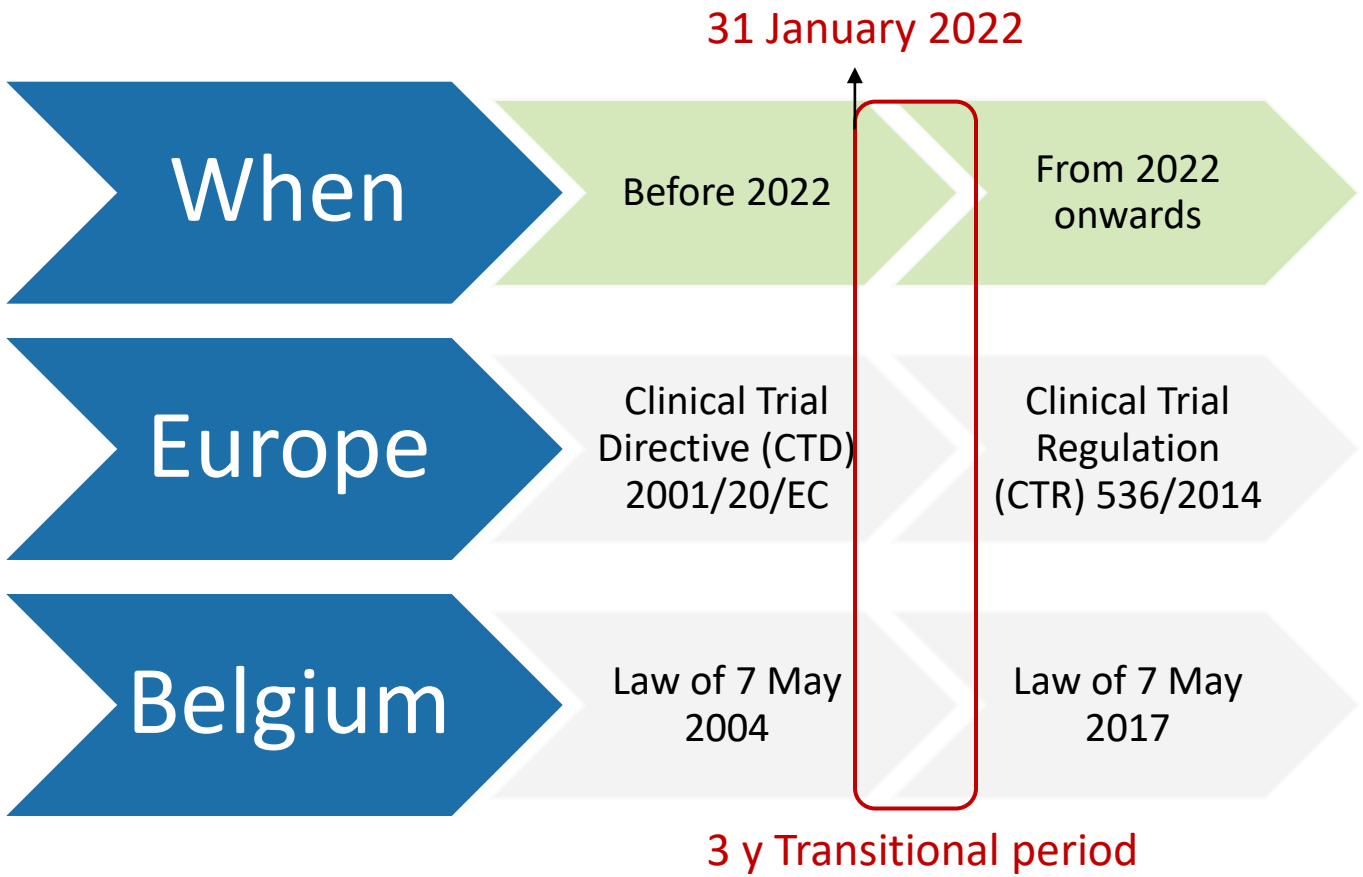
The implementation of the Clinical Trial Regulation (CTR N° 536/2014), Medical Device Regulation (MDR N° 2017/745) and In Vitro Medical Device Regulation (IVDR N° 2017/746) in Belgium

and the impact on the ethical review process

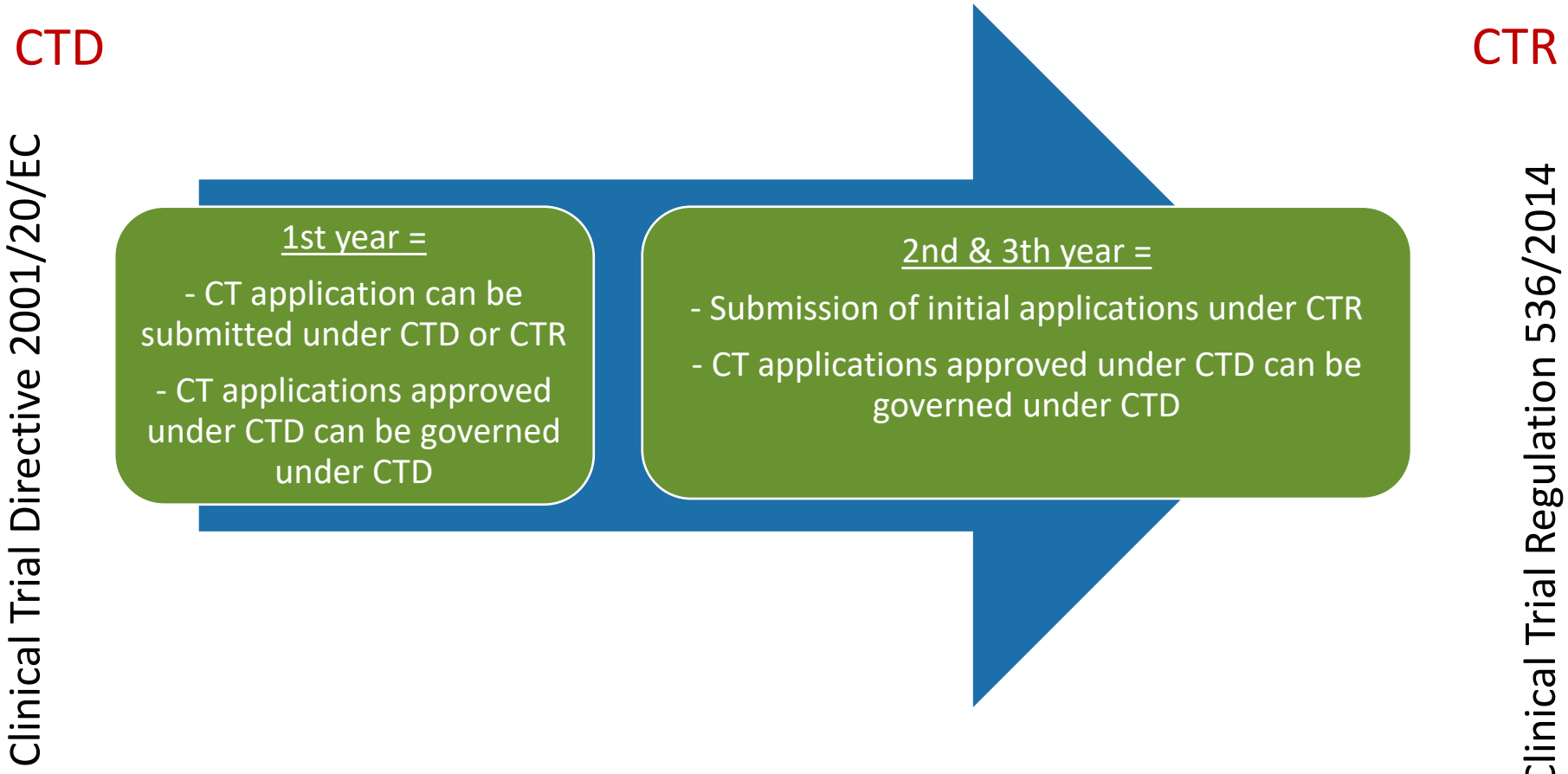
federal public service
HEALTH, FOOD CHAIN SAFETY
AND ENVIRONMENT

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

Legal context Clinical Trials (CTs)



Transitional period (3 years)



2. Europe:

Clinical Trial Regulation (CTR) N° 536/2014
Medical Device Regulation (MDR) N° 2017/745
In Vitro Medical Device Regulation (IVDR) N° 2017/746

Objective:

To **simplify** and **harmonise** the submission and evaluation process of CT (clinical trial) & CI (clinical investigation) 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 & CIs in Europe

Highlights for Ethics Committees (ECs)

CTR

- 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

  and are free of any other undue influence
- Involvement of laypersons is mandatory (in particular patients or patients' organisations)
- Need for sufficiently large expertise and experience amongst the members of the EC

MDR/IVDR

- 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

⇒**coordinated assessment is not yet possible**

- Persons assessing the application independent of :
  - The sponsor
  - The investigators involved
  - natural or legal persons financing the clinical investigation

  and are free of any other undue influence
- Involvement of laypersons is mandatory (in particular patients or patients' organisations)
- Need for sufficiently large expertise and experience amongst the members of the EC

European Legislation

CTR

a) Development of a European Portal and Database
   - by EMA
   - CTIS=Clinical trial Information system
   - CTR is applicable only when CTIS is available (**31/01/2022**)

Coordinated review

a) 1 single application via **CTIS** for all member states (MS) concerned

b) 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)

c) within the timelines as set out in this Regulation

MDR/IVDR

a) Development of European database on medical devices Eudamed
   - by European Commission
   - MDR entered into force on **26/05/2021**, even when Eudamed is not yet available for the coordinated review
   - IVDR entered into force on **26/05/2022**, even when Eudamed is not yet available for the coordinated review

Coordinated review (future)

a) 1 single application via **Eudamed** for all member states (MS) concerned

b) One of these MS is designated as **coordinating** MS and provides a single opinion to the sponsor (incl coordinated review by other MS concerned)

c) within the timelines as set out in this Regulation

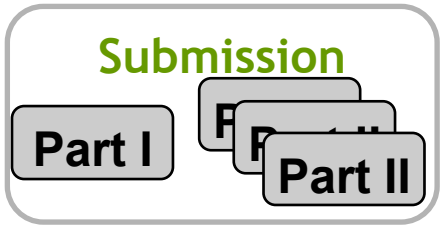
CTR No 536/2014: some major changes

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

harmonisation

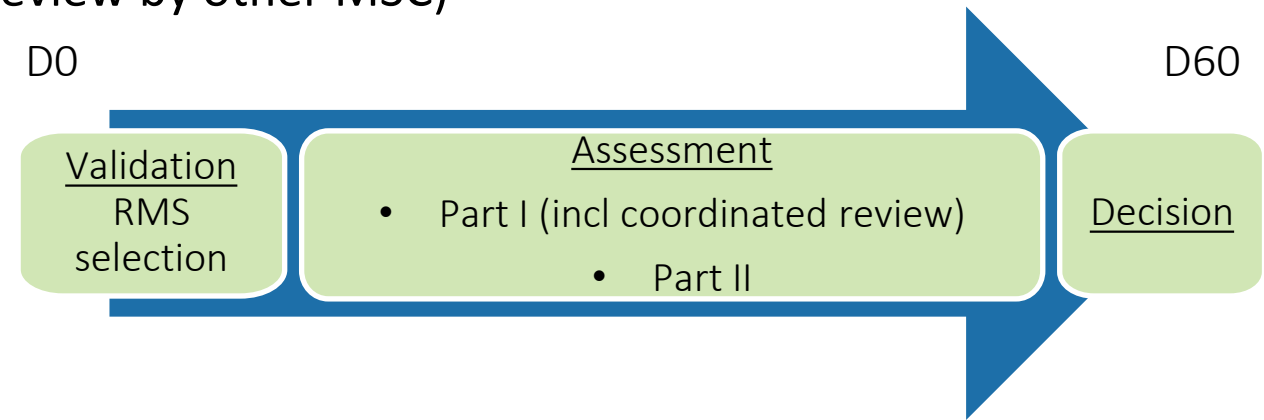
B. Development of a European Portal and Database (https://euclinicaltrials.eu/home)

C. 1 single application via the EU portal for all member states concerned (MSC)



D. One of these MS is designated as Reporting MS (RMS) and provides a single opinion to the sponsor (incl coordinated review by other MSC)

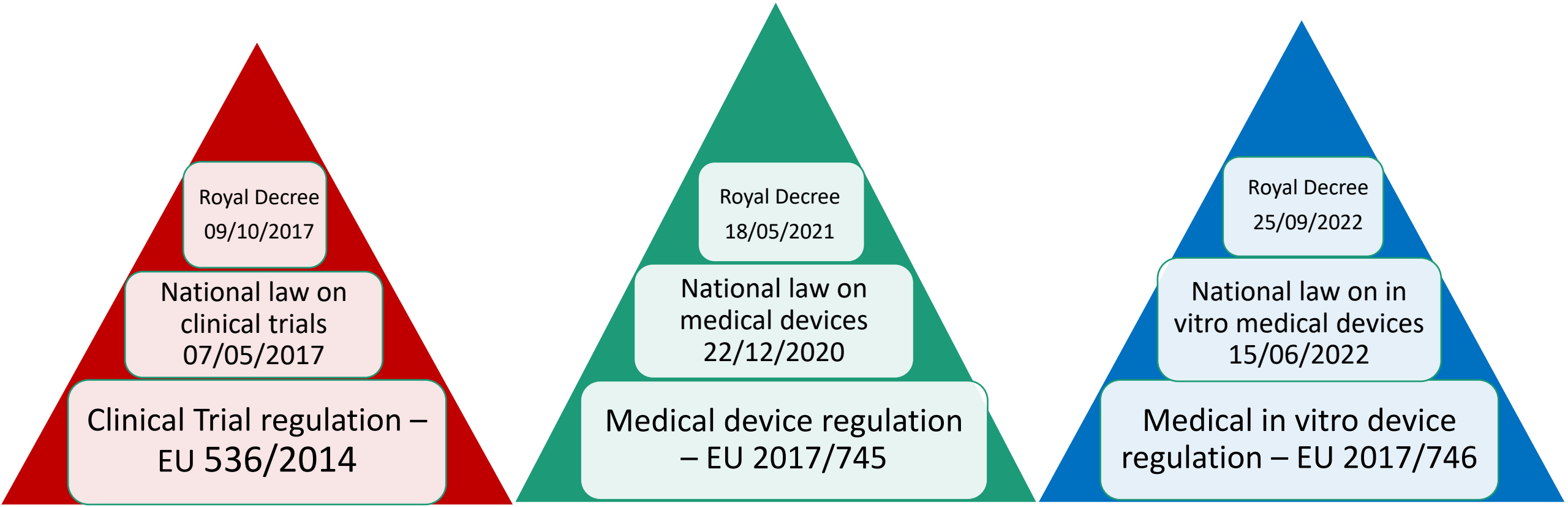
E. New timelines + deadlines (tacit agreement)



3. BELGIUM:

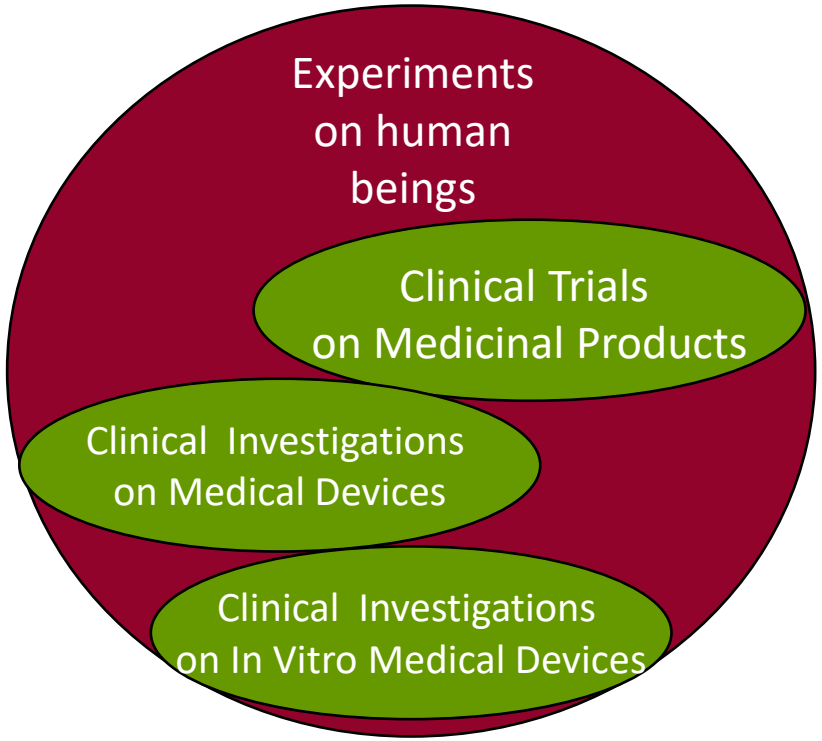
Translation of the CTR, MDR and IVDR Requirements into the Belgian Law and the Belgian System

Belgian Legislation on CTR, MDR & IVDR



Belgian Law:

- Previous situation



Law of 7 May 2004

- Current situation

Other experiments on human beings

Law of 7 May 2004 (To be revised)

Clinical Trials on Medicinal Products

NEW Law of 7 May 2017

Clinical Investigations on Medical Devices

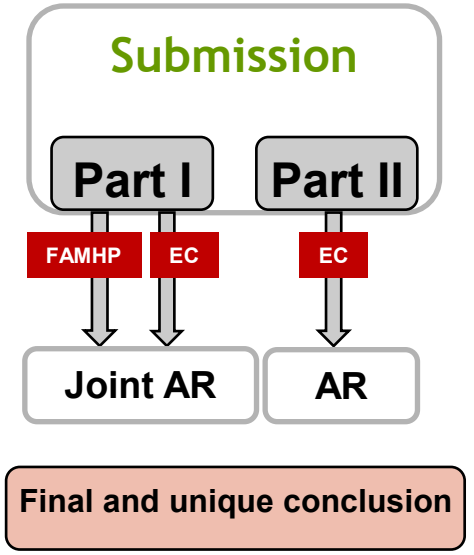
NEW Law of 22 December 2020

Clinical Investigations on In Vitro Medical Devices

NEW Law of 15 June 2022

Implementation of CTR, MDR & IVDR in Belgium: highlights

- FAMHP = National contact point (NCP, 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



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)
    - Appointed 26/05/2021
  - Support of Administrative Staff within FPS of Health for the daily operations

Role of the CT College

- **Single point of contact between the 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 of ECs

More information:
www.ct-college.be

The college <u>does not</u> take part in the evaluation

Ethics Committee (EC) evaluating applications

Previous 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

Procedure 2004
ECs recognized Law 2004

Current situation

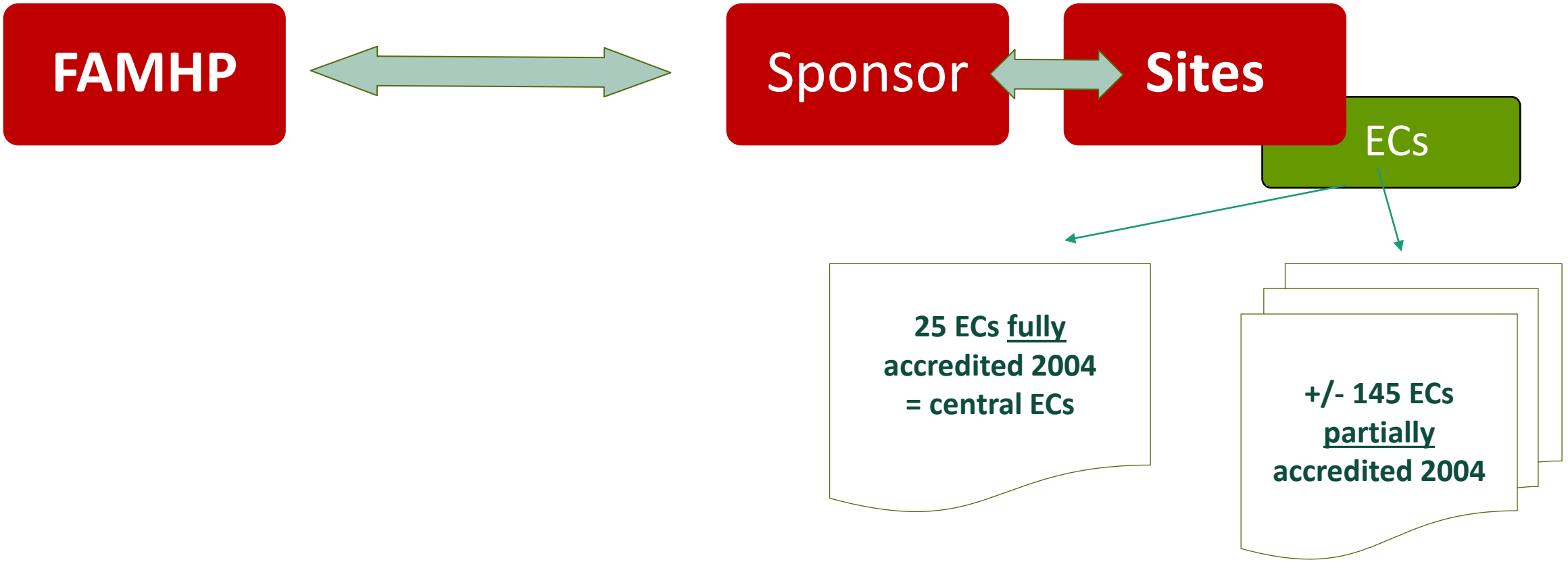
Law of 7 May 2017
Law of 22 Dec 2020
Law of 15 June 2022

- +/-15 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 CT College
  - For CTR: EU Portal CTIS
  - For MDR/IVDR: EU Portal Eudamed (not yet available)
- Harmonised procedures amongst ECs

Procedure 2017
ECs recognized Law 2017

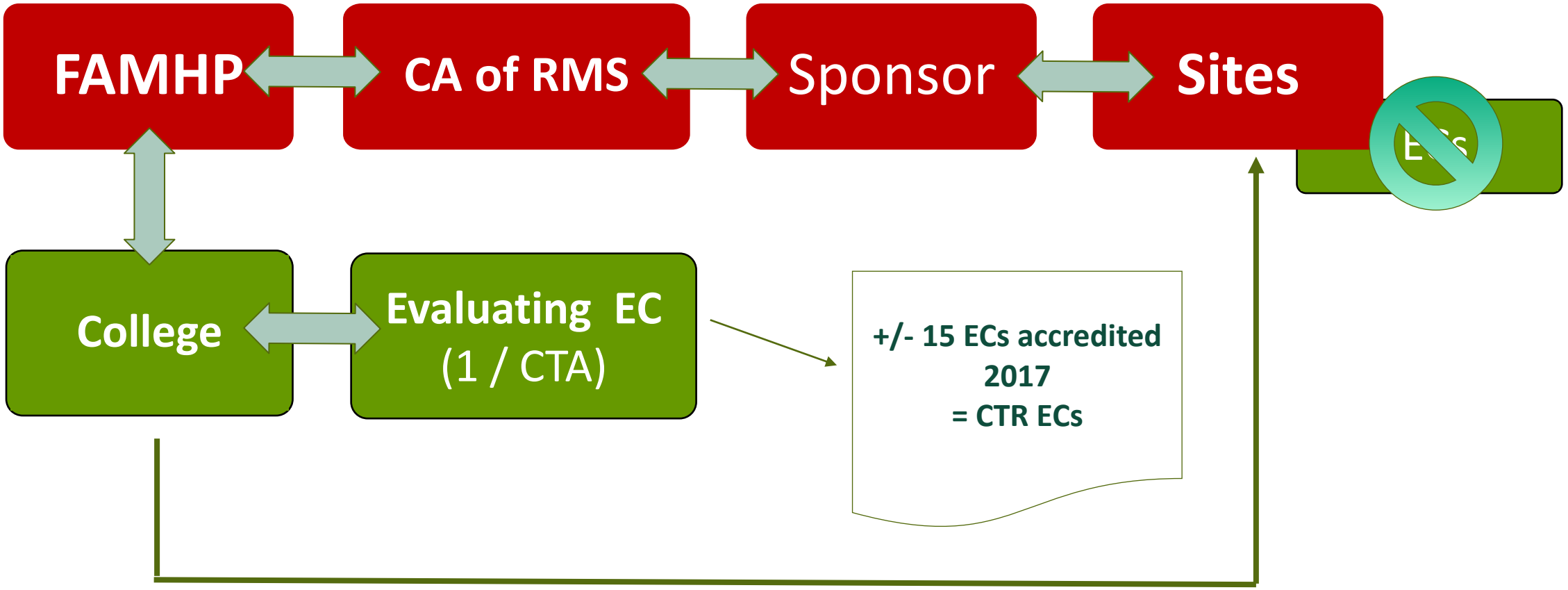
Organization of ethical review in Belgium under CTD

- **CTD & Belgian Law 2004**



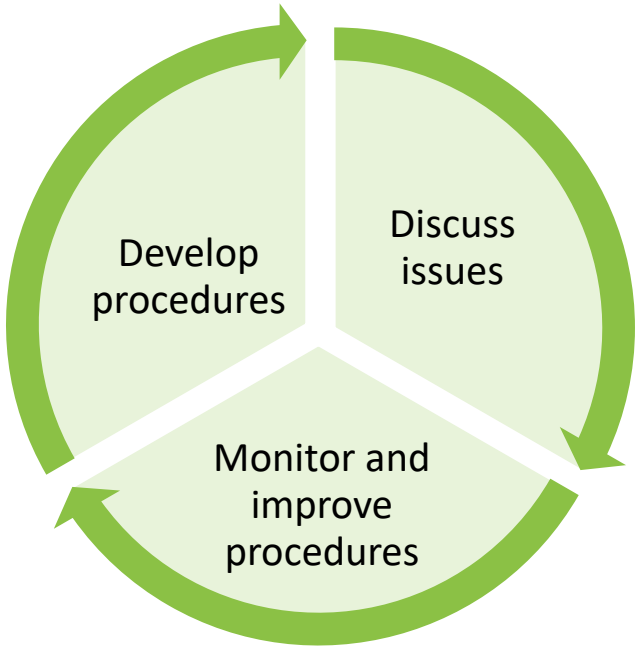
Organization of ethical review in Belgium under CTR/MDR/IVDR

- **CTR & Belgian law 2017, MDR & Belgian law 2020, IVDR & Belgian law 2022**



Belgian CTR Pilot Project

- 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
- Ended: October 2021 (follow-up of dossiers within the pilot project until January 2025)
- Sponsors can participate on a voluntary basis (letter of intent)
- (Fully accredited) Ethics Committees can participate on a voluntary basis (letter of intent)

Pilot project procedure

The pilot project follows the **SPIRIT** of the regulation :

- CTR submission dossier with Part I and Part II
- FAMHP is NCP for sponsors (NCP = National Contact Point)
- CT college selects an independent EC (law of 7 May 2017)
- CTR assessment report templates
- One single decision and approval **E-mail** at the end of the process
- Modifications of approved pilot initial dossiers submitted as SM within the CTR pilot project

BUT:

- Only for national dossier (no international consolidation)
- Within the timelines of the law of 7 May 200**4**
- With 2 **approval** letters attached to final conclusion (Law 7 May 200**4**)
- Without EU Portal and database
- SUSAR and DSUR are not included in the pilot project

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)

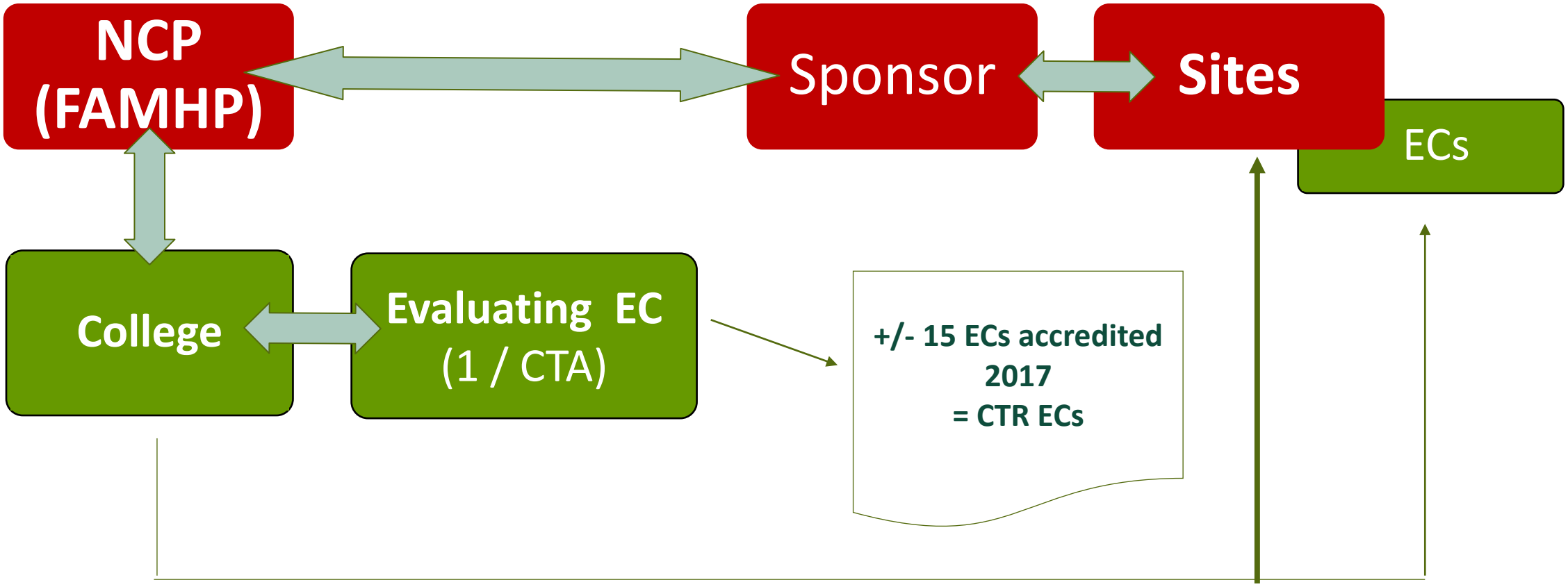
External expert(s)

- Provide advice as needed on request of the EC

Organization of ethical review in Belgium under CTR

Pilot

- **CTR Pilot & Belgian law 2017**



MDR: definitions

see also guidance FAMHP website

- CE marking of conformity: manufacturer indicates device is in conformity with the applicable requirements set out in the MDR & other applicable union legislation

- Clinical investigation: any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance (including clinical benefits) of a medical device.

- PMCF: Post-market clinical follow-up investigation

Scope of the MDR

The “administrative pathways” are much more complex and can be schematized to ease their understanding (see diagram at next page).

The diagram shows the flows involving the College (and thus the EC recognized under the law of 07/05/2017):

1. PMCF applications with additional burdensome and/or invasive procedures,
2. CIA out of the scope of a given MD already authorized,
3. CIA with a MD not yet authorized,
4. CIA with a custom-made MD.

In this presentation, these 4 flows are summed up into 2 flows for initial MDR dossiers:

- PMCF applications (“green pathway”) and
- CIA with a consolidated opinion (“red pathways”).

Diagram of the flows described in the Belgian law of 22/12/2020

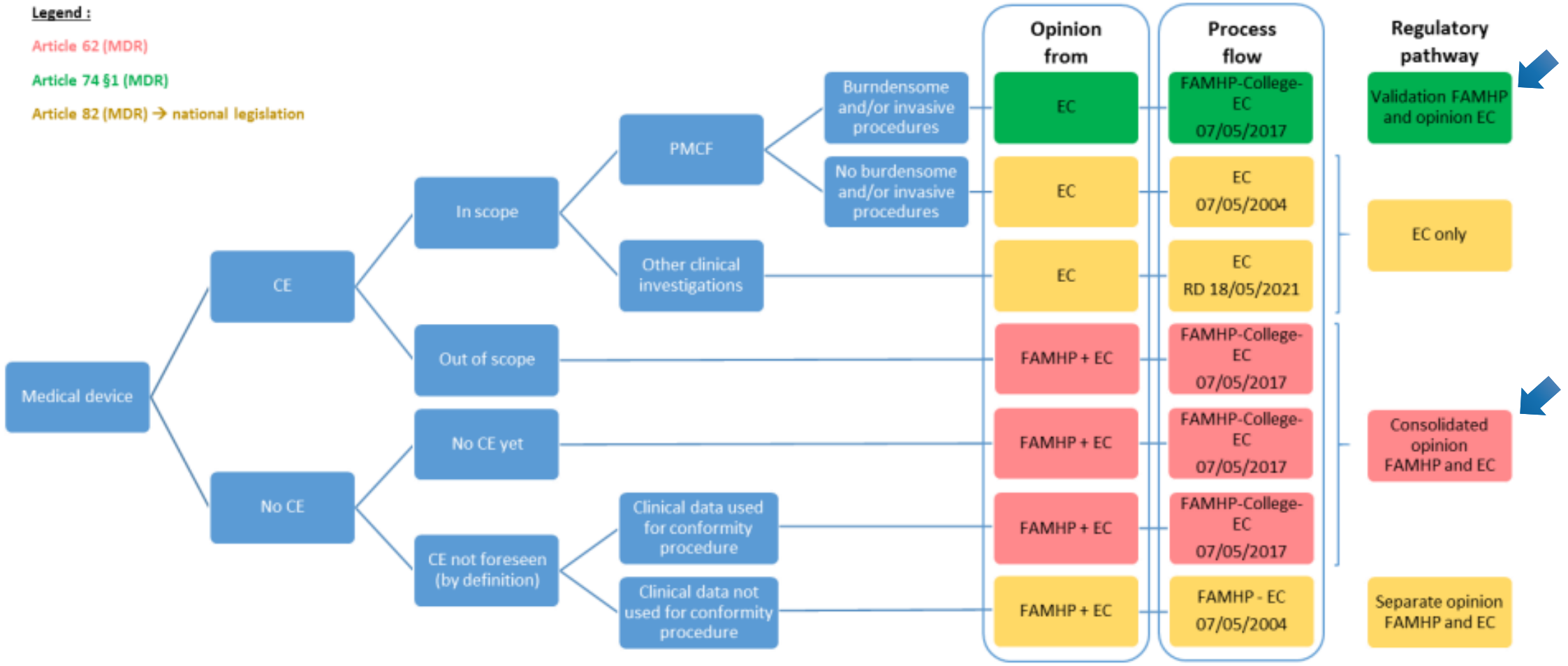


Figure 2. Different regulatory pathways. Different process flows and regulatory pathways are possible depending on the status of the investigational medical device and clinical investigation properties.

Pathways involving the CT-College and the ECs recognized under the law of 07/05/2017

PMCF applications

- PMCF applications are only within the scope of the MDR when the investigation involves additional burdensome and/or invasive procedures
  - A list detailing the classification for additional burdensome or invasive procedures for Belgium is available in the Belgian guideline document on the FAMHP website (Annex III).
- Validation by FAMHP, evaluation by the EC only
- Assessment in 22 days

Applications with a consolidated opinion

- Within scope of the MDR if
  - CIA out of the scope of a given MD already authorized
  - CIA with a MD not yet authorized
  - CIA with a custom-made MD
- Validation by FAMHP, evaluation by the EC and FAMHP
- Assessment in
  - 56 days (initial application)
  - 44 days (substantial modification)

IVDR: definitions

see also guidance FAMHP website

- CE marking of conformity: manufacturer indicates device is in conformity with the applicable requirements set out in the IVDR & other applicable union legislation

- Performance study (PS): a study undertaken to establish or confirm the analytical or clinical performance of a device

- PMPF: Post-market performance follow-up

Scope of the IVDR

The “administrative pathways” are much more complex and can be schematized to ease their understanding (see diagram at next page).

The diagram shows the flows involving the College (and thus the EC recognized under the law of 07/05/2017):

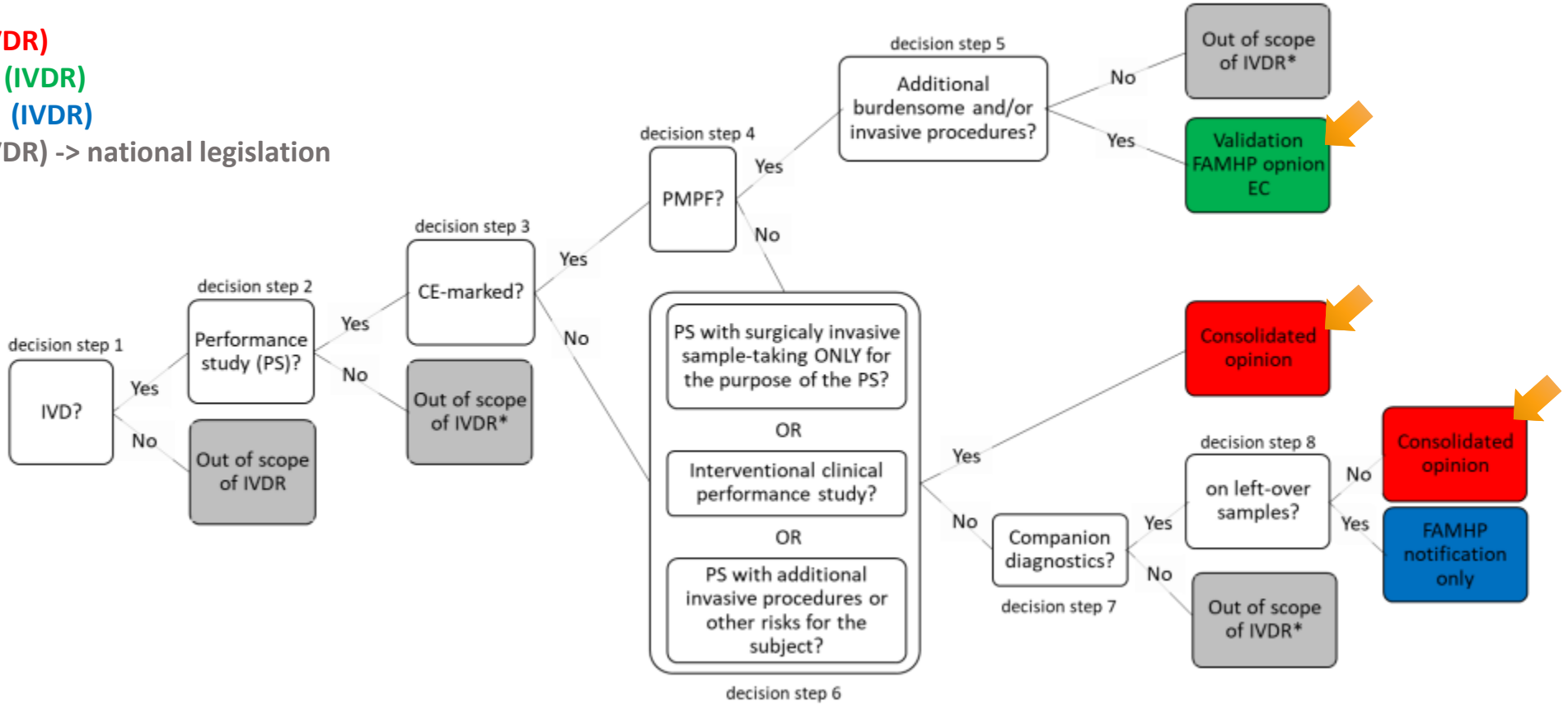
1. PMPF applications with additional burdensome and/or invasive procedures,
2. PS with surgically invasive sample-taking only for the purpose of the PS,
3. PS which are interventional clinical performance studies,
4. PS with additional invasive procedures or other risks for the subjects
5. PS involving companion diagnostics (not on left-over samples)

In this presentation, these 5 flows are summed up into 2 flows for initial IVDR dossiers:

- PMCF applications (“green pathway”) and
- CIA with a consolidated opinion (“red pathways”).
- There is also a blue pathway for PS involving companion diagnostics using left-over samples. This pathway is in scope of the IVDR but does not involve the College or the EC recognized under the law of 07/05/2017

Diagrams of the flows described in the Belgian law of 15/06/2022.

Legend:
Article 74 (IVDR)
Article 70 §1 (IVDR)
Article 58 §2 (IVDR)
Article 57 (IVDR) -> national legislation



Pathways involving the CT-College and the ECs recognized under the law of 07/05/2017

PMPF applications

- PMPF applications are only within the scope of the IVDR when the investigation involves additional burdensome and/or invasive procedures
  - A list detailing the classification for additional burdensome or invasive procedures for Belgium is available in the Belgian guideline document on the FAMHP website (Annex II).
- Validation by FAMHP, evaluation by the EC only
- Assessment in 22 days

Applications with a consolidated opinion

- Within scope of the IVDR if
  - PS with surgically invasive sample-taking only for the purpose of the PS,
  - PS which are interventional clinical performance studies,
  - PS with additional invasive procedures or other risks for the subjects
  - PS involving companion diagnostics (not on left-over samples)
    - In case of PS involving companion diagnostics only on left-over samples: in scope of IVDR but only notification to FAMHP needed
- Validation by FAMHP, evaluation by the EC and FAMHP
- Assessment in
  - 56 days (initial application)
  - 44 days (substantial modification)