Federal agency for medicines and health products

The implementation of the EU CT Regulation: Overview of the different projects in progress

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KCE Symposium, 12th October 2016
1: Overview of the Regulation

Scope:

- Only interventional studies of medicinal products
- No distinction between « commercial » and « non commercial sponsors »
- Risk based approach: introduces the concept of ‘low-intervention trials’.
- NIMPs (now auxiliary medicinal products) are included.

Major advantages:

- Streamlined submission and review process for trial applications via the EU portal and database
- Enhanced communication and cooperation between Member States
- Simplified safety reporting
- Increased transparency
1: Overview of the Regulation: New simplified procedure:

- Single EU Portal & Database
- Single dossier and single submission
- Sponsor can propose Reporting MS
- Coordinated assessment for multi-state clinical trials
  Part I – joint assessment by all concerned MS (NCA+EC), led by RMS
  Part II – National assessment only (R&D offices and Ethics Committee)
- Clear timelines (extended compared with Directive), concept of tacit approval
EU Multi-national clinical trials: current situation

Overview of CTR
EU Multi-national clinical trials: under new Regulation

Overview of CTR
1: Overview of the Regulation: Transparency:

The Regulation requires that information contained in the clinical trial database shall be **publicly available** unless one or more of the following exceptions apply:

- protection of personal data
- protection of commercially confidential information, in particular taking into account the marketing authorisation status of the medicinal product, unless there is an overriding public interest
- protection of confidential communication between Member States in the preparation of their assessment
- protection of the supervision of clinical trials by Member States
1: Overview of the Regulation : Transparancy :

• Disclosure rules published in October 2015: EMA/42176/2014

• Includes descriptions of what and when documents may be made public depending on stage of development, type of trial (therapeutic vs non-therapeutic) and type of document.

• Publication rules based on three categories of trials
  Category 1: Phase 1, bioequivilance / bioavailability / biosimilar trials
  Category 2: Phase II and III (ie not Cat 1 or 3)
  Category 3: Phase IV and low-intervention trials

Provides balance between encouraging innovation and providing extensive public information on clinical trials conducted in EU.
The publication of some information from the EU Portal and Database will be deferred. The length of this deferral is dependent on the trial’s categorisation which is explained in the table below:

<table>
<thead>
<tr>
<th>CATEGORY 1</th>
<th>CATEGORY 2</th>
<th>CATEGORY 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmaceutical development clinical trials</td>
<td>Therapeutic exploratory and confirmatory clinical trials</td>
<td>Therapeutic use clinical trials</td>
</tr>
<tr>
<td>• Phase I trials</td>
<td>• Phase II trials</td>
<td>• Phase IV</td>
</tr>
<tr>
<td>• Phase “0” trials</td>
<td>• Phase III trials</td>
<td>• Low-intervention clinical trials</td>
</tr>
<tr>
<td>• Bioequivalence and bioavailability trials</td>
<td>• Similarity trials for biosimilar products</td>
<td>• Other trials to determine equivalence</td>
</tr>
</tbody>
</table>

Exceptions to the transparency are the paediatric trials (all phases) which still need to be submitted within 6 months to NCAs and should be published as per Regulation (EC) No 1901/2006: this has not been amended by the CT regulation.
<table>
<thead>
<tr>
<th>Section of trial document</th>
<th>CATEGORY 1</th>
<th>CATEGORY 2</th>
<th>CATEGORY 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main Characteristics of the trial</strong></td>
<td>For a subset of information and <strong>up to the time the CT Results Summary</strong> is posted (Justification)</td>
<td>No deferral</td>
<td>No deferral</td>
</tr>
<tr>
<td><strong>Trial related documents</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Subject Information sheet</td>
<td></td>
<td></td>
<td>No deferral</td>
</tr>
<tr>
<td>Protocol</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Product related Documents</strong></td>
<td>Up to the <strong>time of MA</strong> using this trial or <strong>up to 7 years</strong> after the end of the trial, whichever is earlier</td>
<td>Up to the <strong>time of MA</strong> using this trial or <strong>up to 5 years</strong> after the end of the trial, whichever is earlier</td>
<td><strong>Up to the time the CT Results Summary</strong> is posted (usually 12 months after the end of the trial in the EU)</td>
</tr>
<tr>
<td>IB</td>
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<tr>
<td>IMPD, S&amp;E</td>
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<tr>
<td><strong>Assessors documents / data</strong></td>
<td></td>
<td></td>
<td>No deferral</td>
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<tr>
<td>Request for information</td>
<td></td>
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<tr>
<td>Assessment Report (I&amp;II)</td>
<td>MS decides but takes into account the exceptions of the legislation and the deferral time proposed by the sponsor</td>
<td></td>
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<tr>
<td>Conditions</td>
<td></td>
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<tr>
<td>Section of trial document</td>
<td>CATEGORY 1</td>
<td>CATEGORY 2</td>
<td>CATEGORY 3</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Substantial Modification</td>
<td>Deferral possible only for changes or additions to data/documents not yet made public because of the legal deadline is not reached or a deferral was requested. Publication will take place <strong>when the legal deadline is reached or deferral deadline expires.</strong></td>
<td></td>
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</tr>
<tr>
<td>Notifications</td>
<td>Unexpected events, urgent safety measures</td>
<td>No deferral</td>
<td>No deferral</td>
</tr>
<tr>
<td></td>
<td><strong>Up to the time when summary results are posted</strong> - except for early terminations for reasons involving subject safety or if Corrective measures (Justification)</td>
<td></td>
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</tr>
<tr>
<td>Clinical Trials Summary Results</td>
<td>Up to <strong>18 months after the due date for the publication of the summary of results</strong> (usually 12 months after the end of the trial unless article 37(4) applies) (Justification)</td>
<td>No deferral</td>
<td>No deferral</td>
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<tr>
<td>Lay person</td>
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<td>No deferral</td>
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<td>Clinical Study Report</td>
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<td>No deferral</td>
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<tr>
<td>Section of trial document</td>
<td>CATEGORY 1</td>
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<tr>
<td><strong>Supervisory measures</strong></td>
<td></td>
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<tr>
<td>Serious Breaches</td>
<td></td>
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<tr>
<td>Inspections Reports (EU)</td>
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<tr>
<td>Inspections Reports (by third country CA)</td>
<td>If the sponsor requested a deferral up to the time of publication of summary results the same will apply here.</td>
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<td>No deferral</td>
</tr>
<tr>
<td><strong>Supervisory measures</strong></td>
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<td>Union Controls</td>
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<tr>
<td>Corrective Measures</td>
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<td></td>
<td>No deferral</td>
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</tbody>
</table>

Overview of EU Portal and Database
1: Overview of the Regulation : Implementation :

Article 99 shall apply “no earlier than 28th May 2016” (6 months after successful audit of IT system). Now expected Autumn 2018

Transitional aspects: cfr EC guidance document out for consultation (comments till 1st of November 2016)
1: Overview of the Regulation: Implementation: Critical step remains the development of the EU Portal and D-base

<table>
<thead>
<tr>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
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<tr>
<td>Q4</td>
<td>Q1</td>
<td>Q2</td>
<td>Q3</td>
<td>Q4</td>
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System build

<table>
<thead>
<tr>
<th>Iteration 1</th>
<th>Iteration 2</th>
<th>Iteration 3</th>
<th>Iteration 4</th>
<th>Iteration 5</th>
<th>Iteration 6</th>
<th>Production Release (V1)</th>
<th>PGLR (V2)</th>
<th>PGLR (V3)</th>
<th>Maint.</th>
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</thead>
<tbody>
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<td>11/01/2015</td>
<td>06/04/2015</td>
<td>15/05/2015</td>
<td>06/10/2015</td>
<td>10/11/2015</td>
<td>09/12/2015</td>
<td>01/01/2016</td>
<td>01/02/2016</td>
<td>01/03/2016</td>
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UAT

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<th>UAT 10</th>
<th>UAT 11</th>
<th>UAT 12</th>
<th>UAT 13</th>
<th>UAT 14</th>
</tr>
</thead>
</table>

Milestones

- Appendix on disclosure rules endorsed by MB – Oct ’15
- Project delivery timeframe endorsed by MB – Dec ’15
- Interface specifications shared with MS – Jan ’17
- Audit Nov ’17
- Audit completed by MB – Dec ’17
- Interface delivered (Agency side) – Q2 ’17
- Production completed – Jul ’18
- Version – Jul ’18
- EC notice – Mar ’18
- 2-3 months Commission decision making period
- 6 months
- Regulation applies – Oct ’18
- Project closure – Q3 ’19

Other IT

Use Case Specification

Requirements Management

- Production data provisioning
- MS integration testing

- Develop auditor manual
- Develop user manual for V1
- Update user manual for V2 and V3

- V1 Training material ready
- V2 Updates complete
- V3 Updates complete

- Develop training quick guides & demo videos
- Finalise
- Hold training webinars

Key: Auditable release, Production release V1, Post go-live production releases V2 & V3, Maintenance release, Audit, Training, Milestone

13
2: Implementation at national level:

Disclaimers

- Major highlights
- Currently discussed with different concerned partners
- Final validation by the strategic cell of our Minister
2 : Implementation at national level : legislative framework (1)

- New law related to interventional clinical trials with medicinal products (EU CTR Regulation)

- Law 7 May 2004 : to be revisited mid long term?

- Royal decrees
  - Organisation of the workprocesses
  - Fees
  - ...

2: Implementation at national level: legislative framework (2)

- FAMHP: Role of national contact point

- Independent «College» is hosted at the Federal Service of Public Health

- College coöperates in a 1:1 relationship with famhp

- Role and Responsibilities of this «College» are mainly:
  - Coordination and organisation of the work related to the «ethical evaluation»
  - Quality Assurance function
2: Implementation at national level: legislative framework (3)

- Members of the College will be assigned by the Minister

- Decentralised system: evaluation by recognised ethics committees

- Famhp responsible for recognition and inspection of those ethics committees (criteria to be defined by RD)

- Appeal can be introduced @ Commission for medicinal products (famhp activities) and @ College (ethics committees)
1. **FAMHP = National Contact Point**

<table>
<thead>
<tr>
<th>AR Part I:</th>
<th>Quality:</th>
<th>FAMHP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Clinical:</td>
<td>FAMHP (EC?)</td>
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<tr>
<td>Clinical:</td>
<td>EC and FAMHP</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>AR Part II:</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>EC (FAMHP)</td>
<td></td>
</tr>
</tbody>
</table>

**Diagram: FAMHP = National Contact Point**

- **Part I**
  - Q: FAMHP
  - NC: FAMHP (EC?)
  - C: EC FAMHP

- **Part II**
  - EC (FAMHP)

- **Joint AR**

- **AR**
2: Implementation at national level: workflow flow (2)

2. Evolution towards “College” in a one-to-one relationship with FAMHP

3. Independent ethical evaluation
4. Representation of lay-men / patients
5. Added value of co-assessment (touch with medical reality)
6. Short timelines for phase 1 trials will be maintained
7. Pilot joint assessment FAMHP-EC foreseen early 2017
2: Implementation at national level:

- Preparing the pilots:
  - Start Q1 2017
  - Representative sample of different types of trials
  - Open for all sponsors
  - Communication to different stakeholders foreseen in the upcoming months

- Facilitating patient recruitment:
  - Initiative of the Strategic cell
  - Working groups installed
    - Optimisation of collaboration between centres
    - IT systems needed
    - Particularities for Phase 1 trials and Vaccine trials
3: Scientific/regulatory advice @ EU and national level

- New and challenging task

- Link with national innovation office (national scientific-regulatory advice) and SAWP at EMA

- First in men Guidance document revisited (CTFG-CHMP)

- Increasing demands on:
  - Matrix trials
  - Master protocols and appendices
  - Biosimilars
  - ....
4 : EC Regulations

- Implementing regulation on GCP :
  - Second public consultation (end of October)
  - Adoption December 2016

- Delegated regulation on GMP for IMP :
  - Second public consultation to be launched November 2016
  - Q1 2017 Council-EU parliament
  - Publication April 2017
5 : EC Guidelines ( 1 )

- Guidelines on GMP for IMP ( finalised by EC end 2016 and published in April 2017 )

- Transition period : practical organisation ( comments awaited for 1st November )

- Risk proportionate approaches in clinical trials
- Summary of clinical trial results for Laypersons
- Definition of IMP and AMP
- Ethical consideration for clinical trials on medicinal products with Minors ( Ready for publication end 2016/beginning 2017 )

- Rest of Eudralex Volume 10 will be issued as EMA guidelines.
Guideline on risk proportionate approaches in clinical trials within the scope of the Regulation:

*ec.europa.eu/health/files/clinicaltrials*

- Low interventional trials
- Risk assessment areas:
  - Safety reporting
  - IMP management
    - Traceability and accountability
  - Trial management
    - Monitoring
  - Trial documentation
    - Content of the Trial Master File

- Need for further finetuning after adoption?
Thank you for your attention
Contact informations

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