European Federation for Exploratory Medicines Development

EUFEMED Innovation Club Workshop: 13 May 2022

An overview of changing aspects for national Phase I trials under the EU Clinical Trial Regulation

Summary

The new clinical trial regulation (CTR) is replacing the old directive, where the text has to now be implemented in a national legislation. This will mean that all clinical trials in Europe will be done in the same way for the coming years – in stark contrast to what has happened in the past.

The meeting was opened with an overview of changing aspects for national Phase I trials under the EU Clinical Trial Regulation given by Ingrid Klingmann of Pharmaplex bv, Belgium. After a brief Q&A the meeting continued with a session focusing on how European Union (EU) Member States are organizing collaboration between competent authority and ethics committee (EC) in the trial authorization process? The round table discussion involved Sébastien Vanhiesbecq (Belgium), Thomas Sudhop (Germany), Claire Bahans (France), Anne Moulin (France), Pieter de Graeff (Netherlands) and Izaak den Daas as moderator.

The supporting presentations for each of the Session Leads are available on the EUFEMED website

Session moderator:

- Izaak den Daas

Expert panel:

- Ingrid Klingmann of Pharmaplex bv, Belgium
- Sébastien Vanhiesbecq of FPS Public Health, Food Chain Safety and Environment (Belgium)
- Thomas Sudhop of the Federal Institute for Drugs and Medical Devices (Germany)
- Claire Bahans of the National Conference of Commissions for the Protection of Persons (France)
- Anne Moulin of the Ministry of Solidarites and Health (France)
- Pieter de Graeff of the Assessment of Biomedical Research (BEBO; Netherlands)

Introduction

The meeting was opened by Izaak den Daas who summarised how the new clinical trial regulation (CTR) is replacing the old directive, where the text has to now be implemented in a national legislation. After introducing the various participants discussions began with an overview of changing aspects for national Phase I trials under the EU Clinical Trial Regulation given by Ingrid Klingmann of Pharmaplex bv, Belgium.

An overview of changing aspects for national Phase I trials under the EU Clinical Trial Regulation – Ingrid Klingmann

The New Clinical Trial Regulation EU 536/2014

The CTR is a large document, with 85 recitals, 19 chapters and 99 articles. The annexes are also important.

- Annex 1: Application dossier for initial application
- Annex 2: Application dossier for substantial modification
- Annex 3: Safety reporting
- Annex 4: Content of the summary of the results of the clinical trial
- Annex 5: Content of the summary of the results of the clinical trial for laypersons
- Annex 6: Labelling of IMP and auxiliary medicinal products
- Annex 7: Correlation table Directive 2001/20/EC vs Regulation 536/2014

Regulation EU 536/2014 – Single Application Dossier to be entered into the Single Portal

The main development is the application of a single dossier to be entered into a single portal. This single application dossier provides consistency for all participating countries in the EU regarding the national competent authorities (NCAs) and ethics committees (ECs). If a trial spans numerous countries, aspects such as content of the labelling, patient information sheet, informed consent and the suitability of investigator sites will need to be specific to each country. More general documents also need to be included, such as the protocol, the investigator brochure, the Investigational Medicinal Product Dossier (IMPD), and the auxiliary medicinal product dossier. Scientific advice and any paediatric investigation plans need to be submitted as well. There are several templates provided in EudraLex Volume 10 that help fill the content of these documents.

EU DATABASE 'CTIS' (Clinical Trial Information System)

The Clinical Trial Information System (CTIS) is a large underlying database that enables collaboration, communication and coordinated assessment procedures between all the

stakeholders involved. The European Medicines Agency (EMA) had to set up, validate, audit and get approval for this huge database. The aim is to enable cooperation between the competent authorities for the coordinated assessment procedure, but also between the competent authorities and the Sponsors. A third, and crucial, intention is for the public to have access to the database, to enable citizens to view information about clinical trials and the medications being investigated. In addition, Sponsors can refer to previous submissions through a medicinal product number or an EU active substance code for investigational medicinal products (IMPs) without marketing authorisation. All information on this database will be publicly available, with the exception of personal data and commercially confidential data. Communication relating to assessment preparation or supervision of the conduct, such as inspections, will not be open to the public. The existing databases EudraCT and EudraVigilance have been integrated into the CTIS. There is a detailed training programme available to appropriately interact with the CTIS.

Application Dossier – Content and Submission

The application dossier can be divided into two parts.

Part 1 is the more general aspects of the application, such as the therapeutic and public health benefits, aspects, risks and inconveniences for the subject, how this is represented in the protocol, but also the manufacturing importation of the IMPs or the IMPD, for example, the Investigator Brochure and the labelling.

Part 2 involves national information such as informed consent, compensation or rewarding arrangements, recruitment arrangements, data protection rules, suitability of individuals, trial sites, damage compensation and biological sampling. A Sponsor can submit this all as one dossier, or they can decide to only submit Part 1 to see whether the trial concept is acceptable – the Sponsor can then submit Part 2 within 2 years.

The EU-Portal

The portal is very complex. The reporting member state prepares a draft report for Part 1 of the dossier, and exchanges this with any other member states involved in the trial, called the concerned member states. They then come to an agreement on whether this draft assessment is acceptable. Once that agreement has been achieved, the reporting member state informs the sponsor that Part 1 has been approved. Each concerned member state reviews the path to documentation, and checks whether everything is satisfactory.

Assessment Timelines: Part 1 and Part 2 (Best case scenario)

Following the above procedure, an automatic national approval comes through within 5 days. If everything works accordingly, approval for all the countries in a trial occurs within 60 days – with Part 1 and Part 2 occurring in parallel.

Assessment Timelines Parts 1 and 2 (Worst case scenario)

In the worst case, with all requests for further information occurring, the assessment will take 106 days. The first request for further information can occur during the validation of the dossier. If there is something missing, then the Sponsor has 10 days to provide the additional information. Then there is another 5 days to review the additional information before the validation is then confirmed. Another delay can occur during the preparation of the Part 1 assessment report, where the sponsor has 12 days to respond, and then this new information will be reviewed. There is a new agreement with all participating concerned member states. Each concerned member state can review the dossier to assess whether the information is satisfactory, and can ask for further information for the particular aspects in their country. This means that in practical terms when a submission is made, the portal needs to be checked daily for new information and possible changes/additional information. Decision making lines will need to be prepared, especially in collaboration between sponsor and clinical research organisation (CRO), to ensure that these very narrow timelines can be met. If timelines are not met, the application will be considered to have been withdrawn.

Increased Notification Obligations and their Definitions

Through the CTR there is now an increased level of notification. The start of the clinical trial is defined as the first act of recruitment of a potential subject in a member state. For a multinational trial, the start of the clinical trial has to be notified for each individual country. For Phase I studies that are mostly in one country, the Sponsor needs to notify the portal about the start of the clinical trial. The next time point that requires notification is the first study visit of the first subject in a member state. End of recruitment also needs to be notified, which is considered as the last patient involved in a member state. The end of the clinical trial needs to be clearly defined in the Clinical Protocol.

Usually, it is the last visit of the last subject, but there are possibilities to define that differently in the protocol. The end of the clinical trial needs to be notified for the particular member state when all countries in the EU have finished the study, and notified again when the study is globally finished. There are also the possibilities for early termination of a clinical trial, which is defined as the premature end of a clinical trial due to any reason before the conditions specified in the protocol are complied with. All notifications have to be done within 15 days after the respective time point. There is also a definition of

temporary halt of a clinical trial. This is an interruption not provided in the protocol for the conduct by the sponsor, with the intention of the sponsor to resume it. If this temporary halt is due to a safety issue, then resuming requires approval of a 'substantial modification' – which is the new term for the former 'substantial amendment'.

If the temporary halt is not for a safety reason, the Sponsor can decide to continue and simply notify the portal about the fact. Suspension of a clinical trial is defined as the interruption of the conduct of a trial by a member state.

Increased Notification Obligations and their Definitions – Serious Breaches

Notification of a serious breach is another very important aspect of the portal. The definition of a serious breach is very broad, and summed up in a guideline on the EMA website (https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-notification-seriousbreaches-regulation-eu-no-536/2014-clinical-trial-protocol_en.pdf). There have been many changes to what is now considered a serious breach.

Changed Definitions

A substantial modification is defined as any change to any aspect of the clinical trial which is made after notification of the authorisation decision and which is likely to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial. Substantial modifications can only be made once an authorisation has been provided. A substantial modification cannot be entered into a running assessment procedure. This will have a broad influence on strategizing how to handle a trial application from the beginning of the process. Another key definition that has changed is that of an EC.

An EC is now defined as: "an independent body established in a member state in accordance with the law of this member states and empowered to give opinions for the purposes of this regulation". This means it remains a national obligation. The EC needs to take into account the views of lay persons in particular patients and patient organisations. Although this does not mean that patients need to be directly involved, or be members of, an EC.

Article 4: Prior authorisation

The ethical review shall be performed by an EC, but in accordance with the law of the concerned member state. This means every member state has to change their EC system to account for this context. The evaluating EC directly reviews Part 2, but can also evaluate aspects of Part 1. The member states must ensure that the timelines and procedures for the review are adhered to.

Article 9: Persons assessing the application

There is also a relatively vague definition of the people needed assess the Clinical Trial Application (CTA). However, the member states have to ensure that the assessment is done jointly by a reasonable number of people who collectively have the necessary qualifications and experience, and including a lay person. The member states are also responsible for ensuring that those involved in the validation and assessment of the application do not have a conflict of interest, as well as making sure those involved are independent of the sponsor, the clinical trials site, the investigators, and those financing the clinical trial. Furthermore, the member states must ensure that these people are free of any other undue influence.

Adaptation of national ethics committee systems

Many member states have adapted their ethical review system to adhere to the CTR. The CTR and the medical device regulation cover only a limited number of the research investigations that are performed in humans. All other studies that are not following another CTR, or the medical device regulation, will continue to follow the existing national EC review system.

Definition 35

Definition 35 describes the 'Clinical Trial Report' as a report presented in an easily searchable format, prepared in accordance with Annex 1, Part 1, Module 5 of Directive 2001/83/EC and accompanying an application for marketing authorisation. This means that only clinical trials that are expected to be used for marketing authorisation need a full clinical trial report. Overall, especially with multinational trials, the introduction of the CTR will reduce the number of resources required. This is because only one dossier needs to be prepared, even if there are multiple member states. However, more effort will be required at the end of the trial because the CTR is putting emphasis on reporting the results of the trial as quickly as possible.

Article 37.4

Within 12 months of the last subject visit, i.e., the end of the trial – a summary of the results must be submitted along with a Lay Summary. This can be a demanding timeline, but is the legal obligation under the new regulation. The full Clinical Study Report needs to be submitted within 30 days of marketing authorisation being granted. As such, during the clinical development of a product, the study report should be prepared, so that it is ready if the trial ends up in the market authorisation dossier. A summary of results from Phase I trials needs to be uploaded to CTIS within 30 months after the end of the trial.

Annex 5: Content of summary of results of the clinical trial for Lay Persons

Annex 5 relates to Lay Summaries. This can be quite complex because not only is it in lay language, but it must also explain the surroundings context of the trial, as well as the consequences for patients and the results of the trial.

There is a guidance document in EudraLex Volume 10 to guide the writing of a Lay Summary.

Be clear about the applicable EU regulatory framework:

In the future, several legislative systems will be running in parallel. The clinical trials directive continues, and within 2022 a sponsor can start a new trial within the legal clinical trials directive. However, by 2025 all trials that are still running at that time need to be handled within the CTR environment; although this is only for trials that fall under the scope of the regulation. In addition, alongside the CTR will be the medical device regulation and in vitro diagnostics regulation. Other studies will also remain in their current national legislation. The UK and Switzerland have their own legislative framework for clinical trials. Therefore, it is imperative that all aspects of a trial are kept as clear as possible and follow the correct legislative framework.

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

Izaak den Das: A question from the audience: For ESD studies, I thought approval was within 20 days?

Ingrid Klingmann: The approval timelines are the same in all countries. There are national provisions in some countries to assess certain studies faster. But this will be discussed later in the meeting.

Izaak den Das: Another question from the audience: Will the sponsor need to perform any readability tests in patients for the lay summary of a Clinical Study Report?

Ingrid Klingmann: It is recommended in the Good Lay Summary practice. But this is not set in the regulation as a necessity. It is in the spirit of the document to enable a readability test at the end. But it is not a legal obligation.

Izaak den Das: Last question from the audience: What happens if, for example, a document from Part 1 changes while not all submitted countries are approved yet?

Ingrid Klingmann: In this situation you cannot make changes to Part 1. To enter a submission, all countries involved need to have approval, for example, to include additional countries or to make any changes to Part 1. This is an indisputable rule; you can never submit additional applications if there is an ongoing assessment process anywhere in Europe. The process is only deemed complete once all countries involved are satisfied. Therefore, it can be quite challenging to simultaneously handle all requests for additional information in Part 2 if the aim is to minimise the timeline for the overall assessment.

CT College – Sébastien Vanhiesbecq (Belgium)

Along with generating the dossier, Sponsors must submit a written statement along with the principal investigator attesting that the site is suitable for the trial. The sponsor then makes the dossier available on the CTIS. The only contact point for the sponsor is the Belgian NCA, known as the Federal Agency for Medicine and Health Products (FAMHP). The evaluating EC then adds the assessment to the CTIS and informs the FAMHP. In Belgium there are 15 ECs recognised under the 2017 law. To guarantee neutrality the sponsors are not allowed to communicate with the evaluating EC.

The College is an independent federal body than can also select the evaluating EC. It is composed of administrative staff and a board of experts, with physicians, lawyers and quality experts. It is the single contact point between the EC, the independent EC and the FAMHP. The most principal criterion for selecting the evaluating EC is independence. The evaluating EC cannot be from the site where the clinical trial will be held. The College must also ensure a consistent application of the legislation by the EC, as well as appropriate coordination, harmonisation, support, evaluation and follow-up on the quality control. The College does not take part in evaluating the dossier.

When the dossier is submitted, Part 1 is assessed by both the FAMHP and the evaluating EC in a joint assessment. Part 2 is evaluated by the EC only. The EC then makes an assessment report for Part 2. A final and unique decision will then be made for the overall submission.

Early Phase Trials under the EU Clinical Trial Regulation – What changes in the interaction between competent authorities and ethics committees? Situation in Germany – Thomas Sudhop (Germany)

Legal situation in Germany since 31 January 2022

There are two NCAs in Germany, the Federal Institute for Drugs and Medical Devices (BfArM) and the Paul-Ehrlich-Institute (PEI). This introduces difficulties when deciding which is the appropriate NCA for a clinical trial. The national contact point according to Article 83 is BfArM, so all requests for CTA start with BfArM. In Germany there are 30 local authorities and 16 federal member states with 37 registered ECs, which are located at faculties and state medical associations. Laws were amended in January to comply with the CTR, and to regulate aspects the CTR has left to the member states, such as informed consent on incapable subjects and damage compensation. The German Medicines Act regulates the collaboration between ECs and the NCAs.

Procedure for CTA-EC assignment/Scientific Advice

In principle, only one EC is responsible for a CTA and its subsequent procedures. Part 1 is assessed jointly by the NCA and the EC. Part 2 is assessed by the EC solely. The evaluating EC is selected by the 'schedule of responsibilities for registered ethics committees', more commonly known as 'schedule of business' or 'GVP'. This schedule of business is updated at least once a year and is published on the internet. However, it is not possible to find out what the next EC to be selected is, meaning it is essentially by random. In the case of a Scientific Advice procedure, in advance of a CTA submission which requires joint advice by the competent NCA and the EC, the next EC is selected according to the schedule of business. This EC remains responsible for the subsequent assessment of the CTA, its substantial modifications, safety assessment and other CTA related procedures jointly with the competent NCA.

Hour "zero" of a CTA

When a CTA arrives at BfArM an hour "zero" approach is adopted to determine the responsible NCA and EC. The first step establishes whether there has been a Scientific Advice procedure in advance of the CTA. If so then it is a simple process as the NCA and EC have already been chosen. If not then BfArM have to select an EC according to the business schedule. There are certain requirements to be adhered to according to German law, for example if it is a clinical trial using X rays, then the EC must be registered with the Federal Office for Radiation. The responsible NCA also has to be chosen, for which an internal algorithm helps the decision-making process.

Interaction between the French Competent Authority and the French Ethics Committees under the EU Clinical Trials Regulation – Claire Bahans (France)

In France, the NCA is the National Agency for the Safety of Medicine and Health Products. Research ECs are called the Committees for the Protection of Persons. There are 39 ECs throughout France. Each committee is an independent public legal entity composed of volunteers distributed into two groups: a scientific group composed of clinicians, scientists, nurses and methodologists; and a social group composed of ethicists, psychologists, lawyers and lay members. These ECs aim to give prior authorisation for any research on humans, which represent about 4000 dossiers a year, along with the numerous substantial modifications. Each committee meets twice a month, and the dossiers are randomly allocated to an EC.

The NCA is responsible for the evaluation of Part 1, with the EC responsible for the evaluation of Part 2. France is also compliant with Article 4 of the CTR, which states that member states shall ensure the timelines and procedures for the review by the ECs are compatible with the timelines of the evaluation of the CTR. Ethics committees can also make an evaluation of Part 1 if needed.

The CTR has been translated into the French regulation which says that the EC may make ethical observations to the NCA on elements falling within the scope of Article 6, within 22 days of CTA validation. Ethics committees may also forward their ethical observation on the answers provided by the Sponsor within 10 days of their reception.

The French system is coordinated by the Ministry of Health collaborating with the NCA and the ECs. The CTIS is linked with the French information system, so that EC members are not obliged to connect to the CTIS to access the documents. The random allocation system has been adapted to ensure that ECs have the time to send their ethical inputs of the Clinical Protocol. Regular meetings have been organised for several months between the competent authority and ECs.

During the validation phase there is no planned interaction between the NCA and the ECs. The NCA is in charge of the validation of the dossier. However, during the initial assessment, even if the dossier is a mono-national study, the EC can make ethical inputs on Part 1 by Day 22 following validation. Ethics committees can send a written document by mail, following which the NCA informs the EC whether the questions or observations have been taken into account in the reports. Once the sponsor has answered the questions, ECs may forward their ethical evaluation of Part 1 of the Clinical Protocol within 10 days from the day of reception of the answers. Finally, Part 1 is uploaded by the NCA on the CTIS, whereas the Part 2 Final Assessment Report is uploaded on the CTIS by the EC. The final decision is uploaded on the CTIS by the NCA.

Clinical trials regulation – Implementation in France – Anne Moulin (France)

French context

The French organisation focuses on strengthening the methods of the ECs. There have been developments with new information and software systems that have been running for ~1 year. There has also been an increase in administrative staff to allow ECs to work year-round, as well as an increase in the fees for the EC rapporteur, additional training, and a dedicated team to support and coordinate the ECs at the central level. A dedicated team is also being established peripherally to the Ministry of Health to address the organisation and coordination of ECs.

Preparation specific for CTR implementation

The national regulation was adapted with ordinance in 2016 specifically for CTR implementation, followed by decrees in 2016 and 2022. A pilot phase was conducted with the NCA and ECs in two stages: first, to check that the timelines of the future regulation could be respected by both the NCA and the ECs; and second, to coordinate between the NCA and the ECs (joint evaluation) to prepare the results of the assessment of Part 1. In France there are 39 ECs. However, the operation is being adapted to have 20 ECs to evaluate clinical trials, with two secretaries, organising two meetings a month to be able to respect the timelines.

Construction of the French interaction NCA – ECs

The NCA is responsible for the evaluation of Part 1 and for the submission of the final decision. The ECs are responsible for evaluating Part 2. A system has been implemented whereby the ECs send their questions and evaluations to the NCA, and send their responses following a request for additional information. The NCA informs the EC of how it has taken into account the evaluation and their questions. There is a continuous goal to improve and streamline the relationship/process between the NCA and the ECs.

Actions of NCA and EC in the CTIS for evaluation of a first submission of a CTA

Only one file needs to be submitted by the sponsor. Sponsors therefore do not need to often interact with the National Information System, only for appeals. As stated by the European regulation, approvals must be dealt with at the national level. The NCA is responsible for easing the validation or contributing to the validation if it is a multinational clinical trial. When a trial is submitted, an EC is automatically and randomly allocated.

Progress so far

There is limited experience, only 3 months. with the new systems. The first meeting between ECs and the NCA was mostly dedicated to questions on the use of the CTIS, how the files appear on the system, and technical aspects regarding the evaluation of CTAs. There have been questions about the submission of documents facing patients. However, this point is currently being discussed at the European level.

Early Phase Trials under the EU Clinical Trial Regulation – Pieter de Graeff (Netherlands)

Medical Research Ethics Committee BEBO

Beoorderling Eiek Biomedisch Onderzoek (assessment of biomedical research; BEBO) is a large, independent EC from Assam, Netherlands. Importantly, BEBO is non-institutionalised – in contrast to most ECs in the Netherlands which are associated with a hospital. However, BEBO is not completely independent, as it is under the supervision of the NCA, which in the Netherlands is the Central Committee on Research Involving Human Subjects (CCMO). This is the committee that fulfils all the regulations and legal requirements. The CCMO oversee BEBO by setting the criteria, checking members, visiting, and provide updates to the CTR. In the Netherlands there are ~11 ECs which are involved in this CTR.

BEBO has a secretariat, of which half are academics under general management, and have in total ~40 board members who convene in three sessions per month. BEBO is a committee involved primarily in Phase I and Phase II studies. Last year there were ~180 applications: 62% being Phase I and 15% being Phase II. It deals with ~100 national applications per year, ~75% of the total national Phase I and Phase II applications submitted by CROs.

The new CTR has been a long-term project. BEBO has participated in the past with the voluntary harmonisation procedure, which was an exercise to see how the CTR could be implemented. Last year activities started with regular meetings with the NCA and the CCMO. BEBO now have 12 national pilot projects and the first national application soon to be discussed. In the Netherlands the CTR is slowly being implemented by the applicants. The total number of applicants submitted only numbers at five. It is important to emphasise that the responsibility of the CCMO is largely on multinational applications. If the Netherlands is a referenced member state, then the CCMO fill in part of the draft assessment report (DAR), and does all the coordination. Yet with national applications, the lies upon the ECs to complete the DAR, as well as to coordinate the procedure. There are some further differences in the responsibilities between the NCAs and the ECs when it comes to multinational studies versus national studies.

Discussions

Following the individual presentations, a roundtable discussion was held and moderated by Izaak den Daas. He initiated discussion on several topics, and the audience were also asked to submit questions to the panel of experts to feed discussion. Questions from the audience are outlined below as are the individual speakers for each answer.

National single centre trials, especially Phase I trials, will have to follow the rules of the CTA but will not require the multinational coordinated assessment procedure. Did you define rules and processes for these types of national trials? And are there any attempts or possibilities to review and approve those trials faster than the timelines provided by the CTR?

Pieter de Graeff: In the Netherlands, the responsibility for a national procedure is different. The aim has been to speed up the procedure so to not wait a whole validation before the start of the assessment. The primary assessment can start before the whole validation feature is completed. In this sense, the aim of speeding up the procedure is to half the existing 45-day period, to a period of about 16–23 days. This is also facilitated by having four meeting a month rather than only three. The aim is to have the timelines be approximately the same as in the old system. Although it is not only a matter of quality, but also one of quantity. One hundred national applications require substantial work, particularly administrative, such as completing the DAR.

Thomas Sudhop: Germany plans to announce a national declaration on Phase I trials. However, the major issue currently is the CTA system itself as it introduces difficulties for the EC and the NCA. There is an additional national IT tool to support and provide workarounds on the missing information. If this is functions correctly, the total duration of the procedure is expected to be around 30 days.

Claire Bahans: There are currently no specific processes in France. However, ECs are asked to send their evaluation by Day 22.

Sébastien Vanhiesbecq: In Belgium the national legislation foresees that mono-national Phase I trials are evaluated with faster timelines than CTAs. Article 22 of the 2017 law foresees a timeline of 20 days. This timeline can be on hold if the dossier is not complete or if there are further questions. Faster timelines have previously been experiences with a pilot project that was done using shorter site timelines than the CTA. However, the Sponsor dossiers were evaluated according to the requirements of the CTA.

Audience question: *In the Netherlands, organisations are submitting a lot of studies to the BEBO, and is experiencing quick review responses, with lots of experience regarding Phase I trials. Can Phase I trials also be reviewed by other ECs, ones with perhaps less experience in Phase I trials and resulting in longer timelines? This may impact study time.*

Pieter de Graeff: This is indeed the case, especially if there is only one centre involved with one committee, it will need to be assessed in other countries as well. This process may indeed take longer. It is true that if an EC is less experienced then the timelines may be longer. However, it is not only a matter of experience, but also a matter of organisation. One of the initial thoughts of the entire regulation was to make sure that the overall timelines for the clinical trials were shortened, to speed up the trials throughout Europe.

Regarding the 12-day period to answer questions, would a direct interaction, e.g., via telephone, with the competent authorities EC be acceptable?

Thomas Sudhop/Anne Moulin: In Germany and France it is not prohibited to contact via telephone. Official communication, such as for documentation purposes, should be performed with the use of CTIS. But for current clarification requests, communication can be made with the EC directly.

Pieter de Graeff: In the Netherlands a lot of interaction occurs between the CROs and the ECs. The EC members are protective of in terms of clarifications, and if necessary, the secretary will be in communication with the members. In general, the barrier to communication is rather low. Particularly for the CTR, it is important to have communication by telephone, because there is only one round of review. To solve issues having direct contact via telephone is beneficial.

When the CTR was negotiated, related ECs in the EU were very concerned about the maintenance of an independent review of all ethical and relevant aspects of the protocol and study within the very limited timeframes. What has been the strategy in your country to ensure that?

Anne Moulin: The timelines given by the European regulation are very similar to the timelines provided by the French legislation – with only four added days if there are any additional files. For Part 1, when France is a responsible member state, the EC must give their evaluation before Day 26. As such, in the regulations the EC must give their evaluation before Day 22 for all clinical trials so to ensure that it is possible for the EC to evaluate the

submission before this deadline we adjusted the random allocation so that file can be evaluated in a meeting earlier than before.

Audience question: *For mono trials, will it still be possible to use the fast-track process?*

Izaak den Daas (moderator): Many questions are arising from the audience relating to the importance of the speed of the process, especially in early phase.

Pieter de Graeff: One of the main problems with the timelines is filling out the DAR. This is because of how time consuming and repetitive it can be. The relevant data are presented in a different format to the DAR form. As such the whole protocol needs to be searched – and only then do the comments start. Reducing the amount of time on these DAR forms can gain a lot of time in the overall process and make it more attractive for the members of the committee, a suggestion is for the applicants to provide the data in a more consistent manner in relation to the way it's been asked in the DAR. In addition, the dashboards can be streamlined, although this is a decision beyond the scope of the meeting attendees.

Thomas Sudhop: The DAR is developed over years in the voluntary harmonisation procedure, and it was not a simple process to get the majority to use the template. Consequently, it will be an evolutionary process to change the form.

Anne Moulin: In France the fast-track process is possible if the file application is submitted in the national way (transitory disposition). The process for a shared evaluation on Part 1 is still being refined, as such the only way to use the fast-track process currently is submission via the national route.

Which challenges do we expect for trial approval, oversight and communication, under the process of CTR? When the sponsors submit complex protocols that contain several sub studies, like single multiple ascending dose, part food interaction, and elderly pharmacokinetic parts? So this is a question about umbrella protocols. Do you see challenges here for the CTR?

Thomas Sudhop: This introduces some issues in Germany. The substantial modification process is relatively long and each substantial modification blocks a new submission. If several substantial modifications are submitted in parallel, they will block one another. It could be beneficial to re-strategize, to include every step in one protocol. Having different protocols could speed up the process, because different protocols allow substantial modifications in parallel. Also, the timeline for substantial modification is only 1 week

shorter when compared to an initial application. This was intended by the commission to reduce the number of substantial amendments. Initially, four Substantial Amendments could be made per trial (2004), currently nine Substantial Amendments can be made per trial application, due to complex trials. There have been several large platform trials, which are umbrella trials with extension periods and new products, that the commission asked for submission of single CTAs because of result reporting. This is because if there is only one CTA, results reporting is needed after the last stage of the platform trial, which could be in 10 or 20 years. There are some ideas to provide mechanisms that you have to submit these as single CTAs, to meet the timelines for result publication, which is in the interest of the patients.

Pieter de Graeff: This is also the case for the Netherlands. In the yearly oversight, one of the problems arising with these umbrella trials is the need to assess more than one IMP, which is time consuming. If there is a situation where four or five amendments have been submitted, it will be almost impossible to accommodate this within the timelines. Although this is still yet to be seen. It would be much better to reduce the number of amendments; start with one or two and then extend on the basis of substantial amendments.

Audience question: *Is there value in differentiating/specialising part of the ECs specifically for early phase, aiming for linear process focusing on smooth turnover of submission assessment?*

Pieter de Graeff: In the Netherlands, there will likely be 'natural selection' with the ECs, resulting in specific committees that are specialised in certain aspects. This also has to do with expertise, especially regarding multinational trials; although the process may end up regulating itself. Ultimately, with shorter timelines, expertise and specialisation is required. We can perhaps expect the number of ECs to reduce in the coming years and they will be assessed under the CTR with more specialisation. The number of ECs is also reduced in Germany. But many member states have a random system to assign the EC and this random system is prohibitive in specialised ECs – although not in the Netherlands, where the EC can be chosen.

Sébastien Vanhiesbecq: Belgium has 15 ECs. But this number has reduced from the beginning of the directive for the CTA because they participated to the pilot project. Some ECs are recognised for the Phase I studies and it is also foreseen to train the EC to have a higher quality of assessment – this is reflected in the CT College. The goal is to have some differentiation within the ECs, but to have an overall high level of quality of assessment.

Claire Bahans: In France ECs are not favourable to specialisation. It can lead to conflicts of interest, there is a random system of allocation. Ethics committee specialisation is not generally considered a good idea. There has already been a reduction in the number awaiting clinical trials. There is a way of training and constituting a list of experts that will be available for committees on many subjects so that they can have access to experts quickly.

Are all ECs ready? Are we at risk that local ECs will still want to comment on the trial with multicentre trials?

Thomas Sudhop: For Germany, the system of additionally concerned ECs was stopped. There is only one EC, which has access to all trial centres in Bavaria, North Rhine-Westphalia and Berlin. There is no personal knowledge on the centres. At the moment, the revenue is performed by the documentation dossier.

Abbreviation	**Definition**
BEBO	Beoorderling Eiek Biomedisch Onderzoek (assessment of biomedical research)
CCMO	Central Committee on Research Involving Human Subjects
CRO	Clinical Research Organisation
CTA	Clinical Trial Application
CTIS	Clinical Trial Information System
CTR	Clinical Trial Regulation
DAR	Draft Assessment Report
EC	Ethics Committee
EU	European Union
FAMHP	Federal Agency for Medicine and Health Products
IMP	Investigational Medicinal Product
NCA	National Competency Authority
PEI	Paul-Ehrlich-Institute