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DIRECTORATE- GENERAL FOR HEALTH AND FOOD SAFETY

Health systems and products
**Medicinal products – quality, safety and innovation**

Brussels, SANTE B4/ES/

# MEETING OF THE EXPERT GROUP ON CLINICAL TRIALS

**WEBEX meeting – 16 March 2022**

## MEETING MINUTES

**(from 9.00 till 17.00)**

## 1. Welcome and introductions

It was announced that AT has now fully adopted their national law to allow full implementation and compliance with the Clinical Trials Regulation ('CTR'). (Post-meeting: PO also confirmed that with the adoption of their national law, they can ensure full implementation and compliance with the CTR).

The Clinical Trials Expert Group ('CTEG') was also informed about the outcome of the election of the Clinical Trials Coordination Group ('CTCG'), the new chair is Marianne Lunzer and the vice-chair is Greet Musch. Greet will represent CTCG as observer in CTEG.

CTEG was also informed about the Commission clearance to draft the Delegated Regulation amending Regulation (EU) No 536/2014 of the European Parliament and of the Council as regards labelling requirements for unauthorised investigational and unauthorised auxiliary medicinal products for human use. The Commission will consult the Member States on the draft on 31 March at a dedicated Clinical Trials Advisory Group ('CTAG') meeting as part of the procedure toward adoption. (Post-meeting note: after the successful consultation at the CTAG meeting, the Commission has progressed with the review/adoption process.)

CTEG members were reminded of the joint CTAG/CTEG meeting to provide information and an update with the progress of the ACT-EU initiative on 22 March.

**Adoption of the draft agenda**

## 2. Endorsement of the meeting minutes of the December meeting

The meeting minutes were endorsed by CTEG.

## 3. Session focusing on Ethics committees and ethical review of trial applications

- Tacit approval

The new QnA clarifies the legal validity of Member State decisions of initial applications or substantial modifications via tacit approval. Accordingly, a tacit approval of an application is a legally binding decision at Member State level.

Importantly, the CTR does not put any obligation on the sponsor to verify that an ethical review or an assessment of the part II documentation has taken place and this is implicitly assumed (in light of article 4). This means that the sponsor can start the clinical trial when its application is authorised by tacit approval in any Member State Concerned.

The new QnA was endorsed by CTEG and published on Eudralex-10 (CTR QnA v6).

- Relationship between CTR and ICH GCP

The QnA was revised to reinforce the message of recitals 5 and art 24, stating that the content of the application dossier should be harmonised to simplify the application process for clinical trials. The CTR takes precedence over conflicting rules in guidelines, albeit ICH or other guidelines. When Member States are allowed margin for national practices it is explicitly provided in the CTR itself, see for example Article 34 (military, prison), Article 74 (legal representative/contact person) or Article 86 (fees, cost recovery).
The updated QnA was endorsed and then published.

- Appeal procedure

The new QnA with clarifications was endorsed and then published.

Additional discussions will be necessary to clarify further the **documentary requirements for transitioned trials following transition** as well as regarding the **submission of patient facing part I documents**.

Regarding documentary submission following transition, the Commission proposal remains that in addition to the documents in the transitioning application, only those documents that are affected by the next SM or addition of a new MSC should be submitted with the SM application in accordance with the requirements of Annex I and all structured data in CTIS needs to be correct.
The reasoning for this approach is to support easy transitioning from the CTD to the CTR and respect the validity of previous assessments and decisions need. If additional information is needed (e.g. for oversight), MSCs can request them. At the same time, COM supports voluntary submission of the full trial documentation in CTIS as basis for increased transparency. As an alternative approach, some MSs would require the submission of the full trial documentation (in the latest approved format) at the time of the first SM. The topic will be discussed at the next CTAG meeting on 29 April.

## 4. Additional changes to the Q&A

- Signature requirements

A survey in CTEG with twelve responding Member States (BE, CY, CZ, EE, FR, IT, LV, NL, DE, NO, PT, SK) confirmed that there are divergent signature requirements in Europe. To address this matter, QnA 1.4 was updated to state that documents and/or information that are not required as per the CTR, including signatures are not part of the clinical trial application and can not therefore be requested by Member States.

The QnA was endorsed and then published.

- Transparency (deferral vs. redaction)

The objective of the new guidance is to provide a harmonised strategy to requests for deferrals. To support increased transparency helping patient recruitment, increased scrutiny and trust trial documentation (at least the protocol and the ICF) should be published early, following the redaction of personal and proprietary information (for more clarification on personal and proprietary information, see also the relevant EMA draft guidance[1]). In addition in accordance with EU2022/123, the publication of at least the protocol of trials with potential to address public health emergencies has become mandatory since 1 March.

The new QnA was endorsed and then published.

- GMP in transitional period

The GCP-IWG group is currently adopting a new guidance for GMP requirements regarding batch release, technical agreements and shipment of IMPs. It will complement the detailed Commission guidelines No C(2017) 8179 on GMP (the new Annex 13). It will soon be published on Eudralex-4 and 10. During these discussions, additional clarifications were added regarding GMP requirements during the transition phase in our QnA.

The updated QnA was endorsed and then published.

- Decision tree (annex I)

The updated decision tree was endorsed and then published.

## 5. First experiences with transitioning trials

- Submission of a single master protocol in a complex trial

Commission presented a draft procedure describing the possibility to submit one single master protocol in CTIS in a 'reference' trial in certain cases and under specific conditions, when a complex trial is split up to be submitted under several CT numbers as individual sub-protocols. In these cases, the daughter trials would refer to the master trial but would include only the sub-protocol specific documentation and data. Submission as several individual trials for increased flexibility with the management of substantial modifications and increased transparency, is a recommendation by regulators. The proposed approach with a shared master protocol would help to maintain the master protocol harmonised through the entire trial at all time and could help mitigate the disadvantage to the sponsor for using such submission strategy.

DE was against the proposal, other Member States (BE, SE, DK, NL) are open to explore further this possibility.

- Overview on submissions:

[1] https://www.ema.europa.eu/en/documents/other/draft-guidance-document-how-approach-protection-personal-data-commercially-confidential-information_en.pdf

As of 6 March, 11 clinical trial applications were being evaluated and 108 are being drafted. Proportionally the number of multinational applications seems to be increasing. Some countries stand out as Concerned Member States (DK, DE, BE, IT, PO).

- Site registration in Organisation Management System (OMS)

EMA presented how site registration by sponsors in CTIS will become possible and the session will aim to raise awareness in Member States on how to communicate with sites for timely site registration in OMS.
The request for clarification about how sites should be registered (e.g. to include all addresses of all campuses or only the address of the organisation) was recommended to be taken up by CTIS governance.

**6. First experiences with safety cooperation**

CTCG safety subgroup representatives provided an update on the on-boarding and the available support toward the implementation of the safety cooperation.

**7. KPIs for the performance of CTR– including metrics on trial application submissions in CTIS**

Commission explained its reporting obligation under Art 97 including an impact assessment of the CTR on scientific and technological progress, comprehensive information of the different types of clinical trials and measures required to maintain competitiveness of European clinical research. This is also part of ACT EU priority action 2. Aiming at the successful and timely implementation of the CTR and its implementing acts and to develop KPIs and dashboard to track performance of the European clinical trials. The draft list of KPIs was shared with CTEG for review. The first set of core KPIs will be generated and published monthly. *(POST-meeting note: the first report of the KPIs available at this link was published on 20 May to mark the International Clinical Trials Day)*

**8. ICH-GCP guidance updates**

EMA colleagues have been asked for comments on ICH M11 template/guidance/technical specification by 1 April.

EMA explained that the expected publication date ICH GCP E6 is October 2022, with planned public consultation in September. ICH GCP E19 is under review. A concept paper to support clinical trials including pregnant and breastfeeding women (for a future ICH guideline) will be voted on in May.

**9. CTR/IVDR guidance**

The QnA was endorsed. It will be published as soon as it is endorsed also by Medical Devices Coordination Group (MDCG). *(POST-meeting note: the CTR/IVDR guidance is now available under Chapter V on the volume 10, also directly available at this link).*

**10. Complex trial Q&A**

EMA and CTCG colleagues presented the QnA for complex trials to CTEG and asked for critical comments by 1 April. A joint workshop will be organised for a systematic review of the draft before end of April. The target date for endorsement and adoption for publication by the ACT-EU SG is 23 May. *(POST-meeting note: the workshop was held on 8 April and the QnA for complex trials has been endorsed it is now available under Chapter V on the volume 10, also directly available at this link)*

## 11. EU4Health Join actions – information

- CT-CURE: BP guidance and status update was provided by the coordinators of the Joint actions. The proposal is under evaluation the moment. A stakeholder meeting was organised on 3rd Feb 2022[2] and a kick-off meeting with participants of the JA 17th February 2022. Regular steering committee meetings and plenary sessions are planned.

- JA for safety cooperation: the proposal was submitted on 15 February with a request for retro-active financing as of 1 May. Each participating MS will be able to co-finance (80/20%) one junior assessor for 33 months. 7 senior assessors volunteered to provide training and expertise.

- Planned JA for SoHo preparation-process authorisation: a JA is planned for the assessment of high-risk blood, tissue, cell products. In order to find synergies and alignments, clinical trial assessing bodies would be welcome to join the planned action.

## 12. AOB

The question regarding different requirements in CTR and CTD for the archival period was raised to be agreed on in the future.

[2] https://ec.europa.eu/health/events/joint-action-support-coordinated-and-expedited-assessment-clinical-trials-covid-19-therapeutics_en