you comment on that?

Jelle Klein: I think this will be one of the biggest changes for us, for recruitment of participants, because right now we can actually start recruitment before approval, with pre-approval templates and using a database, so advertisements are not done. When you have approval, you can basically start screening the next day. Now, with the changes introduced by the CTR, we need to wait for approval before starting to contact subjects, which means at least 3 weeks' delay to the start of screening after approval. This will have a significant influence on overall timelines.

Izaak den Daas: Yes, and because Belgium and the Netherlands are some of the fastest countries to start a trial, timelines will now be more equalised over the whole of Europe, I presume.

Jelle Klein: Yes, that's true. Of course, we still need to see how much influence it actually has in the end. The benefit now is that we can submit any day for the CTR, whereas in the past, we needed to wait till the committee came together. In our case, that's once a month. If you

just miss a meeting, you're a month late already. And now, you can submit in a timelier manner. In that case, it might help to reduce those times a little. But we have had no CTR submissions yet, because everyone is trying to avoid it. This month, it's very busy with everyone still trying to do it with the CTD before they have to go to the CTR. What the practical consequences will be, we will see, but I assume that there will be some changes.

Izaak den Daas: Yes. Anyone else on the panel?

Ingrid Klingmann: Just a question—would it not be possible to change the approach to the general recruitment of healthy subjects into your database? It does not fall within the CTR definition, if you say we have we expanded our database with people from whom we have a broad range of parameters, so that we know whether in principle, they fall within the inclusion and exclusion criteria. Then we could directly approach those that look the most suitable. Wouldn't that help with timing? It could perhaps then require only a few days of delay, but not 3 weeks, because I think 3 weeks is really a lot.

Jelle Klein: That's true. Actually, that's the way we work at the moment, we recruit subjects for our database, and that can happen at any moment. When we have approval for a new trial, we send it out to them. So we can still do the first step, that's no issue. The problem is that participants, of course, look at the agenda of the trial itself to see if they can participate. It takes some time for them to check that. The evidence now is that before approval, they can check their diary because we have templates to send to them, and then they can say after approval, okay, I will be screening on this day minus 21. So now we can start screening. Whereas with the new system, we have to wait to send it to the subjects and they have some time checking their diary to see if it is even possible to do the trial. And that's the reason for the delay, but of course, there will be a lot of fine tuning once we have a few trials actually running.

Ingrid Klingmann: I think it would be helpful practically for phase 1 units to create a standard text on the recruitment process, because that now needs to go into the protocol. If you have a standard approach to doing that, then I think protocol writing can be facilitated in that regard. It can also be laid out very clearly how you're doing it and how you define the start of the first recruitment activity for this particular trial. I think there are also opportunities to improve the wording here.

Jelle Klein: I agree. I think we work with certain templates a lot more, not only for that but for the entire recruitment, for the screens, things like that [inaudible] you now need a lot of templates that you can use when you need them.

Izaak den Daas: Okay, thank you, that's quite clear. I have a question here with regard to serious breaches. Do you know if it will be visible when a member state has completed the

review of a serious breach, i.e., will the serious breach notification be closed in some way by a member state? To also confirm that no questions/requests are expected.

Ingrid Klingmann: Well, I do not have personal experience of that yet. But the way CTIS works usually foresees a very clearly defined process, and as there is a coordinated assessment procedure there needs to be an outcome. So that information is certainly going into CTIS, but I've not read that there is any timeline for achieving an outcome. So that means the person in an organisation who regularly goes into CTIS also needs to keep an eye on that aspect to see whether there is any final statement on this serious breach or not.

Izaak den Daas: But it's still early days for this, because there's not much experience yet.

Ingrid Klingmann: There's hardly any experience. There are very few phase 1 studies that have been approved. Altogether, we need to be aware that per year, we have about 4000 clinical trials with investigational medicinal products approved in Europe. At the moment through CTIS I have not seen the very latest numbers, but it's perhaps somewhere between 300 and 400. So the vast majority of trials in 2022 have still been authorised through the CTD system.

Izaak den Daas: We can move on to patient involvement, what makes patient involvement in the early phase trials meaningful? And where would you see the real benefits for patients, the phase 1 unit, or sponsors? Thomas, can you react to that?

Thomas Smith: Making patient involvement and engagement meaningful is a “beauty is in the eye of the beholder” situation. Because what you imagined to be meaningful, might not be meaningful to your target demographic, so the only way to find out how to meaningfully engage people is to ask them. This can be difficult, but it can definitely be done, it should be done, and it will be done increasingly moving forward. I can give you an example of what is not meaningful. I work for a research ethics committee in the UK. And you would be—well maybe you wouldn't be—stunned, but to tick the box on patient engagement in your trial design and application, all you need to do, and all that most sponsors do, is to tick “Yes” in a little box in the form in the Integrated Research Application System that says “Have you involved patients? If so, how?”. And invariably the answer is well, we showed patients the recruitment poster. And the conversation probably goes something like, “do you like the colours that we've used in the recruitment poster”, and the patient will probably say “yes, it’s all right”. And that's it. So that particular dinosaur is going to die very soon, hopefully. But don't do that, do more than that.

Izaak den Daas: Yes. Anyone else on this subject? When I think about patient involvement, I always think of the recruitment possibilities for patients in early clinical trials, where there's no therapeutic benefit for the patient, most of the time. But there is still a benefit because there is drug development in an area where there's often a high medical need.

Thomas Smith: Yes, there are other more complicated things you can do like co-developing the protocol and the trial design. The patient community is really changing, and with organisations like EUPATI, increasingly, the patient community has exactly what it needs to contribute to those “meatier” subjects. Recruitment is a huge part of it. But also, you can bring patients into the recruitment process, almost. How to go about recruiting rather than just working away at a particular document that you're going to hang in a clinic waiting room, for example, you can get involved in much more meaningful ways, much sooner than that.

Kerstin Breithaupt-Grögler: I imagine that involvement of patients early in the development process of new medicines could also be helpful for formulation development, i.e., formulations that patients like versus formulations that they don't like so much. For example, we know that geriatric patients have to take very large tablets, and we do not have geriatric adapted formulations at hand. Everyone who takes care of older people knows you cannot swallow these [tablets] when you cannot swallow anyway. I imagine that coming into certain development processes as early as possible would be helpful for the entire process of development to reach a good dose for patients as early as possible.

Izaak den Daas: Indeed, a good suggestion.

Jelle Klein: Can I ask a question regarding this? For later phase trials, this wasn't standard, you ask your patients because they actually need that type of medication, but for a lot of early phase trials this is not the case, because you're looking for healthy volunteers. And as you said, you can use them for input to protocol design, or things like that. But how do you see that in early phase healthy volunteer trials? Who would you contact to see if they are interested in being involved? How do you suggest doing this?

Izaak den Daas: Yes, coming from a CRO as well, I have never met a clinical trial yet where they were asking the lay person, the healthy volunteer to have input in this.

Jelle Klein: No, we have [a lay person] in the ethical committee who also talks about seeing what they think about it, but not in designing things. It’s quite interesting.

Izaak den Daas: That’s true, there is a lay person in ethical committees (in the Netherlands the ethical committee is also the Institutional Review Board), and there's a lot of input about the clarity and the language of the informed consent form. You have to make it understandable to a large group of people with no higher education. And it is in Dutch, so that is a big problem, it's really difficult to explain how the clinical trial works in lay terms.

Ingrid Klingmann: I think we are facing a lot of changes at the moment. Clearly in phase 1, in the healthy volunteer area, we are very much behind the detailed discussion that we are facing in other phases of the drug development process. But the question here is, what is meaningful and what could be done. And I think over time, in phase 1 studies, we will come

to the situation that there are a few healthy volunteers who are interested in supporting contributions from the lay perspective to make these trials more subject friendly and reliable. I think this request to involve subjects as consultants to researchers will become stronger and stronger.

In CTIS there is a question in the application form, did you involve patients in any way in the preparation of the trial? I think in practice phase 1 units or sponsors who are preparing protocols, study documentation and materials will work regularly with a handful of healthy volunteers who have an interest in this to help them make sure that there is a review from the healthy volunteer side. I think it's an important thing to do. Secondly, the advertisement material is considered to make sure it is not promotional or inducing, and that this is reliably happening. The informed consent in the subject information sheet is certainly something as it quite often comes from sponsors when you are working in a phase 1 unit, and this is reviewed independently by a user. It is then possible to say we are doing what we can to make it as subject friendly as possible and as reliably applicable for healthy volunteers, then I think you have fulfilled your obligation. We need to be realistic and pragmatic, in how we find a balance between the involvement of the end users, and the amount of work that we can do and should do. It's important to work efficiently not [inaudible], but really just on those areas where we think there could be issues that we may overlook, or where we may not be as sensitive as a healthy volunteer who is participating in a trial. But I think there is an obligation on each institution/organisation to find the right approach in early phase trials.

Izaak den Daas: I agree. For many years now, the CRO I work for has had evaluation forms that every volunteer or patient gets at the end of the trial, where they can give their opinion. Although most complain about the Wi-Fi, but not about other things.

Ingrid Klingmann: This comes after the fact, but I think it’s important to have this patient engagement before the study is finished.

Izaak den Daas: It is. But still, you can get lessons out of evaluation anyway. It's better to, but at the end of the study there is the beginning of [another] study anyway. Okay, let's go to a couple of questions. There is one regarding the lay summary: it was stressed that primary endpoint and secondary endpoints that are patient related should especially be included. This needs to be taken into consideration at the stage of planning and writing the clinical trial protocol. What are helpful recommendations that should be given to investigators in order to have a good choice of relevant endpoints?

Kerstin Breithaupt-Grögler: You've absolutely got the point right. This starts the focus on patient relevant outcomes. It starts with the writing of the protocol and the trial planning. Which measures could you include in a protocol? I think this very much depends on the

indication, and we'll find some guidance and some of the discussions you need to take into consideration in GLSP. But apart from that, I think there is no “one [size] fits all” approach, you will always have to think about what the indication is, what the compound is, and what patients want would to know about the compound. We have some new standardised patient reported outcome scales available in various indications. But I think there is no general answer, except that pre-definition is required. It helps you to be objective; you're not only looking for endpoints with nice outcomes and you're including parameters that do not show an effect. Pre-planning is really relevant and including patient representatives in specific indications might be helpful at the planning stage. Maybe we can pass on this question to Thomas.

Thomas Smith: I just wanted to pick up your last point about patient representatives. I think you're right, it starts with the planning and it's about collecting complementary voices. There are different kinds of patients: there are regular patients who just want to live their lives and get on with it, there are obviously patient representatives who represent their own wider disease community, there are Patient Organisation representatives who toe the party line of the Patient Organisation. And there are also people like me, who work up above disease level. To define meaningful endpoints, you need to collect as many voices from those different kinds of people as possible; I think it would all be very complementary.

Ingrid Klingmann: Perhaps I can add to this. We have this problem of having to define patient relevant secondary objectives because the EMA uses this term in their question and answer document for the CTR, but they do not give a clear definition of what it means. And therefore, in GLSP, as Kerstin explained, we recommend to the sponsor to have an organisation-wide policy. The policy should define whether in this organisation, only primary endpoints are going to be presented in lay summaries or also secondary endpoints, and how patient relevant is defined. This is so that we can avoid the cherry-picking accusation that is always in the air. Specifically, for early phase PK studies, I think it would be possible to have a policy within the organisation saying we only report primary endpoints in our lay summaries, because first of all, that is really what is most important for the trial. Secondary endpoints in this early phase are not very patient relevant. So why not have a policy right from the beginning that makes your life much easier in preparing lay summaries. Of course, if you have patient phase 1 trials, then you need to go into all the discussions and considerations that Thomas has just mentioned. But for healthy volunteer studies, I think it is defendable to say our organisation policy is to report primary endpoints in a summary, full stop. I don't know what the others think. But for me, that would be a pragmatic approach.

Izaak den Daas: Yes, opinion of others? No opinion—then we are agreeing with what Ingrid says. Can I start with a couple of small questions? People are still concerned with the

transition period. During the transition period, how should annual safety reports be submitted, if we have trials approved by CTD and CTR?

Ingrid Klingmann: EudraVigilance is functioning, so SUSAR reporting in EudraVigilance and only in EudraVigilance is working now. This includes studies that were approved under the CTD, but for annual safety reports, personally, I would continue to send them to the competent authorities and ethics committees in the countries concerned. If it's a short phase 1 study, you don't need to send an annual safety report because the study is finished before the year is over. But in longer studies, I would send them to the competent authorities and ethics committees in all the different countries. If a country doesn't want to have that anymore they will tell you, but I think to be on the safe side, I would continue to send them.

Izaak den Daas: Another small question, is it safe to assume that trials running under the CTD are not yet concerned with the aspects of serious breach?

Ingrid Klingmann: Yes, the legislative framework of the CTD does not express it as clearly or in the same detail. I think it is possible to report serious breaches, but this is very vaguely defined and very rarely happens. I would say using the forms and [following] this process is only for studies that are approved under the CTR.

Izaak den Daas: Yes, thank you. A question from the chat, in case of serious breach, can you continue with the trial or do you need to wait for the green light? We recently discovered a mistake in study procedures and it was immediately corrected. The breach was reported and the corrective and preventive action (CAPA) was described, but I would like to know if we have to wait for the green light before we continue.

Ingrid Klingmann: That is not clearly stated, to my knowledge. I think you can continue your study because you have a CAPA and you have addressed it. We have had protocol deviations before and preparing a CAPA is the right process to avoid this happening again. If it is a major issue that requires a substantial modification, then you are in the approval situation and you cannot continue if it is a study breaking thing. But if there is a single, serious breach that is not an absolute catastrophe, it's not stated anywhere that you cannot continue your study.

Izaak den Daas: A second question, did I understand correctly that we need approval to restart in case of temporary holds?

Ingrid Klingmann: No, only if the hold is because of safety issues, if the study hold occurred because of serious adverse reactions that [required] a stop as you do now. It also happens that we stop trials because we see events that need further consideration and exploration. In such a situation you would need approval to get restarted. But in all other cases, for

example, when you are doing a single or multiple ascending dose study and you want to further evaluate your data before you go to the next step, you don't need an approval or substantial modification. An internal organisational issue has made you decide to stop, and then you continue. Or when you are running out of drugs or anything like that. Now that is more organisational, and you can simply stop and restart.

Izaak den Daas: Thank you. I would like to ask the next question to the panel. Should there be a lay summary template for PK trials to which patients have contributed, to reduce the need for involvement of patients/healthy volunteers in lay summary generation for each big PK trial? Is there an opinion about the lay summary template?

Thomas Smith: It's obviously an option. Different sponsors and relevant parties have different means and experience at their disposal. There are two parts to this answer. One is I don't advise doing it in house. Sometimes, obviously, that can be useful. But if you want to create a framework, collaborate with experts and bring that expertise into your organisation. What can be considered lay language is subjective, and it can cause a lot of problems, so I would look outside to pull that expertise in house.

Just a bit of an anecdote really about my experience, because reviewing plain language documents is one of the things I do to earn a living. One of my biggest clients is by far and away leading in this world. I've raised the issue with them before, of standardising certain things that they want reviewers to look at. They are quite strongly against it. They believe that if they don't standardise things, and they give documents to reviewers to comment on and critique freely at their own will, they will end up with documents that better reflect the variety of perspectives in the outside world in the patient community because not everybody's the same. So, you run the risk of standardising too much and potentially, it could become exclusive, so I can imagine how they will be useful. But there are pitfalls associated with them as well.

Izaak den Daas: I'm always a bit a bit wary about templates. You can never fit in what you want to say if you get a template question, I must admit. And even as a scientist, I have difficulties with that. In a lay summary, that will be difficult, but I'm not sure what the other members of the panel think about this.

Ingrid Klingmann: I think the first guideline that Kerstin presented, which was from the European Commission expert group, provides a template for the structure of lay summaries and also wording. But it is general wording. I think it would make sense to amend it further for a phase 1 template where certain things like “pharmacokinetic” or “single rising dose” are explained so that we have good agreed wording for some of these standard terms. This would mean that not everybody needs to start from scratch, to make it easier and more efficient. Because there are many more phase 1 studies than phase 2/3 trials that need to

be reported. We need to develop a certain type of efficiency in producing these lay summaries.

Izaak den Daas: Yes, there's a little issue here in Dutch because Dutch is not like English. In English, you see a lot of scientific terms in the common tongue. In Dutch, that is absolutely not possible; terms such as “electrocardiogram” cannot be used in a lay summary. There are a lot of medical terms that have to be translated. I'm not sure how it is in German, but in English it is often much easier.

Kerstin Breithaupt-Grögler: Yes, I think we will be working with templates. We already do work with templates. The 10 elements are a template in a way for the lay summary, for what needs to be covered, and the ICH E3 guideline is sort of a template—it sets the scene, but has to be used. I absolutely agree with Thomas that fixed terms and fixed wording probably does not cover all the things that are required in a specific trial. But for these PK trials that more or less follow a standard sequence (what is going to be assessed; what standard PK terms mean), template wording can probably be developed, at least by sponsors who have the means to do that. It facilitates this quick evaluation that needs to be added to the lay summary. It might be very different for a phase 3 trial, and a pivotal trial where we have very different indications and parameters to be reported.

Izaak den Daas: Yes, I wonder how you're going to explain “area under the curve” in a lay summary. This whole lay summary is a totally novel thing for us, working in a CRO.

Jelle Klein: So far, I have not worked with it a lot, but I think for this specific question, the most difficult thing to explain to a lay person is things like the PK because they're not used to it. And as a physician, I know it's much easier to explain to them what safety issues mean, rather than PK issues. Therefore, I agree with the statement that templates are not always good, they make life too easy. You can make mistakes because of them. I think you should think further than just templates. But for PK trials specifically, I think it's not a bad idea, so we have guidance on how to keep our language at the layman's level. I think as scientists, we're too eager to go into details that are not interesting for the patients and they do not understand; they raise more questions and answers. While for safety, it's much easier to do.

Abbreviations

Abbreviation	Definition
CAPA	Corrective and preventive action
CTIS	Clinical Trials Information System
CRO	Clinical Research Organisation
CTD	Clinical Trials Directive
CTR	Clinical Trials Regulation
EMA	European Medicines Agency
EU	European Union
EUPATI	European Patients' Academy on Therapeutic Innovation
GLSP	Good Lay Summary Practice
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
MHRA	Medicines and Healthcare products Regulatory Agency
PK	Pharmacokinetics
SUSAR	Suspected unexpected serious adverse event