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The implementation of the Clinical Trial Regulation (CTR, n° 536/2014) in Belgium

and impact on the ethical review process

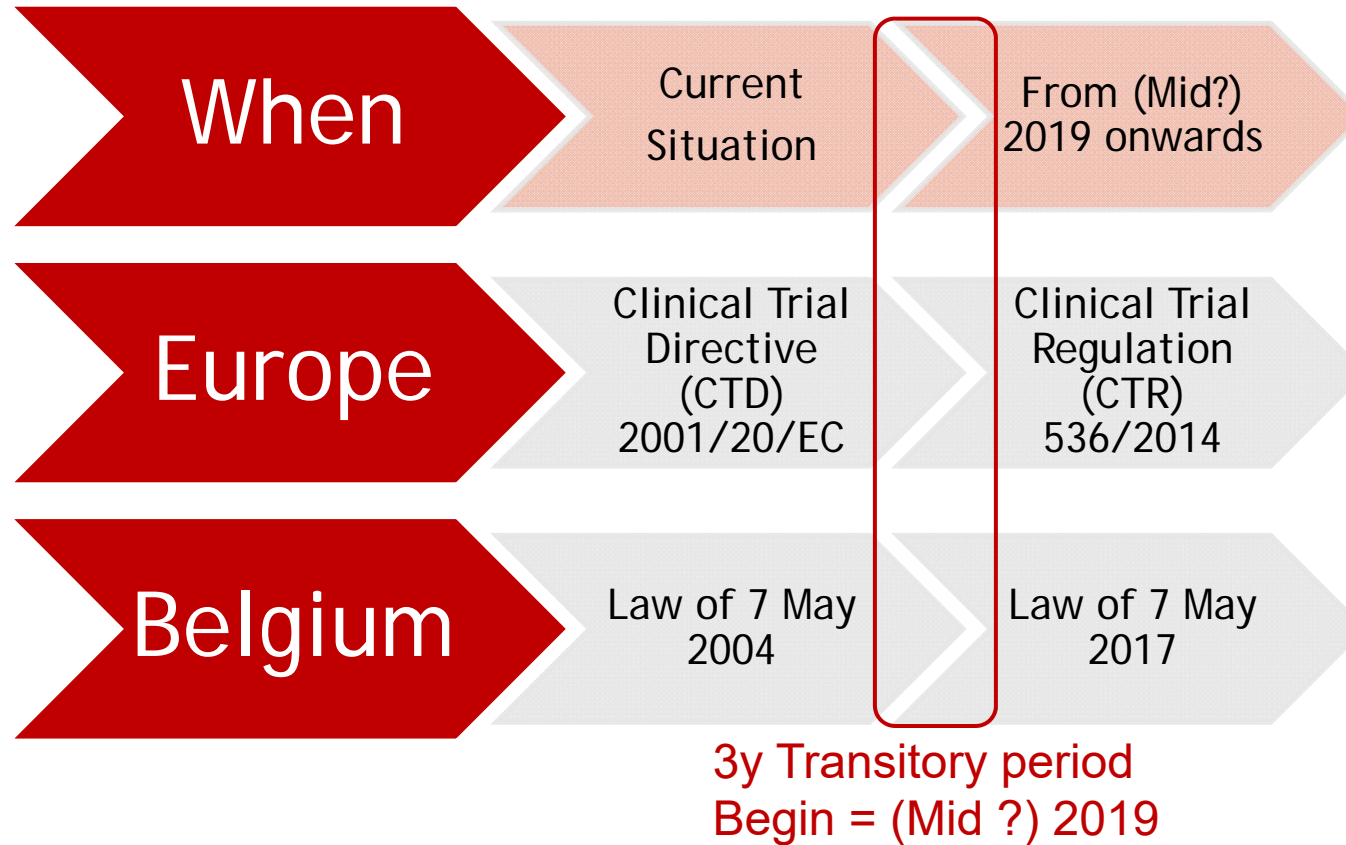


1. Clinical Trials on Medicinal Products for Human Use: Change of the Legal Context



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Legal context Clinical Trials (CTs)



4 Transitory period (3 years)

CTD

Clinical Trial Directive 2001/20/EC

1st year =

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

2nd & 3th year =

- Submission initials under CTR
- CT submitted under CTD can be governed under CTD

CTR

Clinical Trial Regulation 536/2014



2. EUROPE: Clinical Trial Regulation (CTR), n° 536/2014



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Clinical Trial Regulation (CTR) 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



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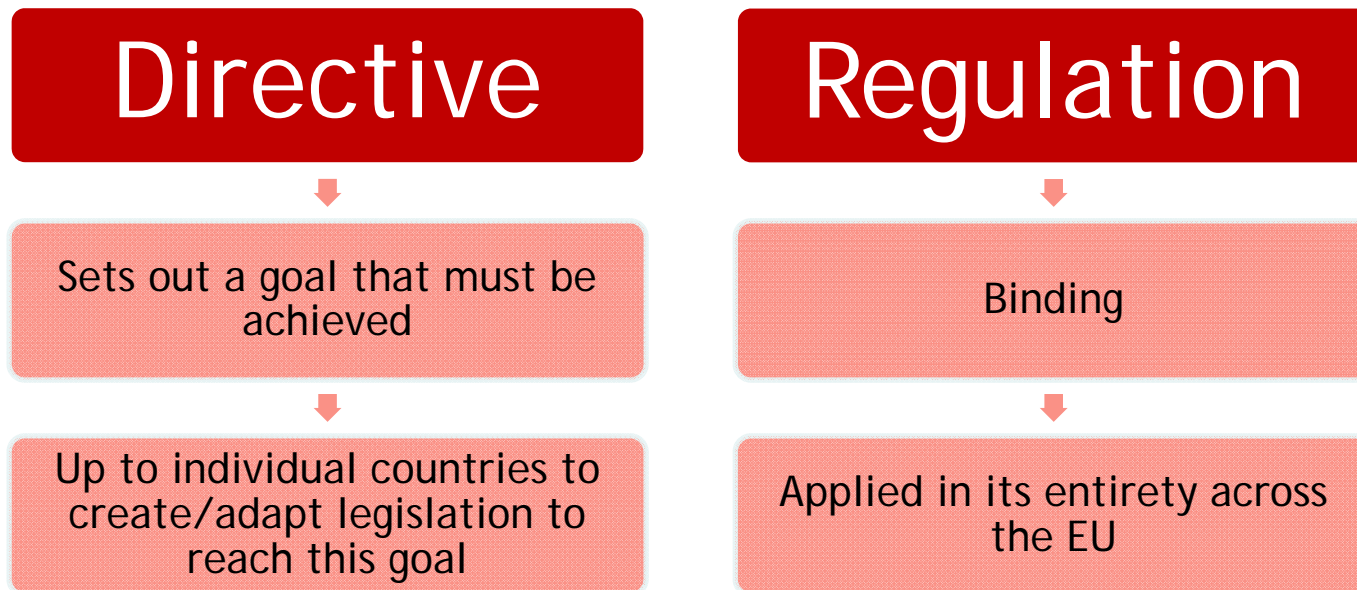
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CTR 536/2014: some major changes

- 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 defined timelines + deadlines (tacit agreement)



8 a) Directive vs Regulation

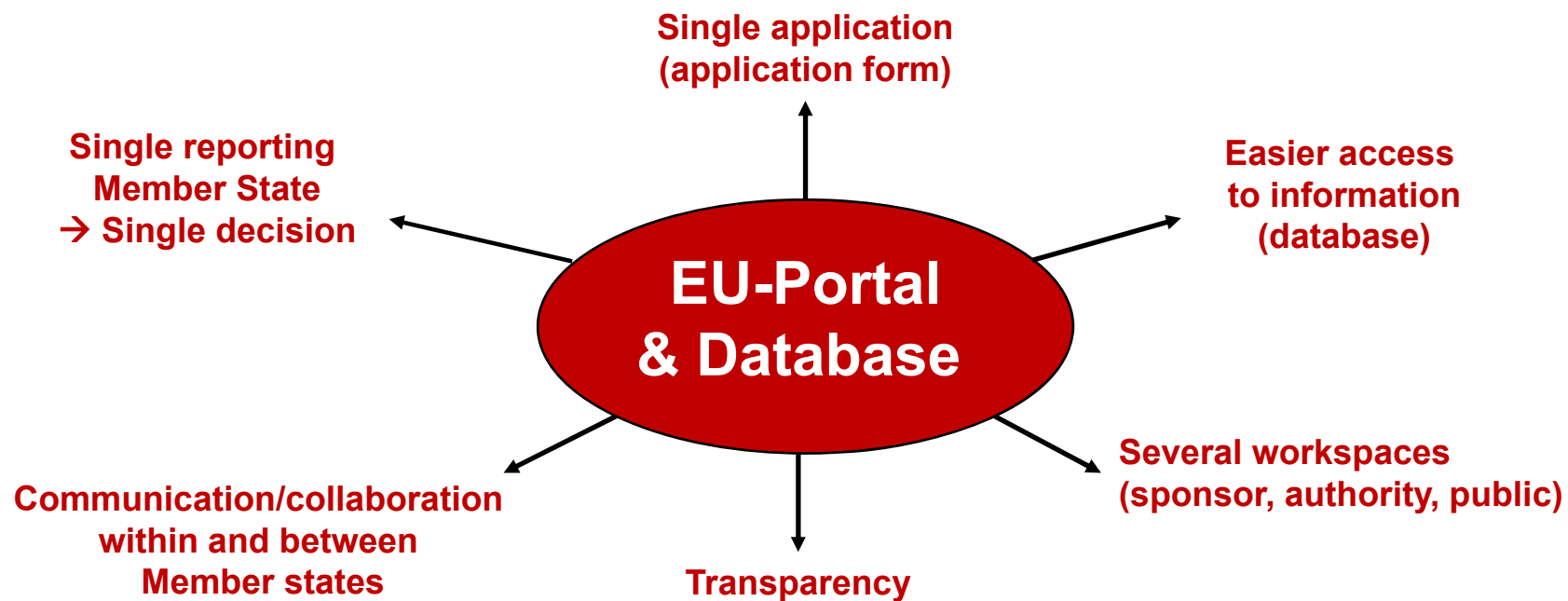


Move towards harmonisation between Member States



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b) Development of an 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



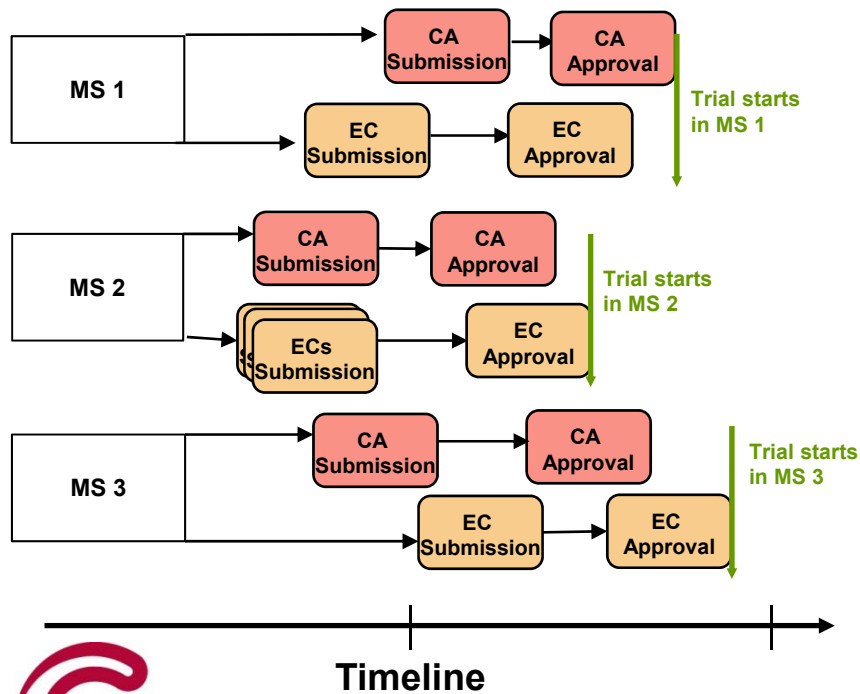
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d) Single opinion: (simplified) example

Current procedure

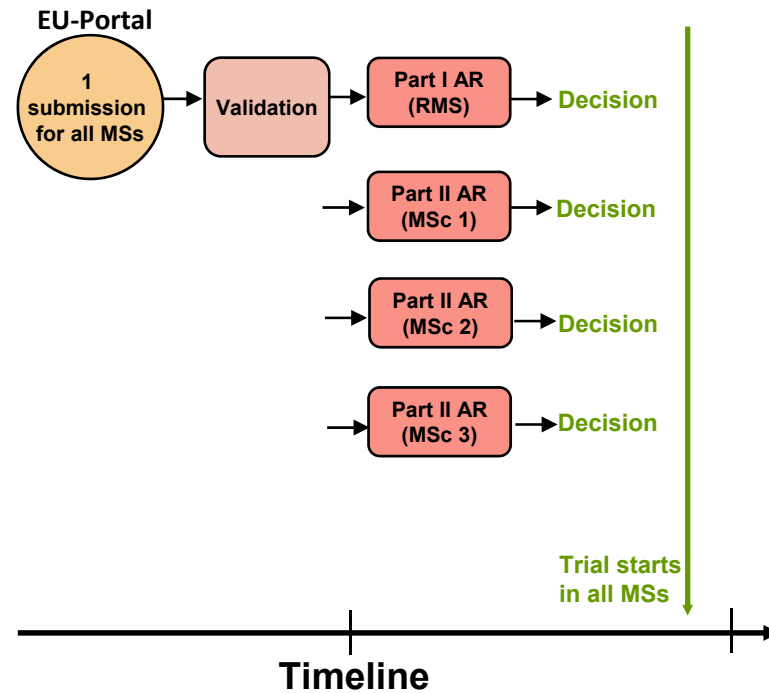
each EU country has its own timeline

=> No EU alignment



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



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e) New harmonized 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 organizes 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** mandatory (in particular patients or patients' organisations)
- Need for sufficiently large **expertise and experience** amongst the members of the EC



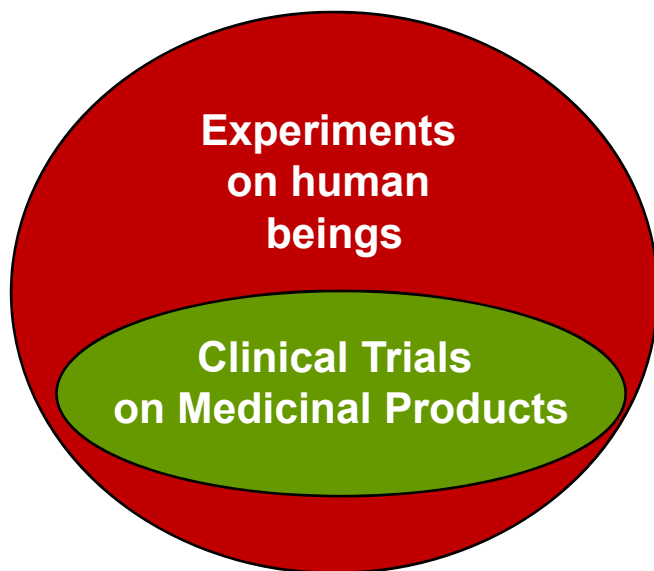
3. BELGIUM:

Translation of the CTR Requirements into Belgian Law and 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



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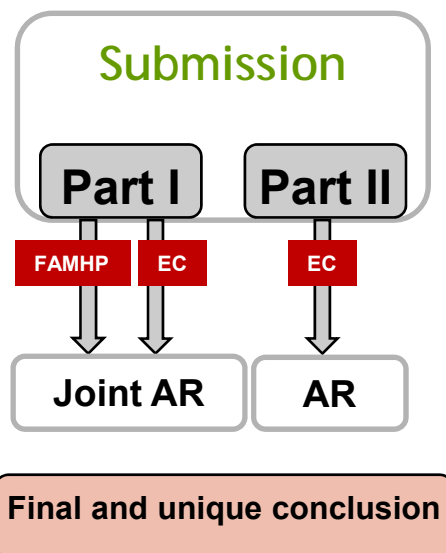
Implementation CTR in Belgium: highlights

- 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 conjointly in charge of the evaluation of the aspects regarding the parts I and II
- Reorganisation of the ethics assessment/ECs
 - Creation of a “College”
 - 1 EC involved per assessment



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Joint assessment FAMHP + EC in Belgium



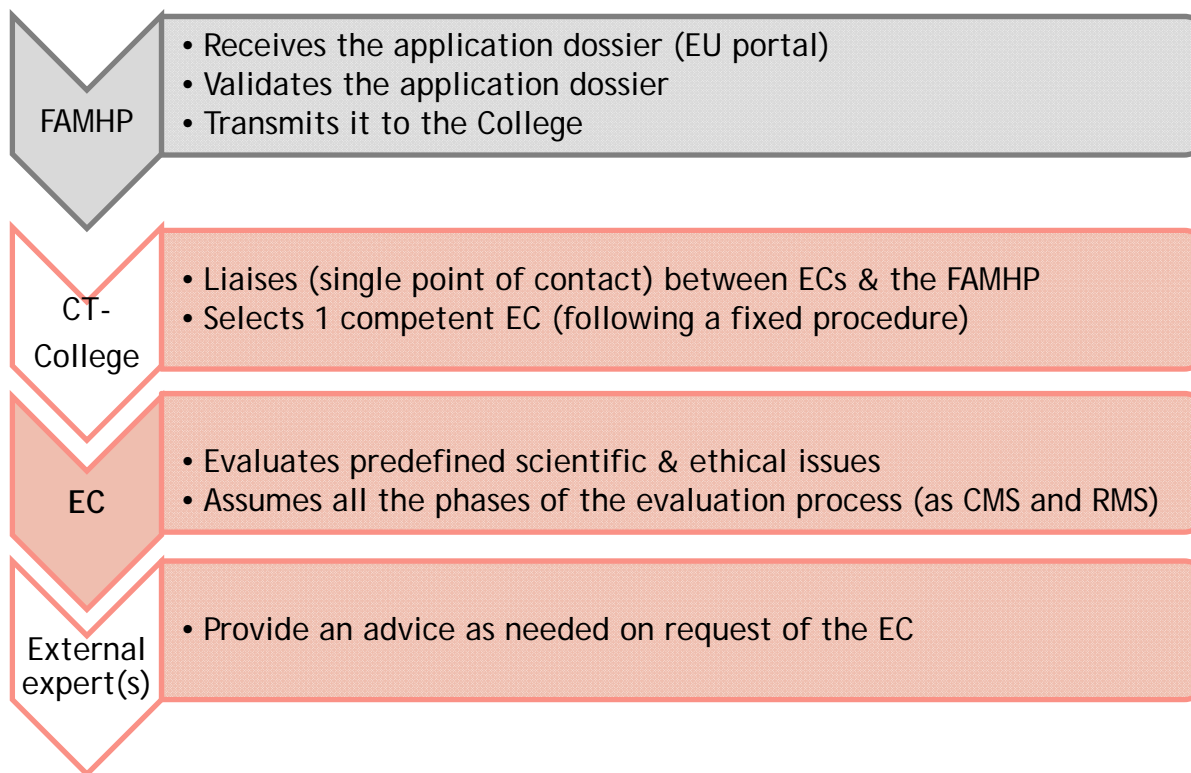
Decision table for the joint AR (Part I)

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

* If FAMHP or EC formulate conditions, they are added to the final conclusion



The ethics assessment



Ethics Committee (EC)

Current situation

Law 7 May 2004

- +/- 145 active ECs
- 26 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 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 procedure amongst ECs



Creation of the CT-College

- Independent federal College created within the FPS 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: 2nd half 2018
 - Support of **Administrative Staff** within FPS 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 FAGG, Ethics Committees, College and Sponsors
- Start: 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 go in the pilot project.



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Belgian CTR Pilot Projects: Context

Evaluation process :

- Respects the law of 7th May 2004, e.g.:
 - fees
 - 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 intention)
 - Information sessions are organised on a regular basis to keep them informed
 - 6 ECs volunteered to participate in working group with College and FAMHP:
 - Meet frequently
 - Continuously discuss and improve procedures
- +/- 10 pilot projects finished in 2017 (# to be increased in 2018)
- 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)Planning first possible submission: Before May 1st 2018

