The implementation of the Clinical Trial Regulation (CTR No 536/2014) in Belgium and the impact on the ethical review process
1. Clinical Trials on Medicinal Products for Human Use: Change of the Legal Context
Legal context Clinical Trials (CTs)

When
- Current Situation
- From 2020 onwards

Europe
- Clinical Trial Directive (CTD) 2001/20/EC
- Clinical Trial Regulation (CTR) 536/2014

Belgium
- Law of 7 May 2004
- Law of 7 May 2017

3 y Transitional period
Transitional period (3 years)

1st year =
- CT application can be submitted under CTD or CTR
- CT applications approved under CTD can be governed under CTD

2nd & 3rd year =
- Submission of initial applications under CTR
- CT applications approved under CTD can be governed under CTD
2. EUROPE: Clinical Trial Regulation (CTR) No 536/2014
Clinical Trial Regulation (CTR) No 536/2014

Objective:

To simplify and harmonise the submission and evaluation process of CT applications across Europe:

• While applying the highest standards of safety for the patient/subject and protecting their rights, dignity and well-being

• Without compromising public health

=> Create a favorable environment for conducting CTs in Europe
CTR No 536/2014: some major changes

a) Regulation instead of directive (country-specific adaptations only for a few aspects)

b) Development of a European Portal and Database

c) 1 single application via the EU portal for all member states (MS) concerned

d) One of these MS is designated as reporting MS (RMS) and provides a single opinion to the sponsor (incl coordinated review by other MS concerned)

e) New timelines + deadlines (tacit agreement)
a) Directive vs. Regulation

**Directive**
- Sets out a goal that must be achieved
- Up to individual countries to create/adapt legislation to reach this goal

**Regulation**
- Binding
- Applied in its entirety across the EU

Move towards harmonisation between Member States
b) Development of a European Portal

- **EU Portal & Database**
  - Single application (application form)
  - Single reporting member state → Single decision
  - Communication/collaboration within and between member states
  - Transparency
  - Easier access to information (database)
  - Several workspaces (sponsor, authority, public)
c) A single application dossier per CT

**Part I**
- **Assessed centrally** by the Reporting Member State (RMS)
- During a *coordinated review* phase, all MSc jointly review the application based on the draft assessment report of the RMS.
- **Covered aspects**: anticipated benefits, risks and inconveniences, IMPs & AMPs, labelling, the IB

**Part II**
- **Assessed separately** by each Member State concerned (MSC): national review
- Submitted in **parallel** with Part I or separately but within 2 years of assessment Part I
- **Covered aspects**: ICF, patient compensation, suitability of investigators and sites, privacy, insurance, biological samples
d) Single opinion: (simplified) example

**Current procedure**
each EU country has its own timeline

**CTR procedure**
with 3 countries (including 1 RMS)

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**Timeline**

**EU Portal**

- 1 submission for all MSs

**Validation**

- Part I AR (RMS)

**Decision**

- Part II AR (MSc 1)
- Part II AR (MSc 2)
- Part II AR (MSc 3)

**Timeline**

- Trial starts in all MSs

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CA=Competent Authority, EC=Ethics Committee, AR=Assessment Report
MS=Member State, RMS=Reporting Member State, MSc=Member State Concerned
e) New harmonised timelines and deadlines

- **Validation phase**
  - RMS selection
  - Max 10d

- **Assessment phase**
  - Part 1 (including coordinated review): max 45d
  - Part 2: max 45d

- **Decision phase**
  - Max 5d

In case of questions to the sponsor:

- + Max 10d
- + Max 5d

For the sponsor to answer

- + Max 12d
- + Max 19d

To assess the answer
CTR 536/2014: highlights for Ethics Committees (ECs)

- Each MS organises itself to ensure a **coordinated** review of the application by the authorities and the EC and provides the **single opinion of the MS** within timelines of the review process
  
  => Need for **harmonised procedures** across ECs

- Persons assessing the application **independent** of:
  
  o The sponsor
  o The clinical trial location
  o The investigators involved

- Involvement of **laypersons** is mandatory (in particular patients or patients’ organisations)

- Need for sufficiently large **expertise and experience** amongst the members of the EC
3. BELGIUM:

Translation of the CTR Requirements into the Belgian Law and the Belgian System
1) Belgian Law:

Current situation

- Experiments on human beings
- Clinical Trials on Medicinal Products

Law of May 7th, 2004

Future situation

- Other experiments on human beings
- Clinical Trials on Medicinal Products

Law of May 7th, 2004 (To be revised)

NEW Law of May 7th, 2017
Implementation of CTR in Belgium: highlights

• New Belgian Law (7 May 2017) and Royal Decree to implement it (9 Oct 2017)

• FAMHP = National contact point (single point of contact between sponsor and MS)

• The FAMHP and the Evaluating EC are jointly in charge of the evaluation

• Reorganisation of the ethics assessment/ECs
  o Creation of a “College”
  o 1 EC involved per assessment

• Shorter timelines for phase I mononational trials
Joint assessment FAMHP + EC in Belgium

Decision table for the joint AR (Part I)

<table>
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<tr>
<th>FAMHP</th>
<th>EC</th>
<th>Final and unique conclusion Belgium</th>
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* If FAMHP or EC formulates conditions, they are added to the final conclusion
The ethics assessment

FAMHP
- Receives the application dossier (EU portal)
- Validates the application dossier
- Transmits it to the College

CT College
- Liaises (single point of contact) between ECs & the FAMHP
- Selects 1 competent EC (following a fixed procedure)

EC
- Evaluates predefined scientific & ethical issues
- Assumes all the phases of the evaluation process (as CMS and RMS)

External expert(s)
- Provide advice as needed on request of the EC
Ethics Committee (EC)

Current situation
Law of 7 May 2004

- +/- 145 active ECs
- 25 EC fully accredited (“central” ECs)
- Application dossier is submitted to
  - The competent EC of the hospital (monocentric study)
  - One competent EC and the ECs of the sites involved (multicentric study)
- Each EC has its own procedures

Future situation (CT)
Law of 7 May 2017

- +/-10 ECs accredited + 1 independent CT College
- 1 submission of the application dossier through EU Portal
  - received by the FAMHP (national contact point)
  - dispatched to 1 EC by the College
- Harmonised procedures amongst ECs
Creation of the CT College

- Independent federal College created within the FPS of Health, Food Chain Safety and Environment.

- Organisation, composition and relation with FAMHP and evaluating ECs are defined by law, RD and code of conduct.

- Composition =
  - College (Board): meets periodically (extra meeting when necessary)
    - Minimum composition and incompatibility with some other functions (Art. 9 §1-2 of the law of 7 May 2017)
    - Planning: mid 2019
  - Support of Administrative Staff within FPS of Health for the daily operations
Role of the CT College

- Single point of contact FAMHP and ECs
- Coordination of EC activities
- Selection of EC in charge of evaluation
  - Objective criteria defined by RD
  - Cannot be the EC of the study site(s)
- Harmonisation of EC procedures
- Quality Assurance

The college does not take part in the evaluation
Belgian CTR Pilot Projects

- Preparatory step before the implementation of the CTR
  - To gain experience *(learning by doing)*
  - To develop processes and procedures (+ test and adjust them)

- Collaboration between FAMHP, Ethics Committees, College and Sponsors

- Started: May 2017

- Sponsors can participate on a voluntary basis (letter of intent)

- *(Fully accredited)* Ethics Committees can participate on a voluntary basis (letter of intent)

- Substantial Modifications for trials authorised under the pilot project will also be included in the pilot project.
Belgian CTR Pilot Projects: Context

Evaluation process:

- Respects the law of 7 May 2004, e.g.:
  - timelines
  - approval letters

- Follows the spirit of the new EU CTR 536/2014:
  - Single application dossier
  - FAMHP = single point of contact Sponsor
  - Assessment by 1 independent EC (local ECs are kept informed by the College (Submission file + decision))
  - Use of the new European assessment report templates
  - Single (consolidated) opinion
State of affairs and next steps

- 18 ECs are involved in the pilot project (letter of intent)
  - Information sessions are organised on a regular basis to keep them informed
  - 6 ECs volunteered to participate in a working group with the College and FAMHP:
    - Meet frequently
    - Continuously discuss and improve procedures

- +/- 10 pilot projects finished in 2017 (# to be increased in 2018 & 2019)

- Recognition of ECs (under the Law of 7 May 2017):
  - Dossier submitted before May 1st => possible recognition on Oct 1st (same year)
  - Dossier submitted before Nov 1st => possible recognition on April 1st (next year)
  - First possible submission: Before May 1st 2018