**CTR training Day 1 -- QnA**

**General principles/new concepts**

1. What is the status of the persons validating the application can it be a CRO?

No, validation and assessment should be done at Member State level. Member States shall ensure that the persons validating and assessing the application do not have conflicts of interest, are independent of the sponsor, of the clinical trial site and the investigators involved and of persons financing the clinical trial, as well as free of any other undue influence

2. In the first slide you said single approval per member state. Does that mean up to 27-30 approvals or do sponsor get one single approval?

A multinational Clinical Trial Application will get an approval for each Member State concerned.

3. Can a local ethics committee still request/demand to submit a file locally?

No, there is only one submission for a clinical trial application in a Member State. Parallel submissions to local ethics committees are not allowed. The ethical review shall be performed by an ethics committee in accordance with the law of the Member State concerned. The review by the ethics committee may encompass aspects addressed in Part I and/or Part II of the assessment report as appropriate for each Member State concerned. Member States shall ensure that the timelines and procedures for the review by the ethics committees are compatible with the timelines and procedures set out in the CTR for the assessment of the application for authorisation of a clinical trial.

4. How do we deal with transparency of documents submitted and the needed confidentiality of Sponsor projects submitted

Please refer to the disclosure rules that can be found here: https://www.ema.europa.eu/en/documents/other/appendix-disclosure-rules-functional-specifications-eu-portal-eu-database-be-audited_en.pdf

5. Could you please elaborate the Tacit Approval: if regarding Part II, how could it fit with the need of EC approval as required by GCP

See point 3 – the ethics committee approval is part of the authorisation process and can be tacit if the timelines are not respected.

6. The regulation being almost 7 years old. Is its revision & amendments foreseen especially in light of recent experiences (pandemics)?

There is a clear timeline foreseen in the CTR:

The CTR foresees a report on its application to the European Parliament and to the Council five years after the CTR starts applying. That report shall include an assessment of the impact that the Regulation has had on scientific and technological progress, comprehensive information on the different types of clinical trials authorised pursuant to this Regulation, and the measures required in order to maintain the competitiveness of European clinical research. The Commission shall, if appropriate, present a legislative proposal based on that report in order to update the provisions set out in the CTR.

7. Can you please clarify when full entry into force is foreseen?

CTIS is **planned** to **go live** by 31 January 2022. The final go-live date will be six months after the European Commission confirms the full functioning of CTIS through an independent audit.

8. The regulation does not exclude non authorized products by definition according to Art. 2 para 2 lit. a. Normal clinical practice could include (in rare circumstances) also non authorized products. Correct?

On the basis of the definition of "normal clinical practice" , this could be possible. treatment regime typically followed to treat, prevent, or diagnose a disease or a disorder;

9. What is meant by authorisation expiration date of 2 years?

If no subject has been included in the clinical trial in a Member State concerned within two years from the notification date of the authorisation, the authorisation shall expire in that Member State concerned unless an extension, on request of the sponsor, has been approved.

10. Does a contract fall under the assessment of part I or part II? The responsibilities of multiple sponsors should be clear before the start of the study because the safety of the subject may be compromised of none of the sponsors know their respective responsibilities.

Arrangements for rewarding investigators are in the part II. Responsibility division between sponsors is not part of the Clinical Trial Application.

11. When Co-sponsorship concerns commercial and non-commercial sponsors, how should the CT be considered? A commercial or non-commercial trial? Will be valid local laws for this cases?

The CTR does not differentiate between commercial and non-commercial trials. If at a local level differentiations are made, they will need to be governed by local laws.

12. Could nowadays an "individual" really be able to fulfill all tasks and responsibilities as Sponsor?

The definition of a sponsor does not exclude that an individual takes up the responsibility.

**Normal clinical practice (panel)**

1. Unproven Interventions in Clinical Practice. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention (in compliance with national law[1]) if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.
2. what about consolidated use of drugs that in some countries allow the use of drugs in unauthorized indications?

Answer: With regard to off-label use of medicinal products with a marketing authorisation in the EEA it is within the competence of each Member State to determine if established off-label use in principle is considered within their normal clinical practice and can be investigated in a non-interventional study or not. (Remark: it is unclear what "consolidated use of drugs" means. Note that 'unproven interventions' that are medicinal products can only be used if in compliance with national laws).

[1] Post-meeting addition to the original text

3. After informed consent, How is compassionate use or off label use of a commercialized drug regulated?

   Compassionate use and off label use are two different situations and regulated nationally. See: Compassionate use. See also: https://www.ema.europa.eu/en/human-regulatory/research-development/compassionate-use

4. how can we marry the clinicaltrials.gov clinical trial definition with the CTR definition?

Clinicaltrials.gov states: Interventional study (clinical trial):

A type of clinical study in which participants are assigned to groups that receive one or more intervention/treatment (or no intervention) so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes. The assignments are determined by the study's protocol. Participants may receive diagnostic, therapeutic, or other types of interventions. This definition does not appear to be in conflict with the on in Regulation (EU) No 536/2014, Art 3 2 (2).

5. There are many countries where there is standard clinical practice. What happens when standard clinical practice is not established at country level but is established on a site-by-site basis?

   Answer:Normal clinical practice should be defined within the framework of the National Health Care System.

6. Should the sponsor indicate whether the trial is a low-interventional trial? Or the NCP?
   Answer: The sponsor should indicate if the trial is considered low-intervention trial(Art 5.2, Art.25.1.e, Annex I.b.9) but the assessment is made by the Reporting Member State and eth decision by the Member States concerned.
7. In terms of risk, the example given may have additional few mls of blood taken by a) venipuncture done anyway b) venipuntcure done for the specific purpose. Does it make any difference (low intervention anyway)?
   Answer: Drawing samples of blood for medicinal product research with or without additional frequency of blood draws is generally considered an intervention (also taking volume and patient age e.g. if paediatric population into consideration). If the medicinal product is authorised, used in accordance with the terms of the marketing authorisation and no other burdensome procedures are used, this would constitute a low-intervention trial.
8. would indication extension trials ever be applicable or not as low-intervention trials?
   Answer:If the use for the extended indication is evidence-based and supported by published scientific evidence on the safety and efficacy this could be considered a low-intervention trial
9. Could an intervention to increase physical activity be considered in a clinical trial
   Answer:Life-style interventions can only be included if they are linked with a plausible rational to evaluate the safety and/or efficacy of the medicinal product.
10. is it possible to extend the indications of a medicine based on a low-intervention trial?
    Answer:Data obtained from a low-intervention trials are not treated differently from those obtained in other clinical trials.

**Initial application: submission and assessment (Ann Marie, Greet)**

1. What is the difference between the IMPD safety and efficacy and the IB?
   Answer:

   The CTR requires the submission of an Investigational Medicinal Product dossier with different elements:

- Quality data
- Non-clinical data ("safety")
- Clinical data ("efficacy")
- Overall risk and benefit assessment

The applicant may either provide a stand-alone IMPD or cross-refer to the IB for the reference safety information and the summaries of pre-clinical and clinical parts of the IMPD

In contrast to the IMPD safety and efficacy, the IB is used by the investigator and available at the clinical trial site. Most importantly, the IB contains the reference safety information as basis to define expectedness for safety reporting (Annex I.E.30). In the case of IMPs with marketing authorisation and is used in accordance with the marketing authorisation, the IB and the IMPD can be replaced by the submission of an SmPC (Annex I.E.28 and 50),

2. Stating if patients were involved in the design in the protocol - can you provide more details regarding this aspect. What is the rationale for requesting to include it? How do we assess this aspect? Do we only assess if the sposnor ackowledges this or do we request it as part of the assessment?
   Answer:Patients or patients' organisations are recognised in Regulation (EU) No 536/2014 as a key group for providing input to the clinical trial design. If this is the case for a specific clinical trial, the protocol should describe their involvement.
3. should the IMPD include all preclinical results of studies, and should this be results of safety and/or efficacy results? Should preclinical safety studies be performed acc to GLP?
   Answer:Yes, either all non-clinical results should be reported in the IMPD Safety and Efficacy or cross-references should be provided to the preclinical section of the IB. All pivotal non-clinical safety studies should be compliant with OECD-GLP (however pilot/dose-range finding studies are not required to be GCP compliant).
4. How will NCAs ensure that CT proposals are in line with any agreed PIP? will sponsors be required to submit the complete PIP opinion if this is available to them?
   Answer: Assessor should take account of the Paediatric Investigation Plan (PIP). Annex I I.57. If the clinical trial is part of an agreed PIP, a copy of the Agency's decision on the agreement on the PIP, and the opinion of the Paediatric Committee, unless these documents are fully accessible via the internet shall be submitted. In the latter case, a link to this documentation in the cover letter is sufficient (see section B). The Member State is not expected to ensure that the CT is in line with the agreed PIP but can inquire why the sponsor did not comply with the agreed PIP.
5. How to know all public holidays and therefore the overall deadlines?
   Answer:The public holidays of all Member States Concerned published in the Official Journal of the European Union will be taken into account when calculating deadlines (see Regulation No 1182/71).
6. If several member states are interested being RMS. Who takes the decision which member state is RMS?
   Answer:The candidate RMS with the lowest workshare (lowest number of RMS-ships for multinational trials within the last year) will assign which of the MSCs willing to be RMS will be selected. All MSCs are involved in the discussion. In case no agreement can be found (expected to be rare), the MSC proposed by the sponsor will be selected.
7. what is the rule to complete the AR, copy and past or focus on assessment conclusion and major point so MSC can follow conclusion?
   Answer:The assessment report will include the same templates as those used in CTFG's Voluntary Harmonisation Procedure (VHP) for multinational clinical trials: Introduction, Quality, Preclinical, Clinical, Statistical, Regulatory and Conclusion. The focus is on

evaluation of the major points of the application as defined in Regulation (EU) No 536/2014 Articles 6 and 7 as well as in Annex I. Note that the draft assessment report will contain text sections that should remain confidential (in line with Art 81 4 (c)). A tool to delete all these sections has been prepared and should be used when transforming the Final Draft Assessment Report into the Final Assessment Report. Also note that the DAR Word format should be transformed into a pdf file before being uploaded to the Portal.

8. In case the withdrawal is only in a MSC out of several, resubmision would be an article 14 application isn't it? Answer: withdrawal of the full application in all MSC before prior conclusion part I, publication date Art 12. Thereafter in single MSC only. MSC withdrawal after publication date can be done at any time before the notification of the decision in a specific MSC. withdrawal before the reporting date, applies to the entire application in all MSCs.
9. If an application has validation issues for only part II in one MSC and they are not solved through answer to validation RFI, would this mean withdrawal of the whole application in all MSC? Answer : This is correct , the application is invalid and the process is stopped . A new application must be resubmitted .

## 10. Aspects related to ethics

1. in cluster trials only rejection to participate needs to be documented by the patient isn't it?

Correct, as stated in article 30.4 "The investigator shall document all refusals and withdrawals and shall ensure that no data for the clinical trial are collected from subjects that refuse to participate in or have withdrawn from the clinical trial."

2. Where does the age of 12 come from? or can it differ between member states?

This can differ among member states

3. is consent of one legally designated representative in minors sufficient?

We assume the question is related to the parents. For parents it may depend on national legislation whether one or both parents have to sign the consent form. (Note that in Belgium it is left up to the Investigator to assess the situation for the minor to decide if one or both parents have to sign the consent form.)

4. If the clinical trial has to be conducted on healthy people, the balance between the interests has to be considered more than in the other cases?

The interests for healthy volunteers may be different compared to patients but this can also be different among patients depending on the type of clinical trials. The anticipated benefits to subjects or to public health justify the foreseeable risks and inconveniencies for the subject. This is part of the assessment of the clinical trial by competent authorities and ethics committees.

5. Principal Investigator is responsible of GCP compliance and Investigator only has delegated tasks of these responsibilities?

That is correct. In the Regulation is described:

- in Article 47: "The sponsor of a clinical trial and the investigator shall ensure that the clinical trial is conducted in accordance with the protocol and with the principles of good clinical practice."
- in Article 73: "A principal investigator shall ensure compliance of a clinical trial at a clinical trial site with the requirements of this Regulation. The principal investigator shall assign tasks

among the members of the team of investigators in a way which is not compromising the safety of subjects and the reliability and robustness of the data generated in the clinical trial at that clinical trial site."

6. What is the legal reason that the suitability/ qualification of only one investigatior has to be checked? M No 65 states "the qualification of the investigators...
Answer: see question 7

7. Some sponsors want to identify IP and co-IP in one site. It could be assessed this role as well?
Answer:

- Whether Part II of the application should describe the suitability (curriculum vitae and Declaration of interest) only of one Principal Investigator per site or also of all sub-investigators, may depend on national requirements.
- In the Regulation is given:

Principal Investigator means an investigator who is the responsible leader of a team of investigators who conduct a clinical trial at a clinical trial site

and

Investigator -means an individual responsible for the conduct of a clinical trial at a clinical trial site

- In ICH-GCP is mentioned:
1.34. Investigator
A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
1.56. Subinvestigator Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows).

Therefore it is proposed by the Clinical Trials Expert group to include the suitability of other members of the trial team in the site suitability declaration template.
The site head declares via this document that "other individuals involved in conducting the trial have the suitable qualifications, expertise and training in relation to their role in the clinical trial, and all conditions identified, which might influence the impartiality of any investigators, were addressed".

This is also described as such in the "Harmonisation Guidance": "Therefore, documentation in the application of the suitability of investigators under Article 7 of the Regulation is limited to principle investigator at each site and is not required for other investigators involved in the trial unless national requirements specify otherwise. Other individuals involved in conducting the clinical trial should also be suitably qualified to perform their task (Art 49) and this aspect is covered in the site suitability declaration (Annex I N67)."

8. Sometimes is confused compensation with expenses (i.e. travel expenses)

• Compensation covers everything that is given to a patient for compensating "losses" due to trial participation. Compensation generally includes but is not limited to:

- reimbursement of costs related to trial participation (e.g. travel, accommodation, meals),
- compensation for loss of earnings due to trial participation
- compensation for monetary and non-material loss or damages (e.g. discomfort and suffering).

The reimbursement of some expenses/costs (as f.i. travel expenses) is only one form of compensation.

9. Please clarify if the assessment report Part II can be written in another language than English?

• The template that will be available in CTIS is written in English. The language to be used for completing this report will depend on national requirements.

• During the training it became clear that some members states request their ethics committee(s) to draw up the assessment report in English, while others allow the use of national language(s).

10. There is no definition for 'site'. Based on Article 50, this is The facilities where the clinical trial is to be conducted. This is the closest to definition.

• This is correct

• In addition in ICH-GCP is mentioned:

"1.59. Trial site: The location(s) where trial-related activities are actually conducted."

11. In Bulgaria the legal entity is considered to be the site, the institution that signs a contract with the Sponsor. But in other countries?

•Based on Article 50 of the Regulation, this is "The facilities where the clinical trial is to be conducted."

• According to ICH-GCP:

"1.59. Trial site

The location(s) where trial-related activities are actually conducted.", see above response

**Changes to clinical trials**

1. This type of notifiying SM (old text-new text-justification) makes very difficult to evaluate SM. CEIms need a summary of changes and a justification for each one:
   Answer: SMs will need to be subsmitted in accordance to Annex II of the CTR. This includes the submission of a clean extract showing only the new wording and an explanation of the changes in accordance with D.5. of Annex II

2. Is there also no partial approval if more than one additinal trial site has been applied for and just on is not qualified?
   No. SM can contain multiple changes, but there will be only one decision for the entirety of the application. MS can advice sponsors during the RFI to remove some of the changes in order to allow the authorisation of the SM application. See also QnA 2.7.

3. Could a SM be submitted as part I for certain MSC and part I and part II for others? yes, for example in art 11, it will be part I/II for MSC who authorised the trial and part I for the rest. Part II SM is per definition national in nature, so there could be SM submissions in which all MSC are involved in the part I (even MSC that only received an article 11 submission) , and additional part II submissions for specific others. It should be noted that when the decision of a MSC is negative for the part II, the whole SM will be refused for that MSC.
4. if a substantial modification is needed urgently for the study (for patient's safety), what to do if you can not submit because of an ongoing process and it is not possible to submit the SM?

In this case sponsors shall withdraw the SM application and re-submit it with the additional changes (see QnA 3.7). At the same time, there is no restrictions about implementing urgent safety measures when this is necessary.

5. Can a SM be submitted when an assessment is ongoing? Yes or no?
   A part II SM can be submitted in a MSC if there is an ongoing part II SM assessment in a different MSC

6. Why is there in the AR Part II template then the possibility to specify which sites are NOT authorized?
   Template AR part II was made before all these conditions were known. we need to adapt.

7. SM rules are very challenging especially for sponsors. These guidelines have been developed to allow maximum flexibility which is still compliant with the regulation. we know that it is difficult to understand the rules at first, but the entire process will be different and less flexible with the increased level of coordination. There will be a learning curve. In the meantime, the QnA for changes in trials will be revised and transformed into a stand-alone guidance.

8. How is addition of a trial sites in an existing MS done?
   Addition of a trial site is a part II SM in accordance with Art 15 of the CTR.

**Union controls**

1. Will you start the Union Controls next year in EU?

A : Yes, we plan to start Union Controls next year, shortly after application of the CTR, with the primary focus on preparedness to deliver the requirement of the Regulation.

2. Will there be other union controls - e.g. checking if Member States are fulfilling the regulation not only for 'fact-finding' reasons?

A: Yes, Union Controls will start next year after application and the fact finding is a pilot so to speak. In 2021 we are checking the methodology through these fact finding studies and fine tuning the approach for the Union Controls in the future.

3. Will the plan for Member States be made available?

A: The Union Controls will be organised in cooperation with the Member States involved. The programme for Union Controls in third countries will be prepared in cooperation with the Member States through the relevant working groups. It is proposed to make the programme for Union Controls in Member States available also.

4. Can you tell us which MS you are reviewing at the moment?

A: Netherlands and Ireland have volunteered for fact finding studies. These are pilots intended to check the methodology and fine tune the approach for the Union Controls in the future.