EUROPEAN COMMISSION
DIRECTORATE- GENERAL FOR HEALTH AND FOOD SAFETY

Health systems and products
Medicinal products – quality, safety and innovation
Head of unit

Brussels, 25th April 2017

Minutes (final)
Meeting of the Expert Group on Clinical Trials
25th April 2017,
Centre de Conference Albert Borschette CCAB, room AB-1A, rue Froissart 36, 1040 Brussels

1. Approval of the agenda and of the minutes of previous meeting (agenda item 3)

The Agenda was adopted.

Minutes of the meeting of 30th June 2016
EMA requested an amendment to the minutes in order to clarify the EMA contribution to the discussion on the transitory period. Following the revision of the amendment, the minutes were adopted.

Minutes of the meeting of 26th January 2017
Minutes were adopted.

2. Nature of the meeting

Non-public meeting.

3. List of points discussed

A. Discussion on the principles for the transitory period (agenda item 4)

COM presented the main points to be discussed on the arrangements for the transitory period.

After intense discussion, the consensuses was reached that procedure should be as simple as possible to avoid extra workload to sponsors and Member States and that the technical solution should rely on the existing functionalities in the EU Portal and Database (no new functionalities will be developed). Member States agreed in principle, that for the purpose of the switching the regime applicable to clinical trial the sponsor should be able to rely on the documents already existing. The sponsor should however complete the application dossier to fully align with the requirements of Annex I on the first opportunity of additional request for assessment submit after the switch (e.g. substantial amendment). The procedure for switching the multinational clinical trials should be further discussed in order to address the additional challenges, namely the lack of the reporting Member State and the existing differences in the nationally approved protocols. Those challenges are relatively minimal as regards the VHP harmonised trials, those constitute however only a part of the multinational trails. In this context the idea of advising sponsors to prepare the consolidate protocol will be explored by CTFG.

Those ideas will be collected by COM in a written document which will be consulted with the legal service and several stakeholders. The document will be also circulated to the Experts Group.

The Commission will gather the stakeholders' feedback on the estimated number of the multinational studies which may be concerned. EMA will also check that data on their databases.

Q&A on transitory period is expected to be finalized after the expert group meeting in June.

B. Outcome of the public consultation on the Expert Group Recommendations (agenda item 5):

- **Ethical considerations in paediatric clinical trials;**

NL representative, on behalf of the responsible task group, presented the main modifications introduced to the draft guideline following the public consultation. Several comments were raised: it was suggested to delete the indication that anaesthesia presents a risk of brain toxicity in the annex 3 since this issue is under discussion in EMA (SE), rewording several points (SE), clarification on the scope (ES) and update of the version of biomedical research (ES).

COM asked the group for feedback, to be sent to the task group within two weeks.

COM clarified that the owner of this document on *Ethical considerations for clinical trials on medicinal products conducted with minors* is the Expert Group on Clinical Trials. These recommendations can be modified or updated whenever the Expert Group on Clinical Trials considers this necessary.

- **Risk proportionate approach in clinical trials;**

UK representative presented, on behalf of the responsible task group, the main modifications made after the last Expert Group meeting. Minor comments, in relation with the drafted, were suggested by SE and IE during the meeting.

After a revision of the document in line with those comments, *Recommendations on Risk proportionate approach in clinical trials* was adopted by the Expert Group.

- **IMP and AxMP.**

DE representative, on behalf of the responsible task group, presented the main modifications introduced in the text after the public consultation. Several comments were raised, focusing the discussion in two of them without reaching any agreement: inclusion of a clarification on the absence of background treatment in single arm studies and the wording on safety reporting requirements for non-authorised AxMPS.

ES representative highlighted that the document does not consider 'Concomitant MP systematically prescribed to CT patients' category, which is present in the current NIMP guidance document. Provided that there are many cases where there are MP systematically prescribed to CT participants as requested per protocol and these MP do not fit with any of the 4 proposed categories in the document, it was requested to maintain the 5th category in current guidance.

COM asked the group for feedback, to be sent to the task group within two weeks.

C. Draft text of the revised Q&A document on the CT Regulation (agenda item 6)

COM informed that the discussions on the Q&A will be re-launched in order to finalise the document. The latest version of Q&A is the one circulated to the group in December 2015. Minimal progress was made since then. The discussions will be scheduled section par section. SE asked COM to circulate the whole Q&A document in order to avoid confusion about the last version available. COM replied that there are different groups currently working on different sections and clarified that the last whole version circulated was sent in December 2016. DE pointed out that the section related to safety reporting has to be revised.

COM will circulate the latest version of the Q&A document.

- **Emergency clinical trial**

SE representative, on behalf of the task group, presented key aspects which should be addressed in the Q&A on emergency clinical trials. The Expert Group members were invited to provide examples on emergency situations trials.

Following the reception of further examples, a draft written document will be prepared to be discussed in the June meeting.

SE suggested clarifying the use of data if subject does not give consent or dies. COM replied that data obtained can be used unless the person objects to the use of data obtained from the clinical trial. However, *responsible service will be consulted by COM for further clarification on the use of data if subject does not give consent or dies.*

- **Reply on ES paper**

COM pointed out that the majority of points in the ES paper have been already addressed in the Q&A document. However, there are two points, which are not currently included in the Q&A and could be further discussed: the concept of single consolidated protocol (as discussed already under the point on transition of clinical trials) and single application on a SM affecting several CT of the same sponsor and the same IMP.

It was agreed that the issue of consolidated protocol will be discussed by the CTFG.

In relation to single application on a SM affecting several CT of the same sponsor and the same IMP, Member State agreed on that the collaboration and coordination between Member States is necessary, as well as collaborative attitude of the sponsor. It is important that IT system supports such submissions. The issue of division of work for such submission should be discussed among Member States. IT suggested similar approach to work sharing as the one applicable in assessing variations of marketing authorisations.

The issue will be further discussed.

D. Update by EMA on the development of the EU CT Portal and Database (agenda item 7)

The EMA presented the EU Portal and Database project status update (release plan, UAT, audit and meetings). EMA confirmed that the development of the EU Portal and Database is delayed. Serious shortfalls have been identified during release 6. Mitigation measures agreed with MB in March 2017 have been invoked. Several use cases have been simplified and other postponed. Key enhancements for both sponsor and Member states functionality are already being prioritised for post audit implementation. Remedial action plan from contractor is awaited by 28th April. Revised plan and timeframe (including Audit dates) is expected to be

presented to the MB in June. EMA was not in position to give further details on new timelines.

Member States expressed their concerns about the news but also on the way to share the information and not being involved on the elaboration of the mitigation plan.

EMA confirmed that the new list of mitigated use cases was approved by the MB and sent to all head of the HMA. *EMA will check internally if the new list with the use cases and the letters explaining the situation on 21st and 24th April can be directly shared with member of the Expert Group on Clinical Trials or at least with the representative of the Member States.*

Member States expressed their wishes to be involved in the prioritization of use case and functionalities to be implemented after the audit or any other potential delay on use cases for release 8 at the time of the implementation of the Clinical trial Regulation. A teleconference, including the representatives of the Member States, was proposed at the mid of June, before to the MB, to discuss the mitigation plan which will be presented to the MB in June. *COM and EMA took note of Member States wishes and the proposal for teleconference will be checked internally by EMA.*

Member States expressed their concerns on the delay of development of certain functionalities after the audit. COM and EMA clarified that no functionalities are dropped, only simplified or postponed in release 8.

SE and EI expressed their concern on the fact that no a fully functional system is going to be properly tested. EMA replied that system will be tested during the User Acceptance Testing and to report bugs, suggest improvements and CT changes.

EMA confirmed that meetings are not changed for now. Meeting on 16th May stays in. However, UAT6 and UAT7 and training date will be likely modified.

UK expressed their wishes to be involved on UAT testing release 6 or 7.

E. Member States preparedness for the implementation of the Clinical Trials Regulation (agenda item 8)

Few proposals were received so far for sharing of best practices and discussion of challenges regarding aspects related to the preparation of national law. Therefore, COM proposed to postpone this discussion for the following meeting in June and invited the Member States to suggest further issues to be discussed.

The following topics were proposed by the COM: legal representative, damage compensation, cluster trials.

IT suggested to be focused on national legislation which could have impact on the implementation of others Member State, such as suitability on the investigation of Clinical Trial site. Others topics suggested by the Member States were: GMP equivalent standards referred to Clinical Trials Regulation (UK), concerns on use of data outside of CT protocol according to Art 28 (2) and recital 29 (FI).

COM asked for written feedback on the issues to be discussed on the June meeting.

F. Interplay between the Clinical Trials authorisation requirements and GMO authorisation requirements (agenda item 9)

COM informed that after the February GMO/Pharma workshop on the GMO and Pharma interplay a small group was set up in order to discuss the interplay between the authorisation procedures under the GMO legislation and Clinical Trials Regulation. The first TC of that

small group will be soon organised. The objective is to work on good practices of articulating GMO/CT authorisation processes.

COM kindly invited the Member States to inform on the currents state of play as regards the requirements of GMO authorisations in the context of clinical trials.

G. Data to underpin future Clinical Trial Union controls by the Commission in non-EU countries (agenda item 10)

COM (SANTE F5) presented the legal framework for the Union controls by the Commission in non-EU countries.

COM asked the Member States for the advice how the data on the third country clinical trials referred to in the applications for the clinical trials authorisation could be gathered. Those data are not foreseen to be captured as structured data in the EU Porta and Database. COM (SANTE F5) asked the collaboration of the member of the Expert Group to consult internally this issue with the national colleagues who will process applications for new clinical trials in the EU. COM (F5) would appreciate if a (non-retrospective) system could be put in place by the time the Clinical Trial Regulation becomes applicable.

Member States (EI, SE, DE) pointed out that this information should be collected by the EU Portal and Database (ideally as a structured data or at least as document uploaded by the sponsor).

EMA replied that uploading the document as an attachment is not a concern. However, capturing that information as structured data is a challenge. In any case, if this is an important issue, it could be discussed internally.

Several comments were raised in relation to: the entitlement for the EU to audit third countries (UK), the procedure of the Union control in third country (PL and SE); potential implications for Member States (SE), consequences of these controls on clinical trials conducted in those countries (ES).

COM (F5) clarified that these controls would not be conducted until the clinical trials regulation becomes applicable. The union controls consist of the system audit of the state in question. In this context some observed inspections may be conducted, but it is important to stress the difference between the inspection of clinical trials in third country and Union control of a third country. Consequently, recommendations would be to the health authorities not to the sponsors. All the issues raised will be further discussed.

Further comments or ideas can be sent in the following two weeks to the COM.

H. Any Other Business (agenda item 11)

- **Access to data**

CTFG chair informed on the state of play of the consultation on access to data. Member States were asked to provide feedback whether applicable national legislation allows sharing documents of sponsors, sharing documents of Member States or none. 20 Member States provided requested feedback so far (17 choose to share documents of sponsor and of Member States, one not to share anything and two need more time to decide).

CTFG chair invited the member of the Expert Group to push their Ministry of Health or HMA to respond in to those Member States where their answers have not been sent yet.

- **Question raised by IE: Appeal in the situation when a RMS issues negative assessment report and all others MS concerned are obligated to follow issuing negative decision**

COM pointed out that this is in principle an issue of national procedural law. The right to effective remedy is recognized in the Charter of Fundamental Right of the EU. This will be the question of an argumentation how the negative decision of a Member State will be justified. The requirements of EU law may be provided as justification for such a national decision. It seems to be more a matter for courts, than for Clinical Trial authorities.

IT suggested that there would be several options at national level as a voluntary basic. The Member States with a positive position could be reflected in the final letter and the sponsor could apply for an authorisation in those Member States.

- **Independence of the ethics committee (LT); Ionising radiation (UK); No definition of a clinic (UK); EMA - Biological samples of the subject**

Other questions from the expert were not discussed due to the time constraints.

Conclusions/recommendations/opinions

The group adopted the Recommendations on the Risk proportionate approach in clinical trials.

Next steps

Actions to be performed by Member States

- MS to provide comments on *Recommendations on Ethical considerations in paediatric clinical trials*.
- MS to provide comments on *Recommendations on AxMP in Clinical Trials*.
- MS to provide any additional examples on *emergency situations* trials without prior informed consent also fulfilling the regulation requirement of clinical relevant benefit.
- MS invited to propose additional topics to be discussed *on Member States preparedness for the implementation of the Clinical Trial Regulation* by two weeks.
- MS kindly invited to propose ideas to be discussed is the meeting on the *GMO/Pharma interplay* by two weeks.
- MS invited to provide additional comments or ideas how to gather data necessary for preparation of *future clinical trial union controls by the Commission in non-EU countries*.

Actions to be performed by COM

- COM to collect the ideas on the *principles for the transitory period* in a written document, which will be consulted with several stakeholders.

Actions to be performed by EMA

- EMA to check database looking for estimation on the *number of multinational studies authorised under Clinical Trial Directive and ongoing 3 years after the implementation of Clinical Trial Regulation.*
- EMA to *check internally* and share with the group the presentation, the communication of EMA to MB of 21 and 24 April, and mitigation measures adopted on 16 March 2017.

- EMA to *check internally* if a teleconference, including the representatives of the Member States, at the mid of June, before to the MB, to discuss the mitigation plan which will be presented to the MB in June can be conducted.

Next steps

- *Recommendations on Ethical considerations in paediatric clinical trials* to be adopted on the Expert group meeting in June.
- *Recommendations on AxMP in Clinical Trials* to be adopted on the Expert group meeting in June.

Potential topics to be discussed in the following meeting:

- Publication of new recommendations in volume 10 of Eudralex
- Draft written document on *emergency situations*
- Arrangements for transitory period
- *Q&A document*
  Member States preparedness for the implementation of the Clinical Trials Regulation

4. Next meeting

COM stated that the next meetings of the expert group are tentatively planned for 28th and 29th June 2017. Formal invitations and agenda will be sent out at a later stage.

5. List of participants

COUNTRY	ORGANISATION
AT	AGES - Austrian Medicines & Medical Devices Agency
BE	Federal agency for medicines and health products
BG	Ethics Committee for Multicentre Trials
CZ	State Institute for Drug ControlLucie
DE	IBE - Ludwig Maxmilians University - Association of Research Ethics Committees
DE	BFARM
DE	Federal Ministry of Health
DK	The Danish Ministry of Health
DK	Danish Medicines Agency
EC	European Commission, DG SANTE
EL	National Organisation of Medicines
ES	Research Institute of Universitary Hospital “12 de Octubre”
ES	Agencia Española de Medicamentos y Productos Sanitarios
FI	The National Committee on Medicinal Research Ethics
HU	National Institute of Pharmacy and Nutrition
HU	Ministry of Human Capacities
HU	Medical Research Council of Hungary
IE	Health Products Regulatory Authority

IT	Agenzia Italiana del Farmaco (AIFA)
LT	Lithuanian bioethics committee
LV	State Agency of Medicines of Latvia
NO	Norwegian Medicines Agency
NL	Central Committee on Research Involving Human Subjects (CCMO)
NL	Health Care Inspectorate
NL	Ministry of Health
PL	Main Pharmaceutical Inspectorate
PL	The Office for Registration of Medicinal Products, Medicinal Devices and Biocidal Products
PT	National Ethics Committee for Clinical Research - CEIC
PT	INFARMED, I.P. (Portuguese National Competent Authority
RO	National Agency for Medicines and Medical Devices
SI	JAZMP
SE	Medical Products Agency
UK	Medicines and Healthcare products Regulatory Agency
UK	Health Research Authority
EMA	European Medicines Agency