Review of EU Clinical Trial Directive

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Overview

- Background of Review EU Clinical Trials Directive
- Key Speech by EU Commissioner John Dalli
- EFGCP Proposals on Key Elements of New Legislation
- Next Steps?
- EMA Reflection Paper on CTs in Third Countries
Review of EU Clinical Trial Directive: Background
Review of EU Clinical Trial Directive: Background (1)

- **Eight years** have elapsed since implementation into national law of EU Member States of the CT Directive (2001/20/EC)
- **December 2008**: European Commission announced review of existing CT Directive
- **October 2009**: European Commission launched public consultation on the assessment of the functioning of the CT Directive
- **February 2011**: European Commission published concept paper setting out policy options addressing key concerns
A. Introduction

The European Commission is planning to put forward, in 2012, a legislative proposal to revise the Clinical Trials Directive 2001/20/EC. To assess the impact of this revision, a public consultation was held from 9 October 2009 to 8 January 2010 (the ‘2009/10 public consultation’). The responses, together with a summary of them, have been published on the ‘clinical trials website’ of ‘Health and Consumers’ Directorate-General (DG SANCO).
Review of EU Clinical Trial Directive: Background (3)
Review of EU Clinical Trial Directive:
Background (4)

- Deadline for comments on European Commission’s concept paper was 13 May 2011
- Commission released a summary of stakeholders’ replies on 7 July 2011 – general comments:
  - concept paper overly optimistic on feasibility of harmonization
  - widespread approval of majority of “preliminary appraisals”
  - not enough focus on ethics; too much on costs and regulatory burdens
  - key problem of dual approval by NCAs and ECs not addressed
Key Speech EU Commissioner Dalli on Review of EU Clinical Trial Directive
Review of EU Clinical Trial Directive: Key speech by EU Commissioner Dalli (1)

Very important speech EU Commissioner for Health and Consumer Policy (John Dalli) regarding the review of the CT Directive on 7 March 2012

“I am committed to putting forward a proposal [...] that addresses the valid concerns that have been raised. [...] This time we have to get it right.”
Review of EU Clinical Trial Directive: Key speech by EU Commissioner Dalli (2)

- 15% decline in clinical trials in the EU in recent years, while costs and resource requirements doubled, and delays increased by 90%

  “Clinical trials are crucial for the development of new medicines, and equally to improve and refine treatments with existing medicines”

- Clinical trials are “key contributor” to growth and jobs and “mean research and investment”

  “Today, clinical trials account for investments of over €20 billion per year in the EU”

  “We must keep in mind that each year sees the authorization of approximately 4400 new clinical trials”
Review of EU Clinical Trial Directive: Key speech by EU Commissioner Dalli (3)

“The Clinical Trials Directive is not the only reason behind the decline in clinical research in the EU. There are many other factors not linked to regulation [...]”

“As regards the regulatory framework, we can and will do better”

“The revision of the Directive is being prepared with the broadest possible involvement of stakeholders with a view to becoming, once again, an attractive place for clinical trials of the highest standards”
Review of EU Clinical Trial Directive: Key speech by EU Commissioner Dalli (4)

Expected Legal Form of Proposal

• Commission intends to propose revised legislation in the form of a Regulation
  – new rules will be directly applicable in EU Member States and no need for national implementation
• Goal is to enhance common interpretation of revised legislation in EU Member States

“However, [...] what matters is that the actual application of the law is done in co-operation by Member States in a fast an efficient way”
Review of EU Clinical Trial Directive: Key speech by EU Commissioner Dalli (5)

Authorization Process

- EU Commissioner John Dalli acknowledged that the current authorization process:
  - “hinders the conduct of pan-European research projects” and
  - “leads to high costs, delays and incoherent research protocols”

- European Commission intends to:
  - propose a streamlined submission process
  - launch a single submission portal
Review of EU Clinical Trial Directive: Key speech by EU Commissioner Dalli (6)

Assessment of Clinical Trial Applications

- Commissioner Dalli does not want “a new, central bureaucracy”, but identified need for a co-operative and flexible approach:
  
  “I want an assessment system that is fast, ‘slim’, pragmatic, and not disproportionately expensive”

- Commissioner Dalli considers this “critical in particular for academic research” to which the new rules will apply as well
  
  “we have to be aware of the limitations for [...] academic sponsors in terms of resources”
Review of EU Clinical Trial Directive:  
Key speech by EU Commissioner Dalli (7)

Assessment of Clinical Trial Applications

- Assessment process for **clinical trials** to be “**strictly separated**” from ‘**scientific advice**’ for development of medicines
  
  - Assessment of whether conduct of trial is acceptable is “**something very different**” from guidance on desirable clinical data for future marketing authorization

  “**Therefore, it is important to keep the body indicating [...] what data is desirable, separate from the one that determines what clinical trial is acceptable. [...] This is a critical point – the potential for conflicts of interest must be avoided**”
Assessment of Clinical Trial Applications

- Assessment of **ethical** and **intrinsically national** or local **issues** to be **assessed nationally**
  - EU Member States to decide on how to organize an independent, timely and qualified review process

- **Catalogue of issues** will set out what issues will be assessed in co-operation by EU Member States, and issues to be assessed nationally will be defined
Review of EU Clinical Trial Directive: Key speech by EU Commissioner Dalli (9)

Risk-Adaptedness

- Commissioner Dalli recognized that there are many clinical trials where additional risk to subject is minimal
  - Mentioned clinical trials with authorized medicines
  - Commission evaluating whether some of the “red tape” can be cut for this category of trials, without compromising patient rights and safety as well as data integrity
Global Aspects

• Commissioner Dalli intends to address “many claims” that globalization of clinical trials leads to decreased patient protection in third countries.

“We do not want to see clinical trials referred to in the EU - for example in the marketing authorization application – disregarding the rules on the protection of patients”

• While recognizing jurisdictional limitations, Commissioner Dalli intends to ensure that the current ‘equivalence rule’ is “properly enforced”
EFGCP Proposals Concerning Key Elements of New Legislation
Review of EU Clinical Trial Directive: EFGCP Proposals (1)

- **European Forum for Good Clinical Practice** (EFGCP) is a non-profit organisation
  - founded with the support of the European Commission and the European Parliament
  - established by and for individuals with a professional involvement in the conduct of biomedical research
  - considered a leading multi-stakeholder forum in Europe

- Members include pharma companies, international research organizations and individuals
Review of EU Clinical Trial Directive: EFGCP Proposals (2)
Review of EU Clinical Trial Directive: EFGCP Proposals (3)

- EFGCP prepared paper with practical proposals regarding key elements of the new legislation.

- EFGCP’s proposals were discussed with European Commission, EMA and EU Member State officials during round-table on 12 March 2012, less than a week after EU Commissioner Dalli’s key speech.

- Expectation is that European Commission will at least take the EFGCP’s proposals into consideration before adopting its legislative proposal.
Review of EU Clinical Trial Directive: EFGCP Proposals (4)

- EFGCP’s paper emphasized need for:
  - mandatory single submission process (also for submissions to Ethics Committees) in English
  - through EU CTA portal developed and hosted by EMA
  - based on one set of documents defined at EU level
  - guarantee of confidentiality
Review of EU Clinical Trial Directive: EFGCP Proposals (5)

- EFGCP suggested:
  - should be no need to make local submissions
  - list of required documents should be agreed and supported by all EU Member States
    - Member States should not be able to request additional local documents
  - application form should follow EudraCT format and should supersede national formats
  - should be central check of completeness and adequateness of the clinical trial dossiers
  - transparency to be achieved through EU Clinical Trial Registry and results posting
Review of EU Clinical Trial Directive: EFGCP Proposals (6)
Review of EU Clinical Trial Directive: EFGCPP Proposals (7)

**Evaluation process:**

- assessment committee composed of concerned MS with 1 NCA and 1 NEC delegate each
- EMA staff should not participate in scientific assessment procedure
- MS on assessment committee should appoint coordinating MS Competent Authority, upon suggestion sponsor
- only one set of questions for sponsor from assessment committee
Review of EU Clinical Trial Directive: EFGCP Proposals (8)

- Evaluation process (continued):
  - decision by qualified majority
  - possibility of appeal
  - EC to communicate assessment through representative on committee
Review of EU Clinical Trial Directive: EFGCP Proposals (9)

- **Timelines** for assessment:
  - 60 day for initial multi-country trials
  - 35 days for amendments of approval multi-country trials
  - 15 days for amendments under the simplified procedure

- **Result**: one scientific and ethical opinion based on qualified majority of concerned MSs with list of countries that accepted and opted-out
Appendix 2: Initial approval of international trials: 60d

Assessment committee
*representatives from all involved MSs: 1 from each CA & 1 from each EC

Single portal

1st check

At t0

Rapporteur CA review

Other CA reviews

ECs reviews

Questions

Single portal

Single portal

Single portal

Single portal

Approval

Trial start

Up to 3 working days check of completeness of the dossier (administrative, by EMA)

Assessment 30d

20 calendar days for CA rapporteur + 10 more for all to review the report

Compilation & reconciliation

15 calendar days

(mail, phone etc…)

Sponsor addresses questions & comments (including PIS/TC)

Approvals & Ops-out

15 calendar days

List of all MSs & status available on portal

Clock stop (max 90d)
Review of the EU Clinical Trial Directive: Next Steps?
Review of EU Clinical Trial Directive: Next Steps? (1)

- European Commission has indicated that the Regulation will be detailed in content and that there will be limited need for delegated and/or implementing acts.

- Publication of the Commission’s proposal is expected by mid-2012.

- Subsequent EU legislative procedure will likely take at least 12 months and possibly much longer.

- In addition, the regulation will usually provide a transition period to industry and stakeholders of at least 6 months.
Review of EU Clinical Trial Directive: Next Steps? (2)

- While there have been many opportunities to provide input into the legislative process, it is important for stakeholders to **continue to be involved:** new legislation will remain in place for many years.

- Members of the **European Parliament** and officials of **EU Member States** can be engaged to achieve amendments to European Commission’s legislative proposal, once adopted.
EMA Reflection Paper on Ethical and GCP Aspects of Clinical Trials Conducted in Third Countries
Clinical Trials in Third Countries: EMA Reflection Paper (1)

- **December 2008:** EMA issued a Strategy Paper on ensuring ethical standards in clinical trials
- **June 2010:** EMA published a Reflection Paper for public consultation on ensuring appropriate ethical and GCP standards for CTs conducted outside EU/EEA
- **February 2011:** Commission launched Concept Paper on revision of CT Directive, including increased focus on data submitted in EU
- **April 2012:** Finalized EMA Reflection Paper suggested regulatory actions clarifying application of ethical principles to CTs carried out in third countries
- **1 May 2012:** EMA Reflection Paper entered into force
Clinical Trials in Third Countries: EMA Reflection Paper (2)

16 April 2012
EMA/121340/2011
The European Medicines Agency Working Group on Clinical Trials conducted outside of the EU/EEA

Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU Regulatory Authorities
Clinical Trials in Third Countries: EMA Reflection Paper (3)

• Reflection paper aimed at strengthening existing processes to ensure that all CTs meet ethical and GCP standards

  – puts forward concrete steps for international cooperation in the regulation of clinical trials, with emphasis on capacity-building initiatives

  – suggests actions that can be taken by EU regulatory authorities in the drug development and marketing authorization phases

• Actions set out in Reflection Paper are potentially far-reaching and burdensome for industry
Clinical Trials in Third Countries: EMA Reflection Paper (4)

International Cooperation

- Reflection paper stresses need for international cooperation to ensure common international approach to oversight of clinical trials
  - Build contact with and between National Regulatory Authorities and Ethics Committees
  - Establish international network of clinical trial regulators

- Countries with limited regulatory systems and high number of recruited trial subjects to be priority for capacity-building activities
Clinical Trials in Third Countries: EMA Reflection Paper (5)

International Cooperation

- EMA identified core set of actions, including:
  - increasing number of inspections in priority countries and encouraging joint / complimentary inspections
  - developing frameworks for information exchange and follow up on inspections
  - assistance with establishment and operation of National Regulatory Authorities and Ethics Committees
  - providing training, support and/or advice
Clinical Trials in Third Countries: EMA Reflection Paper (6)

Clarification of Practical Application of Ethical Standards for EU Regulatory Authorities

- Reflection paper describes how regulatory processes in EU can use existing ethical and GCP standards
- Regulatory Authorities “should” disregard data obtained after failure to, for example:
  - submit protocol to independent EC
  - obtain informed consent
  - properly protect confidentiality trial subjects
  - inclusion vulnerable subjects without EC approval
  - use acceptable study design
Clinical Trials in Third Countries: EMA Reflection Paper (7)

Clarification of Practical Application of Ethical Standards for EU Regulatory Authorities

- MA applicant expected to provide substantial additional information, including:
  - summary of EC and National Regulatory Authority approvals for each clinical trial supporting the MAA
  - summary of informed consent processes used and any significant variations
  - summary of provisions made to provide fair compensation to injured trial subjects
Clinical Trials in Third Countries: EMA Reflection Paper (8)

Clarification of Practical Application of Ethical Standards for EU Regulatory Authorities

• Information to be provided (continued):
  
  - justification for participation vulnerable subjects and/or use of placebo or other comparators
  - description post-trial access to treatment and medical care

• Regulatory Authorities should seek additional assurance for studies that give rise to special ethical concerns
Clinical Trials in Third Countries: EMA Reflection Paper (9)

Practical Steps for Guidance and Advice in Drug Development Phase

• Applicants intending to submit MAA in the EEA are encouraged to **consult EEA regulators** about study design and ethical aspects prior to start of clinical trials outside the EEA

• EEA Regulators encouraged to take “**every opportunity**” prior to start clinical trials “**to influence their design and ensure their ethical conduct**”

• Reflection Paper provides list of issues that EMA Committees and Regulators should “**systematically**” consider when evaluating requests
Clinical Trials in Third Countries: EMA Reflection Paper (10)

Practical Steps for Marketing Authorization Phase

- MA assessors should identify major ethical concerns re: studies included in the MAA dossier and should confirm e.g. the following in Assessment Report:
  - no major ethical issues identified and/or how any ethical concerns have been addressed
  - studies were approved by EC and National Regulatory Authority
  - statement sponsor re: compliance in dossier
  - no major concerns re: conduct of study

- Assessors to seek further clarification from MAA applicant in case of ethical concerns
Clinical Trials in Third Countries: EMA Reflection Paper (11)

Practical Steps for Marketing Authorization Phase

- Reflection Paper sets out study-related inspection triggers as well as **regulatory actions**, including
  - inspection of sites involved in the trial
  - exclusion of data obtained from a non-compliant trial
  - issuance of formal warning to applicants and MAHs
  - discussion of non-compliance in EPAR & PAR
  - MA suspension/revocation & urgent safety restrictions

- In addition, the Reflection Paper states:
  
  “The possibility of applying specific penalties should be considered and the mechanisms for application of those penalties identified”
Clinical Trials in Third Countries: EMA Reflection Paper (12)

- Reflection Paper is further reason for stakeholders to continue to be engaged in the legislative process:
  - EMA Reflection Paper was finalized following an extensive consultation process
  - is likely to have an impact on European Commission’s legislative proposal
  - could lead to regulatory actions by EU Member States
  - could be translated in further guidance documents
Questions/Comments

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