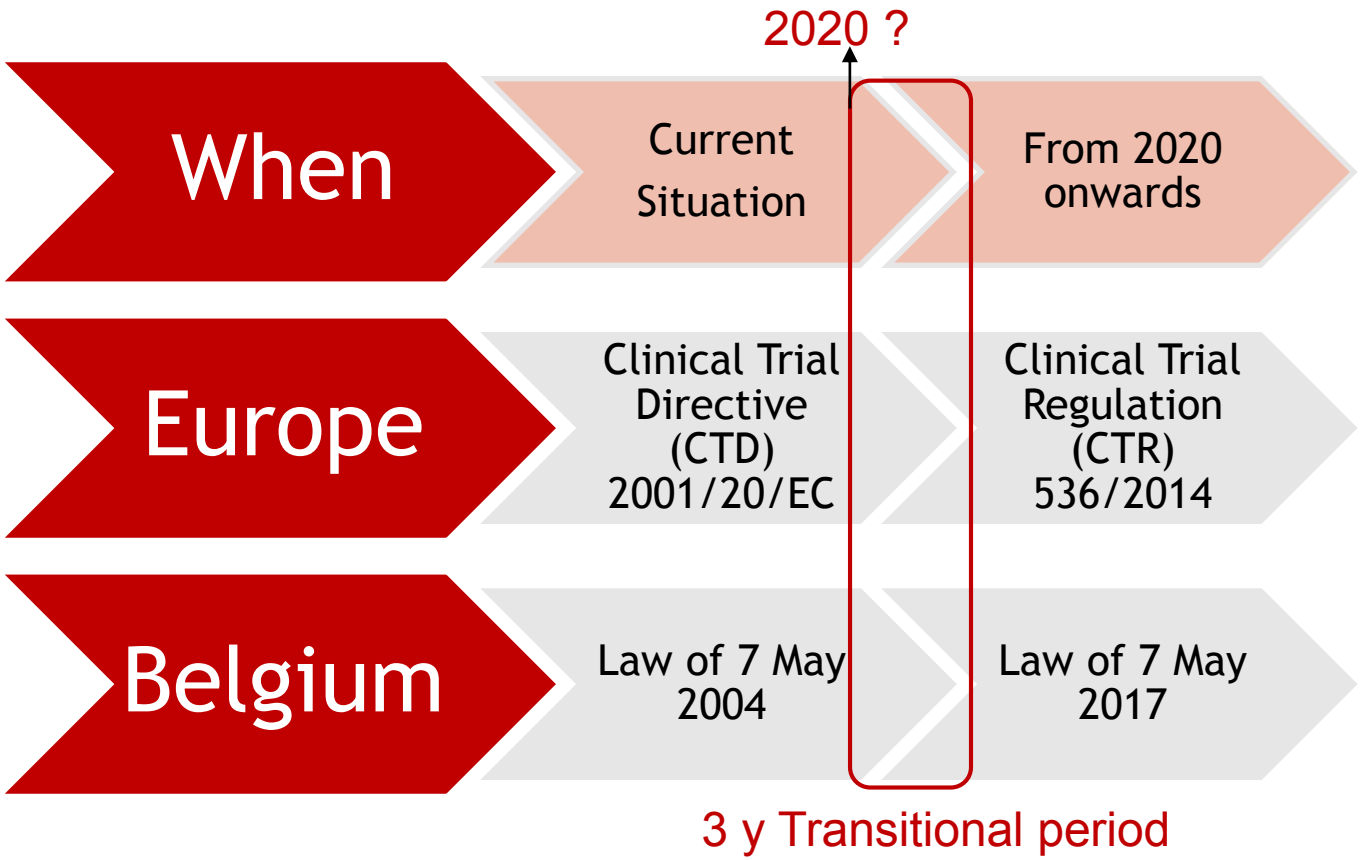
The implementation of the Clinical Trial Regulation (CTR No 536/2014) in Belgium

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)



Transitional period (3 years)

CTD

Clinical Trial Directive 2001/20/EC

CTR

Clinical Trial Regulation 536/2014

1st year =

- CT application can be submitted under CTD or CTR
- CT applications approved under CTD can be governed under CTD

2nd & 3th 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

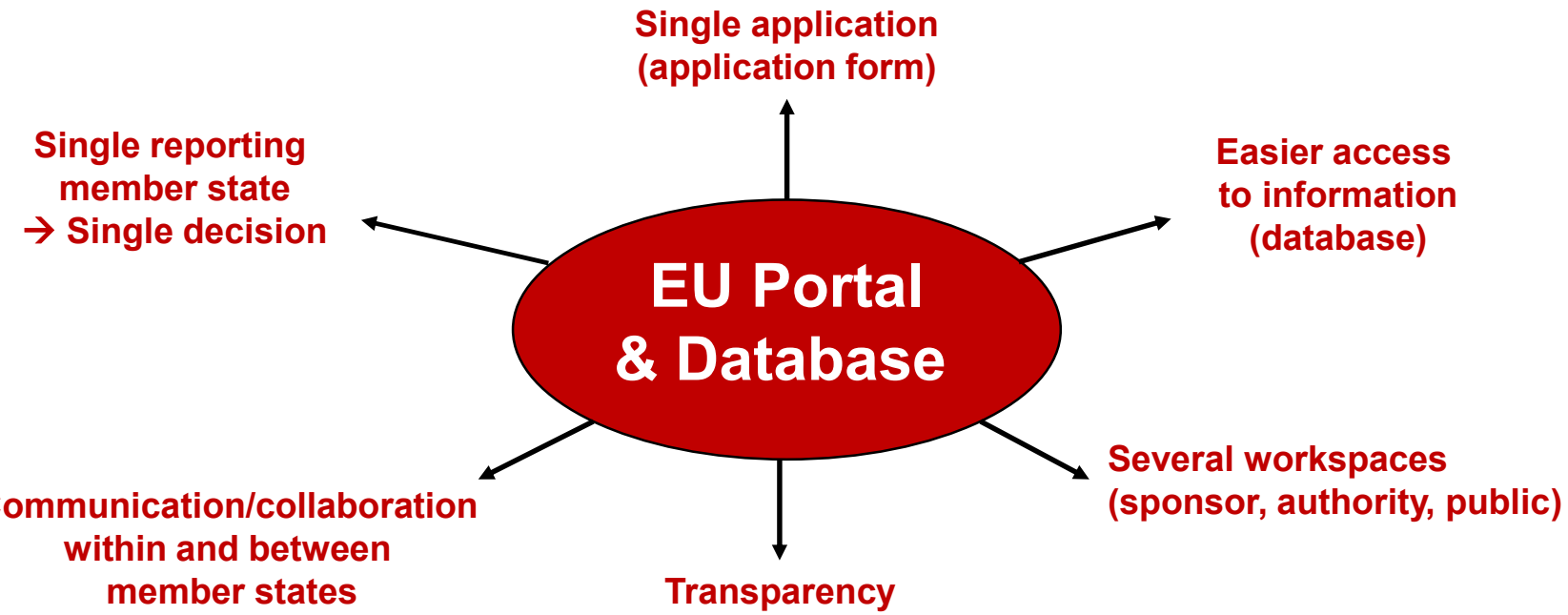
- Sets out a goal that must be achieved
- Up to individual countries to create/adapt legislation to reach this goal

Regulation

- Binding
- Applied in its entirety across the EU

Move towards harmonisation between Member States

b) Development of a European Portal



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

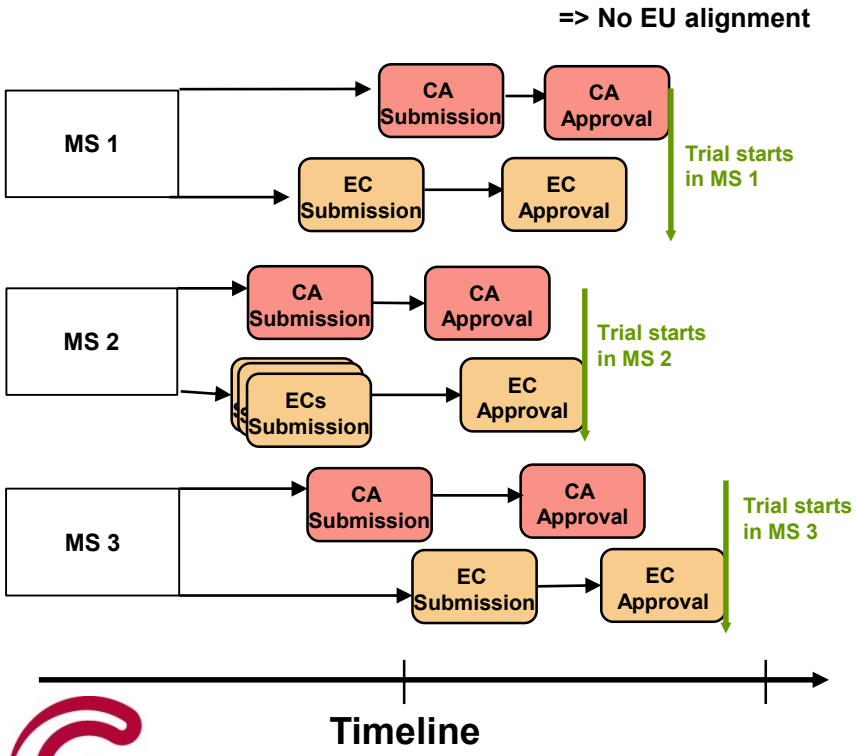
Part II

- **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

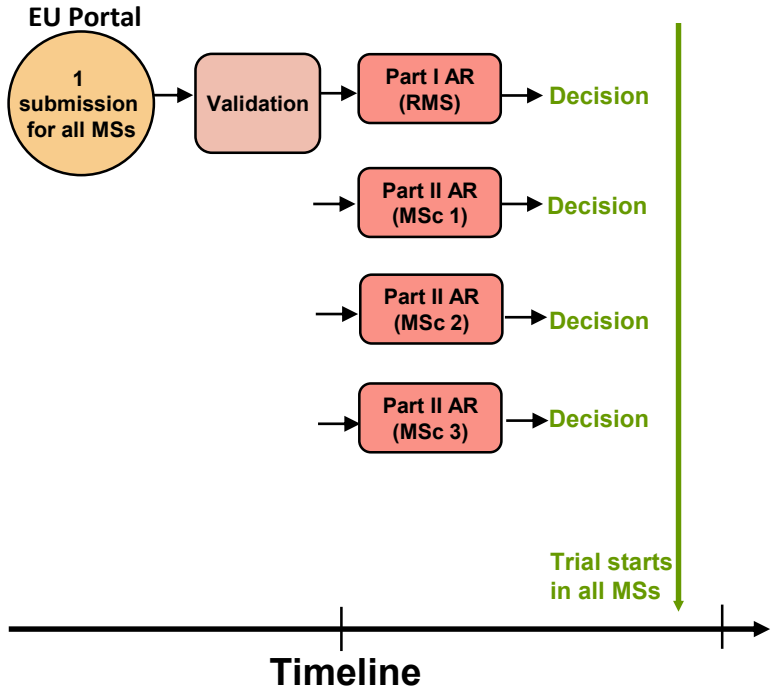
Current procedure

each EU country has its own timeline



CTR procedure

with 3 countries (including 1 RMS)



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

D0 D60

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 To assess the answer	+ Max 12d + Max 19d

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 :
  - The sponsor
  - The clinical trial location
  - The investigators involved

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

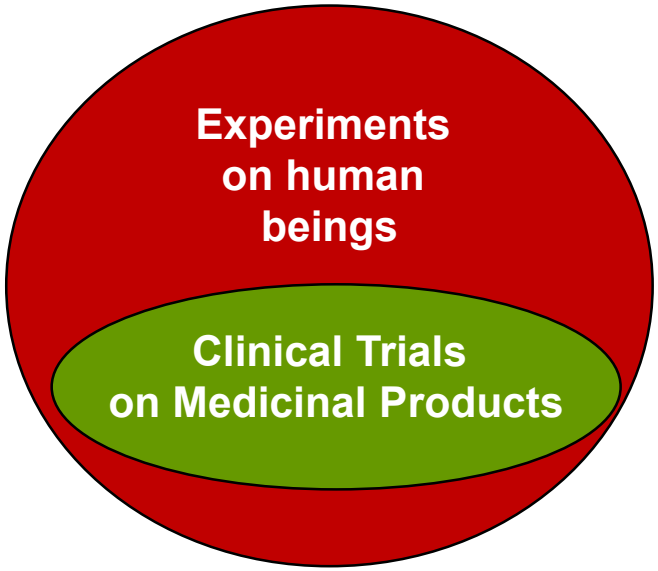
- Need for sufficiently large expertise and experience amongst the members of the EC

3. BELGIUM:

Translation of the CTR Requirements into the Belgian Law and the Belgian System

1) Belgian Law:

Current situation



Law of May 7th, 2004

Future situation

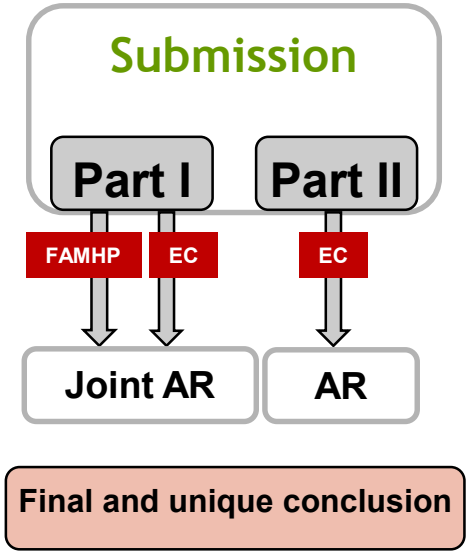
Law of May 7th, 2004
(To be revised)

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
  - Creation of a “College”
  - 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)

FAMHP	EC	Final and unique conclusion Belgium
+*	+*	+*
-	+	-
+	-	-
-	-	-

* 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