Ethical Review in the New Clinical Trials Regulation: What are the Challenges?

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Structure

- Introduction – reasons of the regulatory change for Clinical Drug Trials
- Ethical review related issues raised during the public consultation process on CTR released in July 2012
- Challenges to RECs in the adopted CTR (April 2014)
- Concluding remarks: “marginalization” of RECs or optimization of approval procedure for CDT?

Explanatory memorandum to the CTR

– the existing provisions of the Directive 2001/20/EC appear **to have hampered the conduct of clinical trials in Europe**, therefore the aim of the new Regulation is **to make it easier to conduct multinational clinical trials and to restore the EU's competitiveness in clinical research**

RECs in Directive 2001/20/EC (CTD)

- Main REC related features of the Directive:
  - ***Two parallel procedures: Favorable REC opinion*** in addition to the **approval by the CA**
  - ***Wide scope of review*** by RECs (e.g., both design /methodology and IC documents, etc.)
  - Single decision per country by RECs to be given in 60 days
  - CTD served as a model of ethical review for other types of biomedical research

CTR: two parts of the review procedure

- The draft released for public consultation already divided the review of CDT into two parts:
  - Part I: Evaluated by all MS concerned with the ***reporting MS coordinating the assessment and providing a 'single decision'***
  - Part II: Evaluated ***separately by all MS concerned***, each MS provides its own decision

Aspects covered by Part I

The anticipated **therapeutic and public health benefits/risks and inconveniences for the subject** taking into account:

- characteristics of and knowledge about the ***investigational medicinal products***
- the relevance of statistical approaches, ***design of the clinical trial and methodology***, including sample size and randomisation, comparator and endpoints
- the characteristics of the ***intervention compared to normal clinical practice***;
- ***safety measures***, including provisions for risk minimisation measures, monitoring, safety reporting, and the safety plan
- But also **investigator brochure, labeling, manufacturing**

Aspects covered by Part II

- compliance with the requirements for **informed consent**;
- compliance of the arrangements for **rewarding or compensating** subjects
- compliance of the **arrangements for recruitment** of subjects;
- (d) compliance with Directive 95/46/EC; (**personal data**)
- (e) compliance with Article 49 (**Suitability of researchers**);
- (f) compliance with Article 50 (**Suitability of clinical trial sites)**;
- (g) compliance with Article 76 (**Damage compensation)**;
- (h) compliance with the applicable rules for the collection, storage and **future use of biological samples** of the subject.

- **Ethical review related issues raised during the public consultation process on CTR released in July 2012**

1st EUREC statement: September 2012

- The draft released for the public consultation **missed the reference to RECs altogether**, only refers to the ethical review (which could be carried out by non-REC, e.g., the competent authority)
- "…the choice of the Commission to undo the positive steps established through the current Directive by omitting the clear position of Research Ethics Committees (RECs) in the process is not acceptable." http://www.eurecnet.org/news

2nd EUREC Statement, July 2013

- As a result of consultation process, RECs were included into the document, however,
  - The Regulation still only considers Ethics Committees of the concerned MS as consultation bodies in the authorization process, **since they are only required to "examine" part II of the submission**

EUREC fully supports the ***EP amendments to the Proposal of the Regulation recorded in the Report by Glenis Willmott***:

- the sponsor cannot choose the reporting member state,
- the results of all trials would be made publicly available,
- the Commission will facilitate cooperation between ethics committees and the sharing of best practices on ethical issues including the procedures and principles of ethical assessment.

- **Challenges to RECs in the adopted CTR (April 2014)**

The role of RECs

- Art. 4: 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** of the assessment report for the authorisation of a clinical trial as referred to in Article 6 and in Part II of that assessment report as referred to in Article 7 as appropriate for each Member State concerned.
- But consider the logistics…

The most common scenario in case RECs do encompass Part I

- **Multinational studies where MS can only react to the reports of the rMS**
- **The time frame for Multinational studies:**
  - rMS provides initial assessment report within 26 days from the validation date.
  - rMS and MSc jointly perform a coordinated review phase within subsequent 12 days.
- **Therefore, the CA and REC of the MSc has only 12 days to react/produce a response to the report of the rMS!**

Tacit Authorisation

If the MSc does not respond within the time limits, the resulting ‘decision’ is in favour of the sponsor: the procedure of ‘tacit authorisation’ applies

What happens if the REC does not manage to respond in 12 days period and does not provide its decision in time?
Violation of the Declaration of Helsinki!?

3rd EUREC Statement: November 3rd, 2014

- **guarantee ethics committees full and direct access to the application and data-base** (including downloads) through the EU portal, from the time the application is submitted.
- *This will ensure effective review by independent ethics committees and avoid undesired scenarios such as tacit approvals. The necessary access could be achieved via the existing portal functionalities.*
- To be seen – the Portal is still under construction – new date when it will start operating is the end of 2017

Concluding remarks

- The scope (Part I and/or II) of ethical review is left to the discretion of the MS – therefore in some MS risk/benefit ratio may not be included in the ethical review.
- In case it is included, the timeframe for the input of RECs on Part I requires very flexible REC procedures of decision making (alternatives to face to face meetings…)
- Is the new model of the approval of CDT an unjustified “marginalization” of RECs or an optimization of the approval procedure?

Thank you!