REFORMING ETHICS REVIEW FOR CLINICAL RESEARCH IN BELGIUM

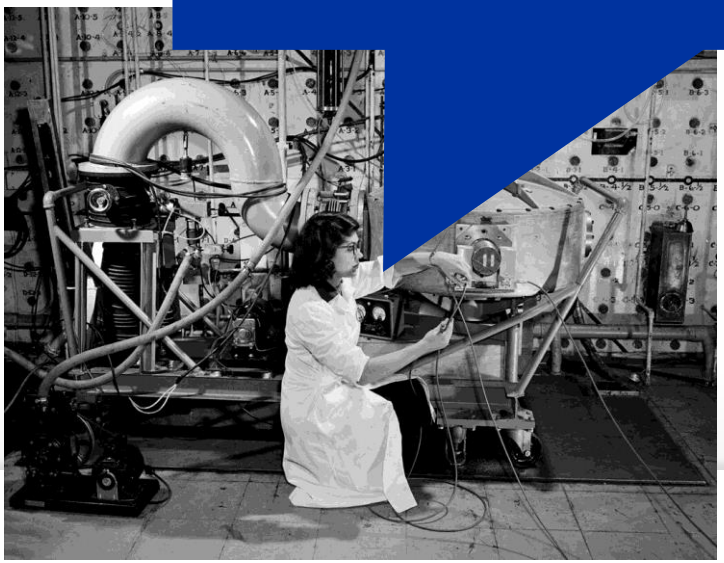
BENELUX NEUROMODULATION SOCIETY (BNS)

Audrey Van Scharen

15/12/2025

A university hospital neurology department initiates a prospective study in patients with drug-resistant epilepsy. The clinical team wants to investigate whether combining continuous EEG monitoring with an AI-based seizure prediction tool can improve treatment decisions and reduce hospital admissions. All participating patients continue to receive standard anti-seizure medication; no experimental drug or new therapeutic intervention is introduced.

From a clinical and scientific perspective, this is a single, integrated research project. It involves one patient population, one protocol, one informed consent process, and one overarching neurological question: can improved interpretation of EEG data support better clinical decision-making and patient outcomes?



From a regulatory perspective, the study does not remain one project. The continued use of anti-seizure medication brings part of the research under the clinical trials regulation. At the same time, the AI-based EEG analysis qualifies as software as a medical device and therefore falls under the medical device regulation. The use of historical EEG data for algorithm training introduces yet another layer, raising questions about data protection and secondary use that sit outside both regimes.

What follows is a study governed by multiple regulatory logics, different documentation tracks, varying ethics committee expectations, and misaligned assessment timelines, all applied to what clinicians experience as a single neurological study.

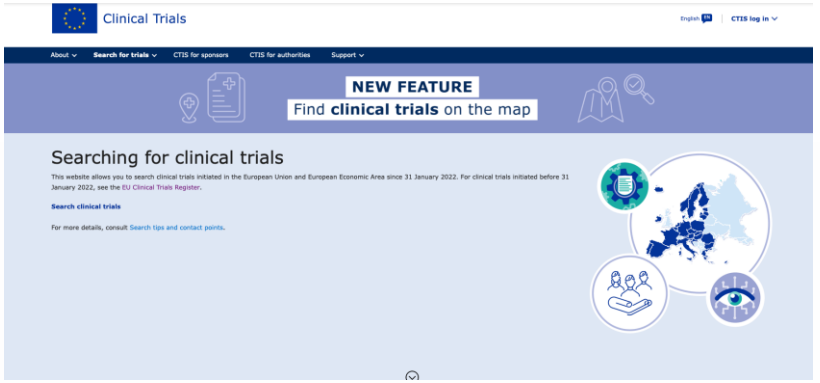
The research question is neurological.

The complexity is regulatory.

EU RESEARCH FRAMEWORK

CLINICAL TRIALS REGULATION (CTR)

- Requires submission through CTIS with a structured clinical trial protocol
- Imposes formal roles and responsibilities for sponsor and investigator
- Sets strict rules for informed consent, amendments, and safety reporting
- Involves ethics review within a harmonised but highly procedural framework



EU RESEARCH FRAMEWORK

CLINICAL STUDY (BROADEST CONCEPT)

- A clinical study includes any investigation in humans related to medicinal products
- It covers research on effects, safety, pharmacology, or pharmacokinetics
- The objective is to assess safety and/or efficacy
- This is the umbrella concept under the CTR

→ **Not every clinical study is a clinical trial.**

EU RESEARCH FRAMEWORK

CLINICAL TRIAL (CTR TRIGGER POINT)

A clinical study becomes a clinical trial if any one of the following applies:

- The therapeutic strategy is assigned in advance and falls outside **normal clinical practice**
- The decision to prescribe the medicinal product is linked to inclusion in the study
- Additional diagnostic or monitoring procedures beyond normal clinical practice are used

→ If any of these apply → the study is a clinical trial → CTR applies (submission in CTIS)

WHAT COUNTS AS "NORMAL CLINICAL PRACTICE"?

Normal clinical practice means the standard treatment regime used in routine care

It is defined at Member State level, not EU-wide

What is "normal" can therefore differ between countries

Practical consequence:

The same protocol may be a clinical trial in one Member State and not in another
→ but once classified as a clinical trial, CTIS applies EU-wide.

EU RESEARCH FRAMEWORK

LOW-INTERVENTION CLINICAL TRIALS

- Low-intervention trials are still clinical trials
- The medicinal products are authorised (no experimental drug)
- Use is either on-label or evidence-based off-label
- Additional diagnostics or monitoring pose only minimal risk or burden

Low-intervention does not mean low regulation.

Low-intervention trials must be submitted via CTIS

- Safety reporting is simplified, with fewer additional pharmacovigilance obligations compared to higher-risk trials
- Monitoring requirements may be reduced, allowing more proportionate oversight

EU RESEARCH FRAMEWORK

NON-INTERVENTIONAL STUDIES (OUT OF CTR SCOPE)

- A non-interventional study is any clinical study that is not a clinical trial
- Treatment decisions are fully independent of study participation
- No additional diagnostic or monitoring procedures beyond routine care

Non-interventional studies are outside the CTR and not submitted via CTIS.

National legislation on experiments: Belgium law 2004

For instance an observational study + questionaire = interventional for Belgian law

ICF, no fault insurance…

EU RESEARCH FRAMEWORK

PUTTING IT ALL TOGETHER: CTIS USE

- If the study is a clinical trial → CTIS is mandatory
- This includes low-intervention trials and academic trials
- Only non-interventional studies remain outside CTIS
- The main risk lies in misclassification at the design stage

The mandatory use of CTIS, if your trial falls under CTR, is not about how risky the study feels:

It is about how the study is designed.

EU RESEARCH FRAMEWORK

NATIONAL AND LOCAL ROLE

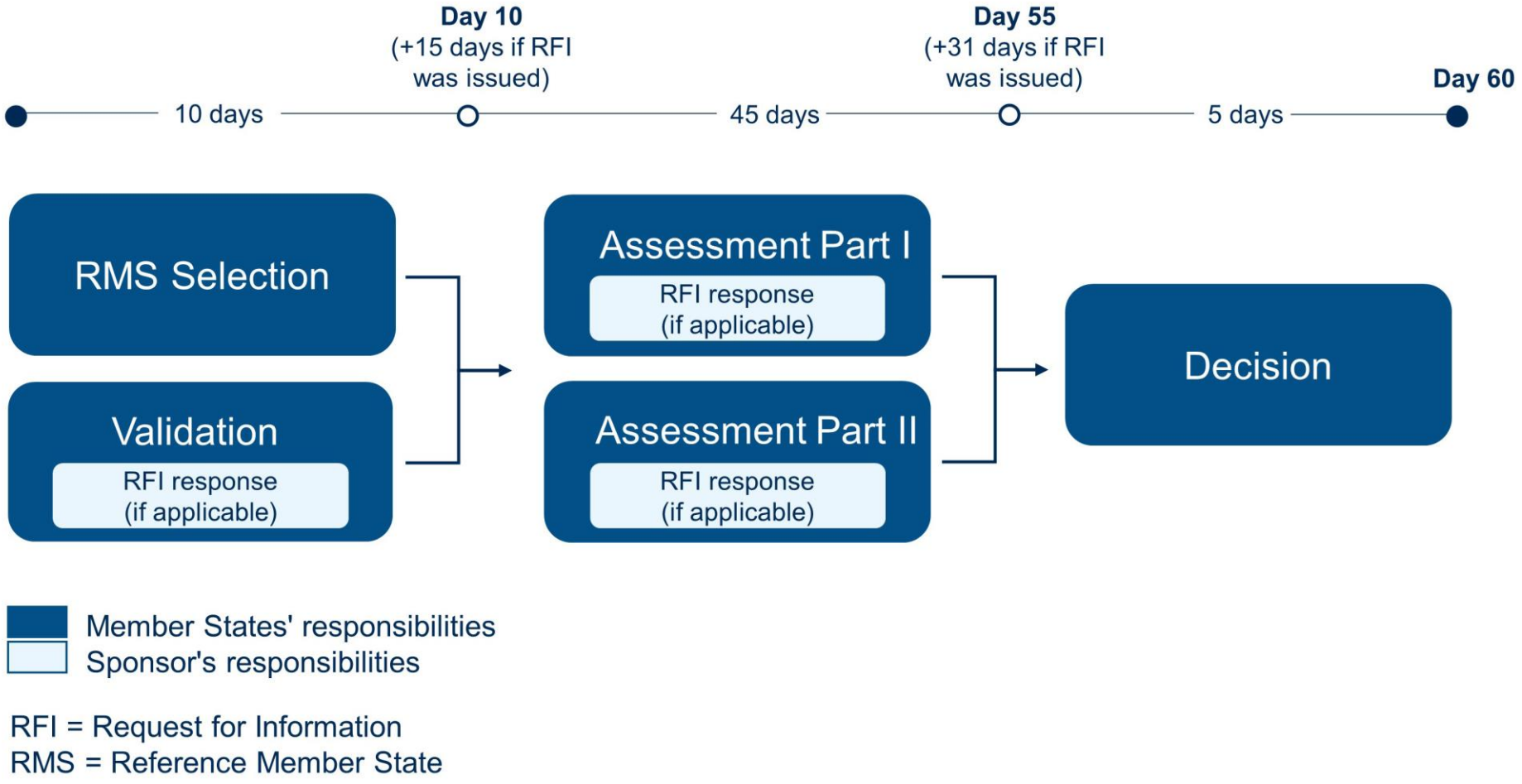
What do competent authorities and ethics committees still do?

- CTIS is the single EU entry point, but Member States still assess, authorise, and supervise trials
- Assessment is structured into Part I (joint/coordination across Member States) and Part II (national aspects), so national bodies retain real decision responsibilities

In practice, the remit shifts from “separate national submission routes” to working inside a coordinated EU workflow with binding timelines

Practical impact: sponsors see one submission, but still encounter national expectations (e.g., ethics/legal elements handled nationally within Part II)

Initial application for approval of a clinical trial pursuant to Regulation EU 536/2014



RFI = Request for Information
RMS = Reference Member State

CTR: WHERE NATIONAL LAW STILL SHAPES PRACTICE

Trial classification

Articles 4 & 7 — What counts as "normal clinical practice" is defined nationally

Article 2(2)(15) — "Minimal risk and burden" in low-intervention trials is interpreted nationally

Ethics review & governance

Articles 5–8 (Part II) — Informed consent, compensation, investigator suitability, recruitment

Article 10 — Organisation and functioning of ethics committees

Article 11 — National coordination between ethics committees and competent authorities

Participant protection

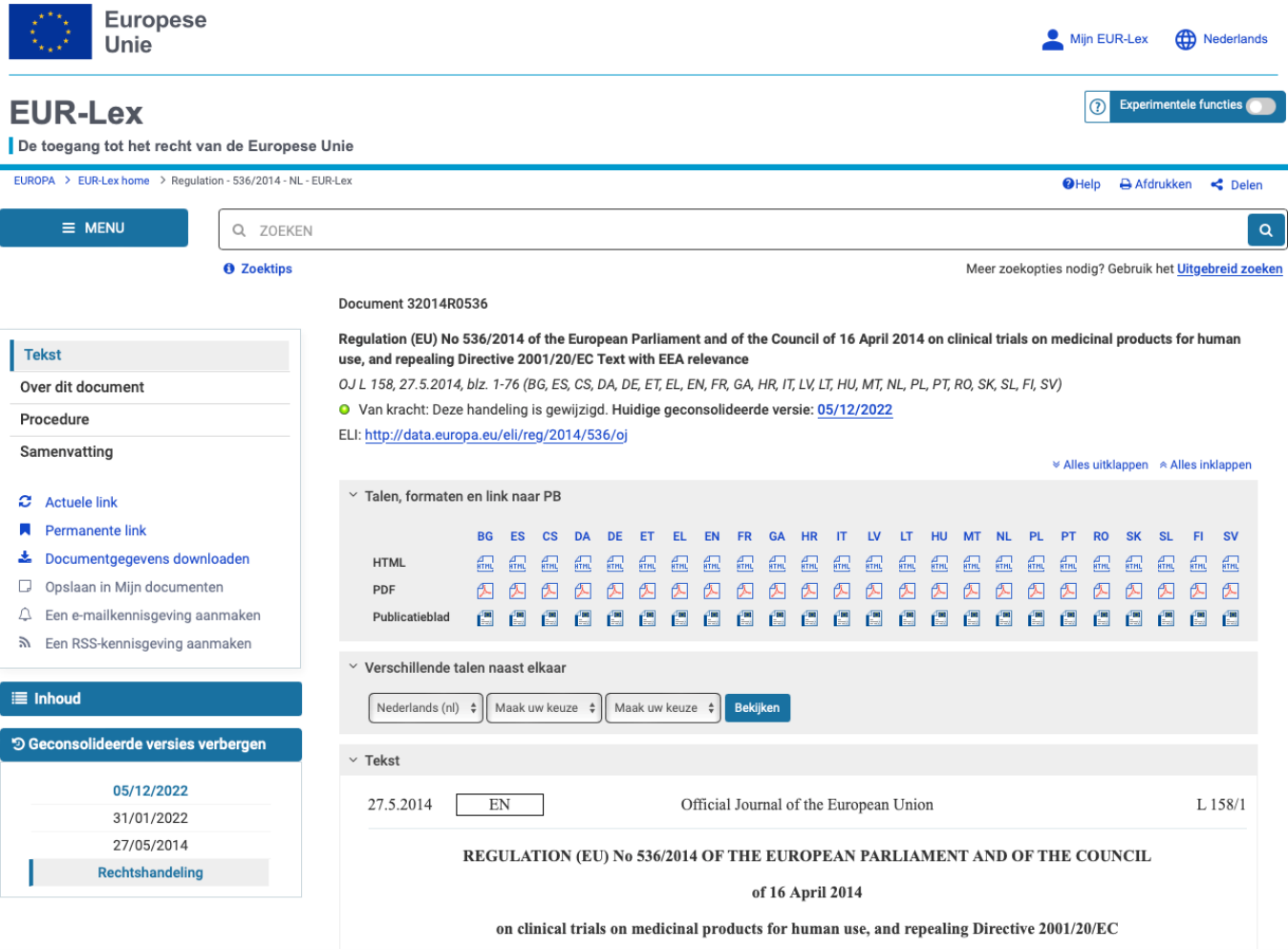
Article 29(1)(f) — Compensation and indemnity under national civil liability law

Article 31 — Protection of vulnerable populations (minors, incapacitated adults)

Articles 34–36 — Deferred consent and emergency research governed by national rules

Oversight & enforcement

Article 76 — Inspections, sanctions, and enforcement mechanisms are national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Experimentele functies
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Rechtshandeling
Document 32014R0536
Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC Text with EEA relevance
OJ L 158, 27.5.2014, blz. 1-76 (BG, ES, CS, DA, DE, ET, EL, EN, FR, GA, HR, IT, LV, LT, HU, MT, NL, PL, PT, RO, SK, SL, FI, SV)
Van kracht: Deze handeling is gewijzigd. Huidige geconsolideerde versie: 05/12/2022
ELI: http://data.europa.eu/eli/reg/2014/536/oj
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of 16 April 2014
on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

Guidance and Q&As

The Clinical Trials Information System (CTIS) supports the business processes of clinical trial sponsors and national regulators throughout the lifecycle of a clinical trial, via secure workspaces. On this page you will find some basic questions about the use of CTIS.

How can we help you?

Search

You can also browse the topics below to find what you are looking for.

On this page

About CTIS

What is CTIS?

The Clinical Trials Information System (CTIS) is the online system for the regulatory submission, authorisation and supervision of clinical trials in the European

Do I need to use CTIS?

If you are a sponsor planning to conduct a clinical trial on an investigational medicinal product in the European Union or European Economic Area, you must

March 2025

The rules governing medicinal products in the European Union
VOLUME 10 - Guidance documents applying to clinical trials

CLINICAL TRIALS REGULATION (EU) NO 536/2014

QUESTIONS & ANSWERS

VERSION 7.1

Amended and endorsed through written procedure
by the Clinical Trials Coordination and Advisory Group

Document history:	
Date of discussion by the Clinical Trials Coordination and Advisory Group:	Written procedure in Q1 2025
Date of publication:	27 March 2025
Supersedes:	7
Changes compared to superseded version:	- Annex II: o patient facing document language for LV: from "EN or LV" to "EN and LV". o labelling for DE: investigational and auxiliary medicinal products for clinical trials may be labelled in English if they are used by

EU RESEARCH FRAMEWORK

MODIFICATIONS UNDER THE CLINICAL TRIALS REGULATION (CTR)

Substantial modification

- A change likely to have a substantial impact on participant safety, rights, or data reliability
- Typically affects the protocol, endpoints, inclusion/exclusion criteria, IMP use, or safety monitoring
- Requires prior authorisation via CTIS
- Assessed under Part I and/or Part II, depending on the nature of the change

Non-substantial modification

- Administrative or organisational changes with no impact on safety or data integrity
- Examples: correction of clerical errors, updates to contact details
- Notification only, no prior authorisation required

EU RESEARCH FRAMEWORK

JOINING AN ONGOING CLINICAL TRIAL

Adding an Additional Member State under the CTR

- The sponsor submits a request via CTIS to add an additional Member State to an authorised clinical trial
- The existing trial authorisation remains valid in the initial Member States
- The additional Member State assesses the trial Part II and comment on Part I
- The Reporting Member State (RMS) continues to coordinate the Part I assessment
- The new Member State may raise national Part II issues (e.g. ethics, consent, insurance, site suitability)
- Trial activities in the new Member State may start only after national authorisation is granted
- Timelines are defined by the CTR, but national interpretation and documentation expectations still apply

2.11 Question: Can the decision on part I of a clinical trial application be changed at the moment of the addition of a Member State Concerned (article 14) ?

112. **Answer**: No.

113. The Clinical Trial Regulation is clear in its instruction to avoid re-assessment of the application by all the Member States concerned which were involved in the initial authorisation of the clinical trial at the moment of an article 14 application. Additionally, article 14 does not foresee a mechanism to revise the conclusion on Part I of the assessment report.

114. Nevertheless, art. 14 (5) foresees that the additional Member State concerned (AMS) communicate considerations on the application to the reporting Member State (RMS) and the other Member State Concerned (MSC). A mechanism to request additional information to the sponsor is foreseen, as well as a coordinated review by all MSC and a consolidation by the RMS. At the end, the RMS shall take due account of the considerations and records how the considerations are dealt with.

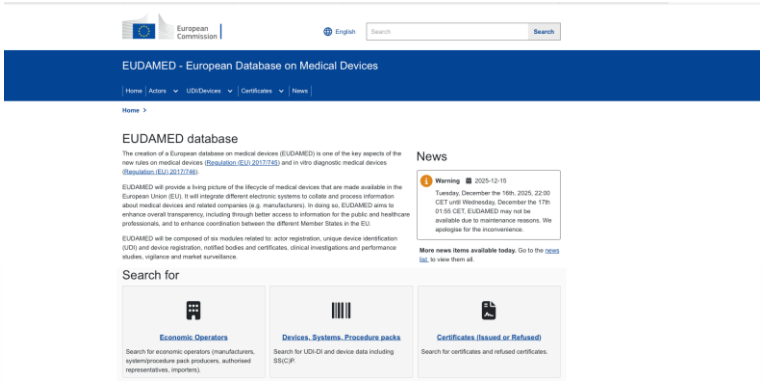
115. In exceptional cases, the RMS and MSC could therefore decide on additional actions leading to changes of the Part I as a results of those considerations, either through the decision of the AMS or through corrective measures as described in art. 77.

MEDICAL DEVICE REGULATION

EU RESEARCH FRAMEWORK

MEDICAL DEVICE REGULATION (MDR)

- Qualifies the AI-based EEG analysis tool as software as a medical device
- Requires a defined intended purpose and risk classification
- Triggers a clinical investigation or performance evaluation pathway
- Focuses ethics review on device safety, performance, and human–machine interaction
- Introduces device-specific documentation and vigilance obligations



WHY CHANGE?

The Medical Device Directive 1992

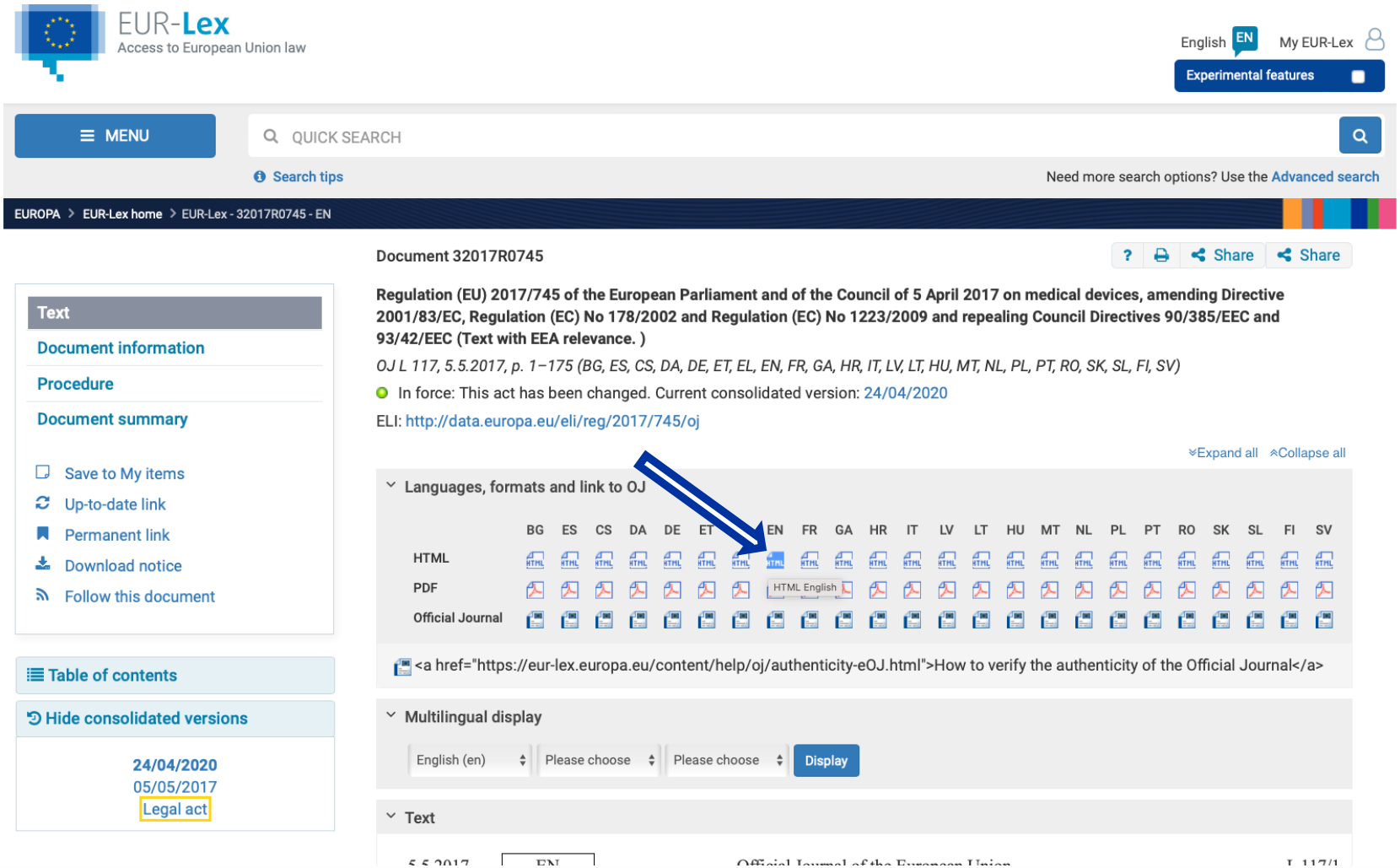
- No software as it exists now
- No apps
- New technology / higher risks
- People live longer, devices used must function longer
- Devices the same safety as medicinal products

RELEVANT SOURCES

1. MDR and recitals
2. CURIA - only autorative interpretation

3. National legislation
4. Medical Device Coordination Group (MDCG) Guidances→ However, please note that the views expressed in this manual are not legally binding, since only the European Court of Justice ("the Court") can give an authoritative interpretation of Community law.

Belgium	Member	MEULDERS Frederique	Federal Agency for Medicines and Health Products (FAMHP) meddev@fagg-afmps.be	Member	JAUGNIAUX Alexandre	Federal Agency for Medicines and Health Products (FAMHP) ivd@afmps.be
	Alternate	NYS Valérie	Federal Agency for Medicines and Health Products (FAMHP) meddev@fagg-afmps.be	Alternate	POELS Jeroen	Federal Agency for Medicines and Health Products (FAMHP) ivd@afmps.be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05/05/2017
Legal act
Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (Text with EEA relevance.)
OJ L 117, 5.5.2017, p. 1–175 (BG, ES, CS, DA, DE, ET, EL, EN, FR, GA, HR, IT, LV, LT, HU, MT, NL, PL, PT, RO, SK, SL, FI, SV)
In force: This act has been changed. Current consolidated version: 24/04/2020
ELI: http://data.europa.eu/eli/reg/2017/745/oj
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REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 5 April 2017

on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union, and in particular Article 114 and Article 168(4)(c) thereof,

Having regard to the proposal from the European Commission,

After transmission of the draft legislative act to the national parliaments,

Having regard to the opinion of the European Economic and Social Committee ([1]),

After consulting the Committee of the Regions,

Acting in accordance with the ordinary legislative procedure ([2]),

Whereas:

(1) Council Directive 90/385/EEC ([3]) and Council Directive 93/42/EEC ([4]) constitute the Union regulatory framework for medical devices, other than *in vitro* diagnostic medical devices. However, a fundamental revision of those Directives is needed to establish a robust, transparent, predictable and sustainable regulatory framework for medical devices which ensures a high level of safety and health whilst supporting innovation.

(2) This Regulation aims to ensure the smooth functioning of the internal market as regards medical devices, taking as a base a high level of protection of health for patients and users, and taking into account the small- and medium-sized enterprises that are active in this sector. At the same time, this Regulation sets high standards of quality and safety for medical devices in order to meet common safety concerns as regards such products. Both objectives are being pursued simultaneously and are inseparably linked whilst one not being secondary to the other. As regards Article 114 of the Treaty on the Functioning of the European Union (TFEU), this Regulation harmonises the rules for the placing on the market and putting into service of medical devices and their accessories on the Union market thus allowing them to benefit from the principle of free movement of goods. As regards Article 168(4)(c) TFEU, this Regulation sets high standards of quality and safety for medical devices by ensuring, among other things, that data generated in clinical investigations are reliable and robust and that the safety of the subjects participating in a clinical investigation is protected.

(3) This Regulation does not seek to harmonise rules relating to the further making available on the market of medical devices after they have already been put into service such as in the context of second-hand sales

Niet gevonden Begint met overige

ANNEXES

I	General safety and performance requirements
II	Technical documentation
III	Technical documentation on post-market surveillance
IV	EU declaration of conformity
V	CE marking of conformity
VI	Information to be submitted upon the registration of devices and economic operators in accordance with Articles 29(4) and 31; core data elements to be provided to the UDI database together with the UDI-DI in accordance with Articles 28 and 29;and the UDI system
VII	Requirements to be met by notified bodies
VIII	Classification rules
IX	Conformity assessment based on a quality management system and assessment of the technical documentation
X	Conformity assessment based on type examination
XI	Conformity assessment based on product conformity verification
XII	Certificates issued by a notified body
XIII	Procedure for custom-made devices
XIV	Clinical evaluation and post-market clinical follow-up
XV	Clinical investigations
XVI	List of groups of products without an intended medical purpose referred to in Article 1(2)
XVII	Correlation table

ANNEX I

GENERAL SAFETY AND PERFORMANCE REQUIREMENTS

CHAPTER I

GENERAL REQUIREMENTS

1. Devices shall achieve the performance intended by their manufacturer and shall be designed and manufactured in such a way that, during normal conditions of use, they are suitable for their intended purpose. They shall be safe and effective and shall not compromise the clinical condition or the safety of patients, or the safety and

European Commission | EN English | Search

Public Health

European Commission > Public Health > Medical Devices - Sector > New Regulations > Guidance

Guidance - MDCG endorsed documents and other guidance

PAGE CONTENTS

This page provides a range of documents to assist stakeholders in applying Regulation (EU) 2017/745 on medical devices (MDR) EN and Regulation (EU) 2017/746 (IVDR) on in vitro diagnostic medical devices EN. The majority of documents on this page are endorsed by the Medical Device Coordination Group (MDCG) in accordance with Article 105 of the MDR and Article 99 of the IVDR. They are drafted in collaboration with interested parties represented in the various groups and denominated by the following format: “MDCG Year-Number-revision”.

The documents on this page are not legally binding. They present a common understanding of how the MDR and IVDR should be applied in practice aiming at an effective and harmonised implementation of the legislation.

MDCG work in progress

Ongoing guidance documents EN

MDR: WHERE NATIONAL LAW STILL SHAPES PRACT

Authorisation & oversight

Articles 62 & 70 — Clinical investigations authorised and supervised through national procedures and timelines

Article 74 — National authorities determine how investigations are assessed and monitored

Ethics review & consent

Article 63 — Role, scope, and procedures of ethics committees are defined nationally

Article 69 — Informed consent requirements are supplemented by national legislation

Participant protection & liability

Article 73 — Compensation and indemnification depend on national civil liability frameworks

Post-market vigilance & enforcement

Articles 87–90 — Incident reporting and corrective actions handled by national competent authorities

Article 101 — Penalties and sanctions are set at Member State level

Transition & implementation

Article 123(3) — Transitional arrangements and enforcement timing depend on national choices

VRIJE UNIVERSITEIT BRUSSEL

EU RESEARCH FRAMEWORK

GENERAL DATA PROTECTION REGULATION (GDPR)

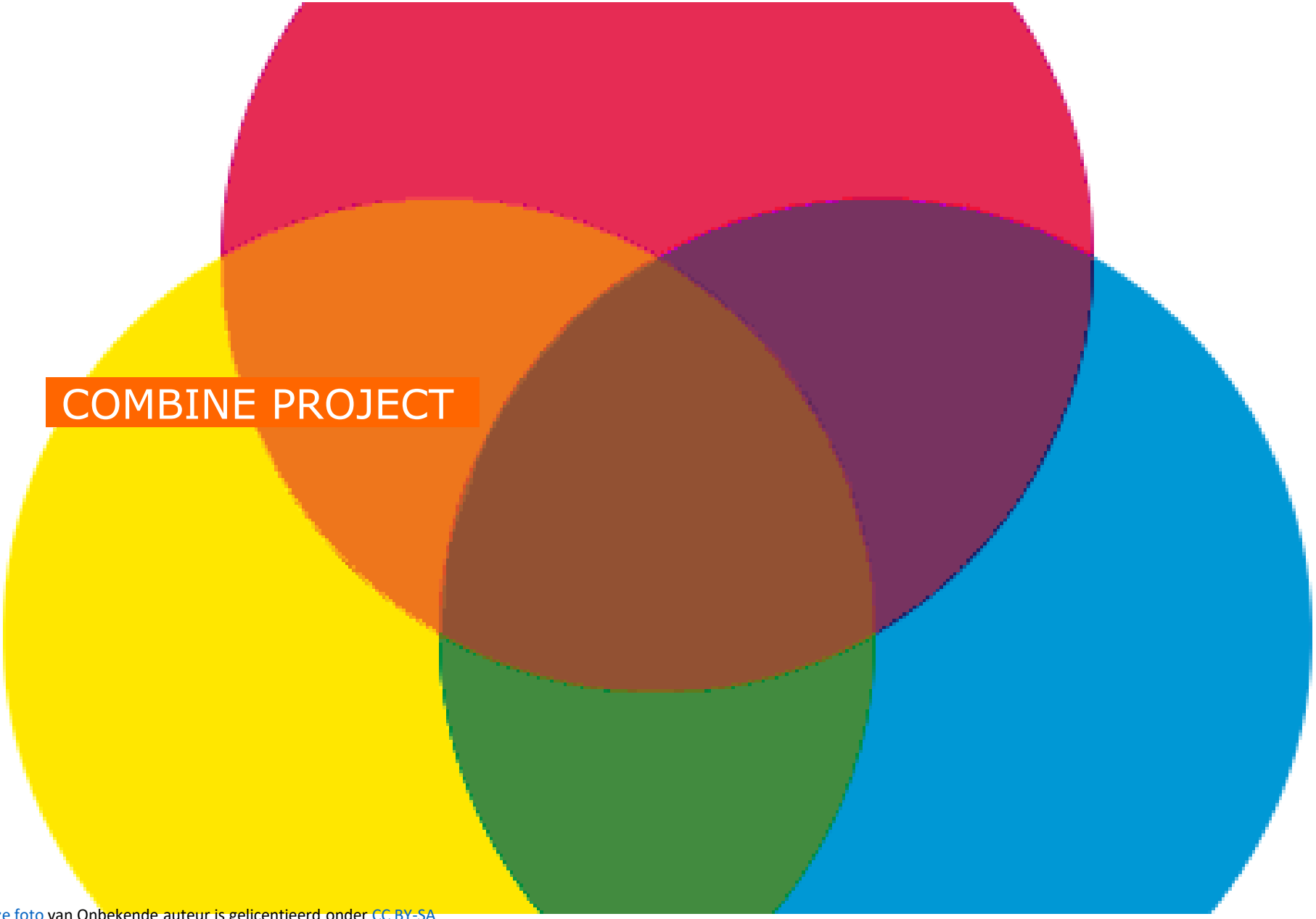
Requires a valid legal basis for processing EEG and clinical data

Distinguishes between prospective data collection and secondary data use

Imposes obligations on transparency, purpose limitation, and data minimisation

Requires safeguards such as pseudonymisation and data security measures

Clarifies roles and responsibilities of data controllers and processors



The EU's COMBINE programme seeks to harmonise and coordinate the regulatory assessment of combined studies involving medicinal products and medical devices (or diagnostics), addressing fragmentation between CTR, MDR, and IVDR. A key element is a pilot "all-in-one" coordinated assessment to streamline submissions, align timelines, and reduce administrative burden for sponsors.

EU COMBINE

RESEARCH WITH A UK PARTNER

REGULATORY OVERVIEW POST-BREXIT

- The EU CTR and CTIS do not apply
- Clinical trials are submitted via UK MHRA and reviewed through the UK Combined Review (MHRA + Research Ethics Committee)
- UK legislation is based on the former EU Directive, with national reforms ongoing
- Data protection governed by UK GDPR, aligned but legally separate from EU GDPR

Running a combined EU–UK study

Two parallel regulatory submissions are required (CTIS + UK national route)

Timelines, documentation formats, and amendment processes differ

Trial governance, monitoring, and safety reporting must be coordinated across systems

Data transfer arrangements must explicitly address EU–UK data flows

MY RESEARCH

CONTEXT & MOTIVATION

- Decentralised system: 15 accredited MRECs, CT-College, FAMHP (NCP), BAREC
- Rising complexity: CTR, MDR, IVDR, GDPR, AI, EHDS

Central PhD question:

"The Sense and Nonsense of the Role Assigned to MRECs in Belgium in Innovative Research

Understanding the Gaps between Law, Ethics, and Practice in Research Oversight"

RESEARCH COMPONENTS 1/3

1. **Literature review**

2. **Legal analysis of Belgian and EU frameworks**

(CTR, MDR, IVDR, GDPR, Declaration of Helsinki, GCP).

3. **Survey**

- A national surveys with all 15 recognised MRECs on CTR, MDR, IVDR, GDPR procedures, training, challenges, and staffing.

4. **Quantitatif and qualitatif analyses of RFIs in CTR & MDR**

5. Stakeholder consultations

- Anonymised *case discussions* with **MRECS** in a Wooclap-based peer workshop to explore divergent outcomes in approval decisions, whether approval with conditions or refusal. (2023)
- Multi-stakeholder *symposium* (2024) and *workshop* (2024) with the 15 accredited **MRECs, NCP.**
- A *survey* to Pharma.be and *workshop* conducted with **Pharma.be** to gather insights into sponsor experiences with clinical trial processes (2024).
- Two *publications* in cooperation with **academic researchers** in health research addressing the challenges encountered by academic researchers in conducting real-world data research and neuromodulation trials with medical devices (2025).

6. EU RMECS Comparative interviews

Representatives of MRECs involved in CTR-MDR-IVDR evaluations examining the functioning of their MREC review systems under the CTR, MDR, and IVDR frameworks, with attention to encountered challenges and potential ways forward

- Ireland
- Denmark
- Latvia
- Spain

1. LITERATURE ANALYSIS

1. LITERATURE ANALYSIS – MOST IMPORTANT PROBLEMS IDENTIFIED

1. **Delays and inefficiencies** in ethics approval due to redundant reviews or unclear procedures.

2. **Vague, inconsistent**, or **overly bureaucratic** feedback causing confusion.

3. Overemphasis on **administrative formalities** over substantive ethical evaluation.

4. **Lack of justification** in decision letters; stipulations often unreasoned.

5. Insufficient **expertise** in new domains (big data, AI, social media).

6. **Inconsistency among MRECs**, especially in multicenter trials.

7. Marginalization of **lay members**; unclear roles.

10. **Regulatory frameworks** lag behind modern research complexities.

2. LEGAL ANALYSIS OF BELGIAN AND EU FRAMEWORKS

EU LEGISLATIVE FRAMEWORK: HARMONISATION, TRANSPARENCY AND INNOVATION

EU CTR, MDR, Belgian implementation, DoH, GCP

Shared EU Objectives

- Create a **single, harmonised system** for the assessment and supervision of clinical research across all Member States.
- Replace divergent national procedures with **one coordinated review** process and **common standards**.

Transparency and Trust

Efficiency and Innovation

- Introduce **streamlined submission and strict timelines** to **accelerate authorisation** while maintaining quality.
- Encourage **cross-border and multicentre research**, making Europe more attractive for clinical innovation.

Protection and Ethics

- Uphold the principle that **participant rights, safety, and well-being outweigh all other interests**.
- Guarantee **independent ethical review**, continuous oversight, and special safeguards for vulnerable groups.

CONVERGING PRINCIPLES ACROSS LEGAL AND ETHICAL FRAMEWORKS

EU CTR, MDR, Belgian implementation, DoH, GCP

Shared Foundations for Ethical Review

- Ethics review is **mandatory before research begins** — a **legal and moral precondition** for authorisation.
- MRECs must be **independent, multidisciplinary, and transparent**, ensuring freedom from conflicts of interest.
- Participant **rights, safety, dignity, and well-being** always prevail over scientific or commercial interests.

Scope and Standards of Review

All frameworks require evaluation of:

- **Scientific validity and risk–benefit balance**
- **Informed consent and data protection**
- **Compensation and recruitment methods**
- **Special protection for vulnerable populations**

Reviews must be **documented, reasoned, and time-bound** within defined procedural timelines.

3. HOW DO MRECS FUNCTION IN PRACTICE IN THE EVALUATION OF INNOVATIVE RESEARCH?

BELGIAN MREC SURVEY

BACKGROUND AND METHODOLOGY

Context: CTR, MDR, and IVDR functionning of Belgian MRECs.

(Sept 2023)

Objective: Assess structure, capacity, challenges, and training needs of

Belgian MRECs reviewing EU-governed research.

Scope: 15 recognized MRECs; **13 responded**, representing a broad national sample.

Respondents: Chairs, coordinators, and administrative staff, reflecting both institutional and individual perspectives.

BELGIAN MREC SURVEY

KEY FINDINGS

- **Structure & Staffing:**
  - Most still follow 2004-law model; 1–9 active members per MREC.
  - "Small committees" used to maintain quorum and manage workload.
- **Operational Backbone:**
  - Back office and scientific staff essential for daily operations and correspondence.
  - 75% receive training, but their role remains undervalued.
- **Remuneration & Resources:**
  - Only 38% of committees offer consistent compensation.
  - Voluntary model increasingly **unsustainable**; recruitment challenges rising.
- **Review Practices & Training:**
  - Hybrid (online + in-person) reviews; 10–30 comments per dossier (mainly on Part II).
  - Frequent issues: ICF quality, GDPR, investigator qualifications, compensation.
  - Limited expertise in IVDR and digital tools; call for structured national/EU training.
- **Harmonisation & Governance:**
  - Broad support for ICF template
  - Inconsistent review practices across committees.
  - Preference for **network-based collaboration** over a single national EC.
  - Calls for clearer legal frameworks and stronger national support.

QUANTITATIF AND QUALITATIF ANALYSES OF RFIS IN CTR & MDR

METHODOLOGY

Design

- Empirical, mixed-method research combining **quantitative RFI analysis** and **qualitative thematic interpretation**.
- Compared ethics review practices for **clinical trials (CTR)** and **device investigations (MDR)** in Belgium.

Data Sources

- **CTR study**: 6,740 RFIs from 266 trial dossiers (2017–2024).
- **MDR study**: 1817 RFI's from 94 clinical investigations (2021–2023), including **10 software-based (SaMD)**.
- Datasets obtained from **NCP**, complemented by **symposium validation** with MRECs.

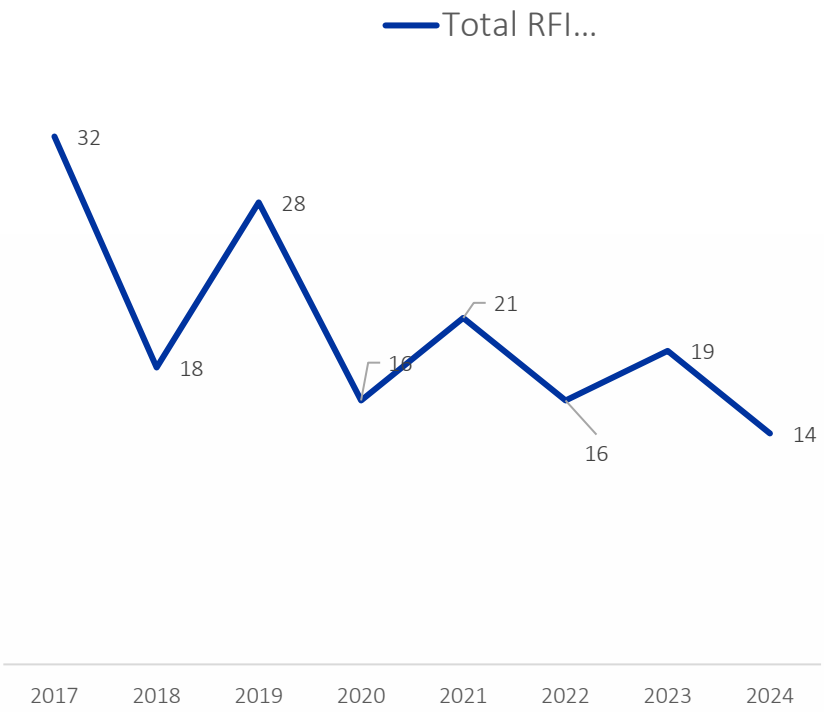
Analysis

- Standardised coding of all RFIs by Part I (scientific) / Part II (ethical).
- Quantitative frequency trends and **reflexive thematic analysis** for recurring issues.

Aim

- To identify patterns in MREC evaluations

WHAT THE DATA SHOW



Ethics review or compliance check? an empirical analysis of 6740 requests for information in Belgian clinical trial evaluations (2017–2024)

Audrey Van Scharen[1,2,3*], Michel Deneyer[1,2] and Pieter Cornu[3,4]

Abstract

The EU Clinical Trials Regulation (CTR) was introduced to harmonize clinical trial evaluations across Member States while upholding participant protection and ethical integrity. This study analyzes 6740 Requests for Information (RFIs) issued by Belgian Medical Research Ethics Committees (MRECs) across 266 trial dossiers evaluated between 2017 and 2024, spanning both the CTR pilot phase and the initial CTIS implementation. Using framework content analysis, we examined the number and content of RFIs in relation to trial outcomes, sponsor type (commercial vs. non-commercial), and the MREC's role as Reporting Member State (RMS) or Member State Concerned (MSC).

Results show a decline in total RFIs over time, mainly due to a reduction in typographical and linguistic remarks, yet significant variability persists in the formulation and scope of ethical feedback. While statistical and methodological concerns remained central in Part I evaluations, RFIs increasingly addressed newer challenges such as decentralized trials, e-consent, and data collection on ethnicity. Part II RFIs continued to focus heavily on informed consent documents. We further observed that MSCs raised fewer RFIs than RMSs for Part I, prompting reflection on the necessity and efficiency of full multi-state review in this section.

The study also highlights a growing emphasis on regulatory compliance—sometimes at the expense of ethical deliberation—and the limited authority of policy advisors to correct inconsistencies, despite their expertise. We recommend clearer guidance, formalized roles for policy advisors in quality control, improved pre-submission processes, and limited direct communication between MRECs and sponsors. These findings support ongoing efforts to improve ethics review efficiency and quality under the CTR, with broader relevance for harmonization across Europe.

Keywords Ethics review, Medical research ethics committees (MRECs), Clinical trials regulation (CTR), Requests for information (RFIs), Clinical trial evaluation, Regulatory compliance, Decentralized trials, Informed consent forms (ICFs), Ethics and compliance, Harmonization of ethics review, Ethics in research

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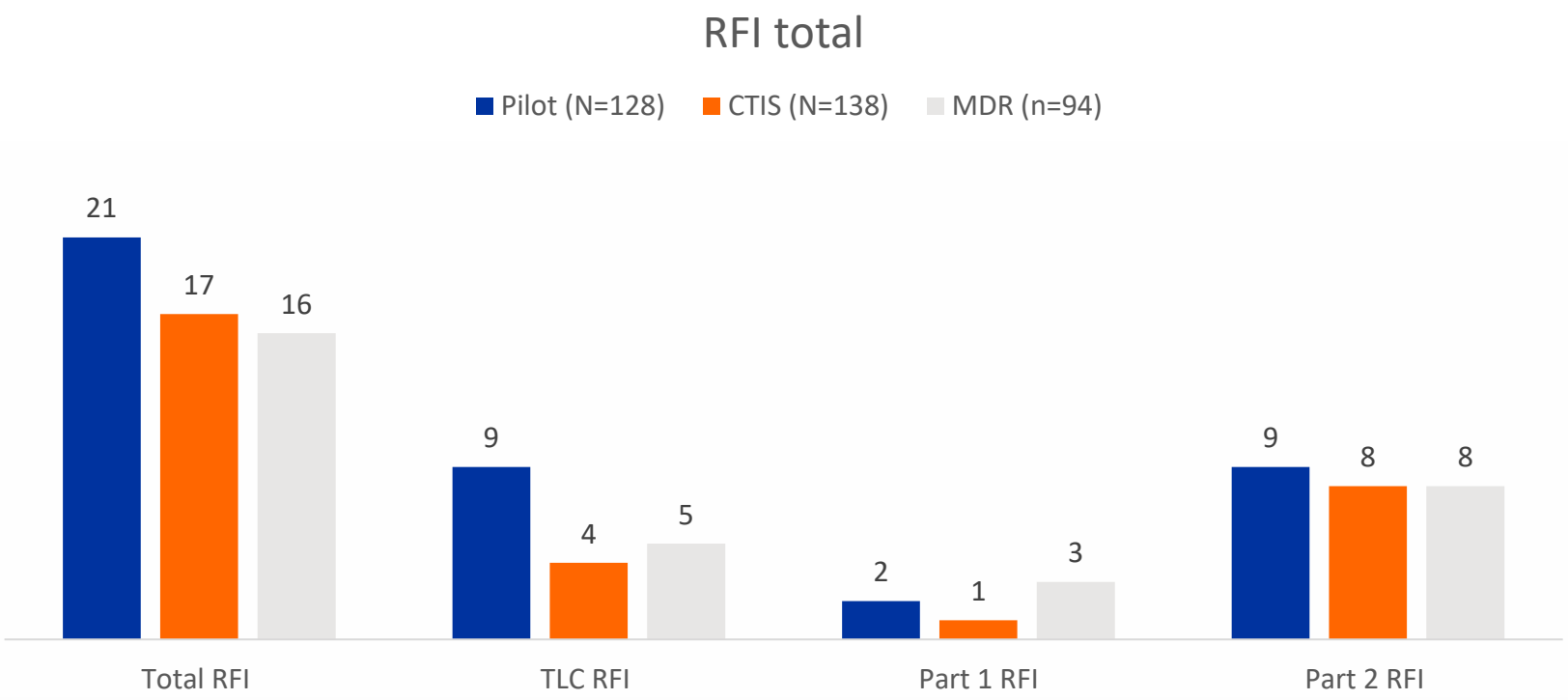
QUANTITATIF AND QUALITATIF ANALYSES OF RFIS IN CTR & MDR

QUANTITATIF OUTCOMES GENERAL



QUANTITATIF AND QUALITATIF ANALYSES OF RFIS IN CTR & MDR

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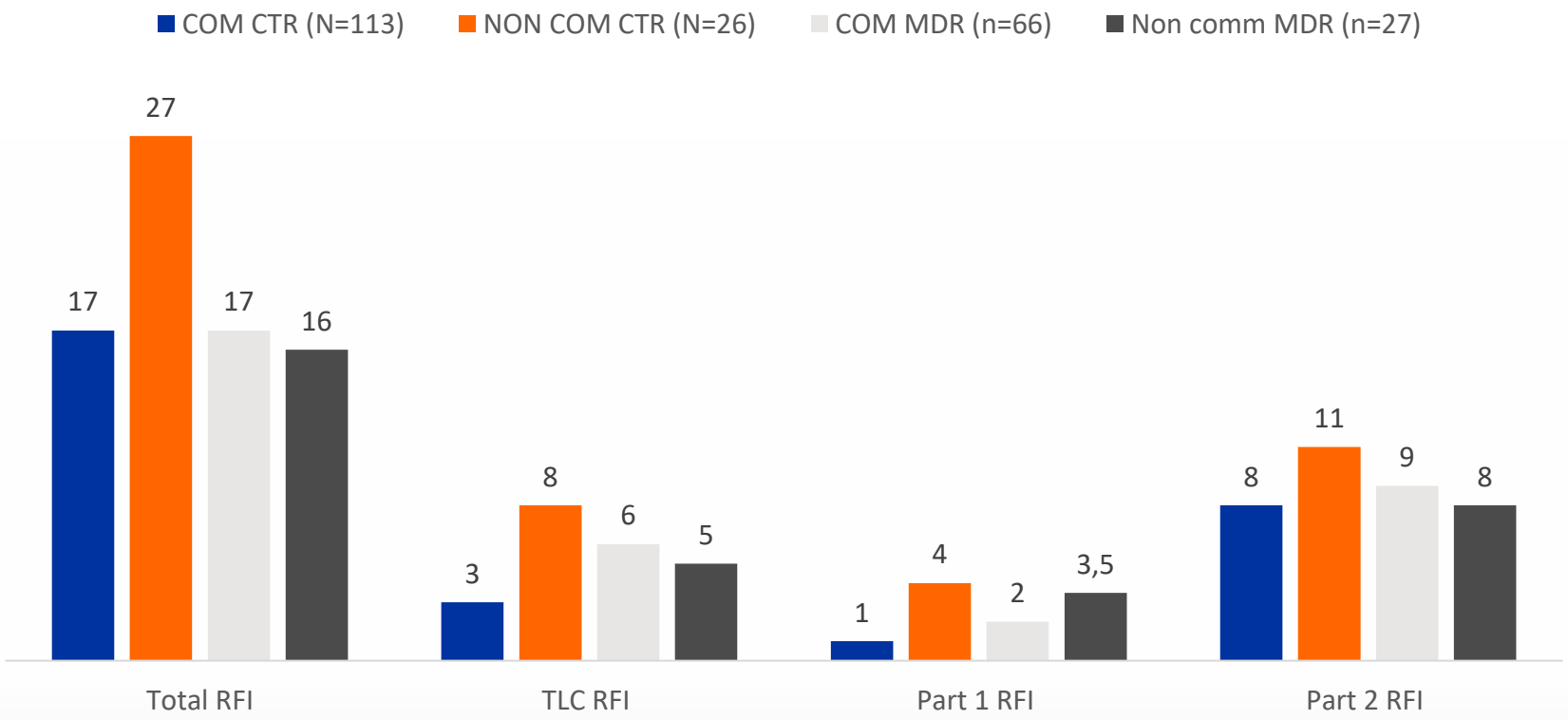


WHAT THE DATA SHOW

6740 RFIS ANALYSED – FEWER REMARKS, BUT MORE LEGALISM

- Overall RFIs declined → especially editorial comments, thanks to ***ICF templates***.
- Most common questions:
  - Part I: *statistics, trial rationale.*
  - Part II: *patient information and consent materials*.
- New themes emerging: decentralised trials, digital consent, AI-supported designs, ethnicity data.

QUANTITATIF AND QUALITATIF ANALYSES OF RFIS IN CTR & MDR

QUALITATIVE

1. Persistent Variability Across MRECs
2. Clarity and Quality of RFIs
3. Regulatory Misinterpretations
4. Overemphasis on Form over Substance

INTERACTIVE CASE VOTING

METHOD AND MAIN FINDINGS

Participants: 14 of 15 recognised Belgian MRECs.

Approach:

- 8 anonymised *real-world cases* (from RFIs under CTR/MDR).
- Interactive **Wooclap voting**: each MREC classified cases as *refusal, conditional approval, approval, or no remark -> one vote per MREC*
- Qualitative analysis of workshop transcripts and post-survey feedback.

Focus areas: Informed consent, insurance, data reuse (GDPR), site readiness.

Main Finding!

- **High Divergence:** Consensus in only 1 of 8 cases
- Major variation in refusal vs conditional decisions.

But should it be the same?

Humans remain humans… even in one central committee.

INTERACTIVE CASE VOTING

RESULTS

Case Description	Original Decision	Votes for Refusal	Votes for Condition	Votes for Approval	Votes for No Remark
Case 1: multiple language remarks and add the option for further use of data	Refusal	0	14	0	0
Case 2: remaining inconsistency between protocol and ICF on risks of the trial and a clarification on the who was the evaluation MREC and a remark on data protection information in the ICF	Condition	3	11	0	0
Case 3: all RFIs on the ICF: 3 RFIs on readability, 1 to add the insurance number, 1 to clarify that no financial compensation is to be expected for the participant	Condition	0	12	2	0
Case 4: combo trial: the main and pre-screening ICFs are still under review by the leading MREC in Belgium. The ethics committee cannot agree to simultaneous review of the same documents by different MRECs.	Refusal	4	1	6	2
Case 5: ICF: clarify the future use of personal data	Condition	1	12	0	0
Case 6: following the RFI round the sponsors answers that he refuses to provide separate approval for further research that is not covered by this study protocol and a separate Tick box for approval for anonymization	Refusal	11	4	0	1
Case 7 IVF performance study on left over material: the objective of the study is not appropriately described in the ICF.	Refusal	6	4	1	1
Case 8: the research facility where the trial is conducted has not opened yet, thus the ec cannot evaluate the site facilities.	Refusal	9	3	0	0

5. STAKEHOLDER CONSULTATIONS

MULTI-STAKEHOLDER SYMPOSIA

BACKGROUND AND AIMS

- Post-CTR/CTIS transition (2022–2024) revealed inconsistent review practices.
- Symposium goal:
  - Identify recurring issues and divergent interpretations.
  - Build consensus on proportionate and harmonised review.
  - Inform BAREC and CT College policy guidance.
- Method:
  - Evidence-based dialogue using anonymised real RFIs, live polling, and structured thematic panels.

SURVEY AND WORKSHOP PHARMA.BE

- **Participants:** pharma.be Task Force and Focus Group.
- **Methods:**
  - **Anonymous online survey** (closed 22 April 2025)
- **Objectives:**
  - Assess sponsor experiences with **CTR submissions and evaluations**.
  - Examine **clarity, scope, and consistency** of MREC RFIs (Part II).
  - Evaluate **national support** (BAREC, CT-College, FAMHP, FPS Health).
  - Gather **proposals for harmonisation and reform**.

SURVEY AND WORKSHOP PHARMA.BE

KEY SURVEY RESULTS

- **Respondent Profile:** 16 participants, most with >10 years of CTR submission experience.
- **Overall satisfaction with CTR in Belgium: 44.3%**
- **Perceived administrative simplification:**
  - Mononational trials: **2.36/10**
  - Multinational trials: **3.13/10**
- **Confidence in internal RFI prevention processes: 6.21/10**
- **Evaluation of national authorities:**
  - FAMHP: **63%** positive
  - FPS Health: **51%** positive
- **Strengths:** Centralised CTIS tracking; high scientific quality of reviews.
- **Challenges:** Lack of harmonisation in MREC feedback; unclear RFIs; slow or inconsistent support.

SURVEY AND WORKSHOP PHARMA.BE

WORKSHOP PHARMA.BE

Participants: Representatives of **19 pharmaceutical companies** active in Belgium.

Main issues identified:

1.Variability in MREC evaluations

1. Same protocol → divergent RFIs.
2. Frequent linguistic/stylistic requests with limited ethical relevance.
3. Limited transparency in committee reasoning.

2.Concerns around BAREC guidance

1. 80% find advices unclear or conflicting with Belgian law/EU practice.
2. Lack of formal authority or harmonised interpretation.
3. Need for unified framework by **BAREC, CT-College & FAMHP**.

3.ICF-related issues

1. Excessive focus on format over content.
2. Support for **shorter, modular, harmonised templates** (possibly hosted centrally).

ACADEMIC RESEARCHERS

ENHANCING MREC FUNCTIONING IN COMPLEX MEDICAL DEVICE RESEARCH

Reference: Van Scharen A. and Goudman L. *et al.* (2025) *Legal and ethical considerations for clinical research in Neuromodulation: the Chimaera Checklist*

In submission in 'Neuromodulation' awaiting revision review

•**Context:** Neuromodulation and other high-risk device trials expose gaps in MREC mandates and expertise.

•**Key Challenges:**

- Ethical tensions around **informed consent, patient vulnerability, post-trial access**.
- Insufficient support for navigating **EU frameworks** (GDPR, MDR, HTAR, AI Act).
- **Legalistic reviews** overshadow ethical reflection.
- Weak integration of **ethics-by-design** and **patient/public involvement (PPI)**.
- Limited device-specific and commercial expertise within MRECs.

ACADEMIC RESEARCHERS

STRENGTHENING MREC ROLES IN BIG DATA HEALTH RESEARCH

Reference: Van Scharen, A., Cruyt, K., Colon, J. et al. Unlocking Health Data for Research: Legal, Technical, and Organisational Lessons from a Belgian Interdisciplinary Case Study. J Healthc Inform Res (2025). https://doi.org/10.1007/s41666-025-00220-w

Context: Based on a five-year case study on secondary use of hospital data and the **EHDS Regulation**.

•**Challenges:**

- Ethical review not adapted to data-intensive research.
- Limited MREC expertise in **data protection, cybersecurity, and health informatics**.

6. EU MRECS COMPARATIVE INTERVIEWS

EU MRECS COMPARATIVE INTERVIEWS

UNDERSTANDING ETHICS COMMITTEE STRUCTURES ACROSS THE EU: PILOT INTERVIEW STUDY

Purpose:

•Benchmark Belgian MRECs against EU counterparts.

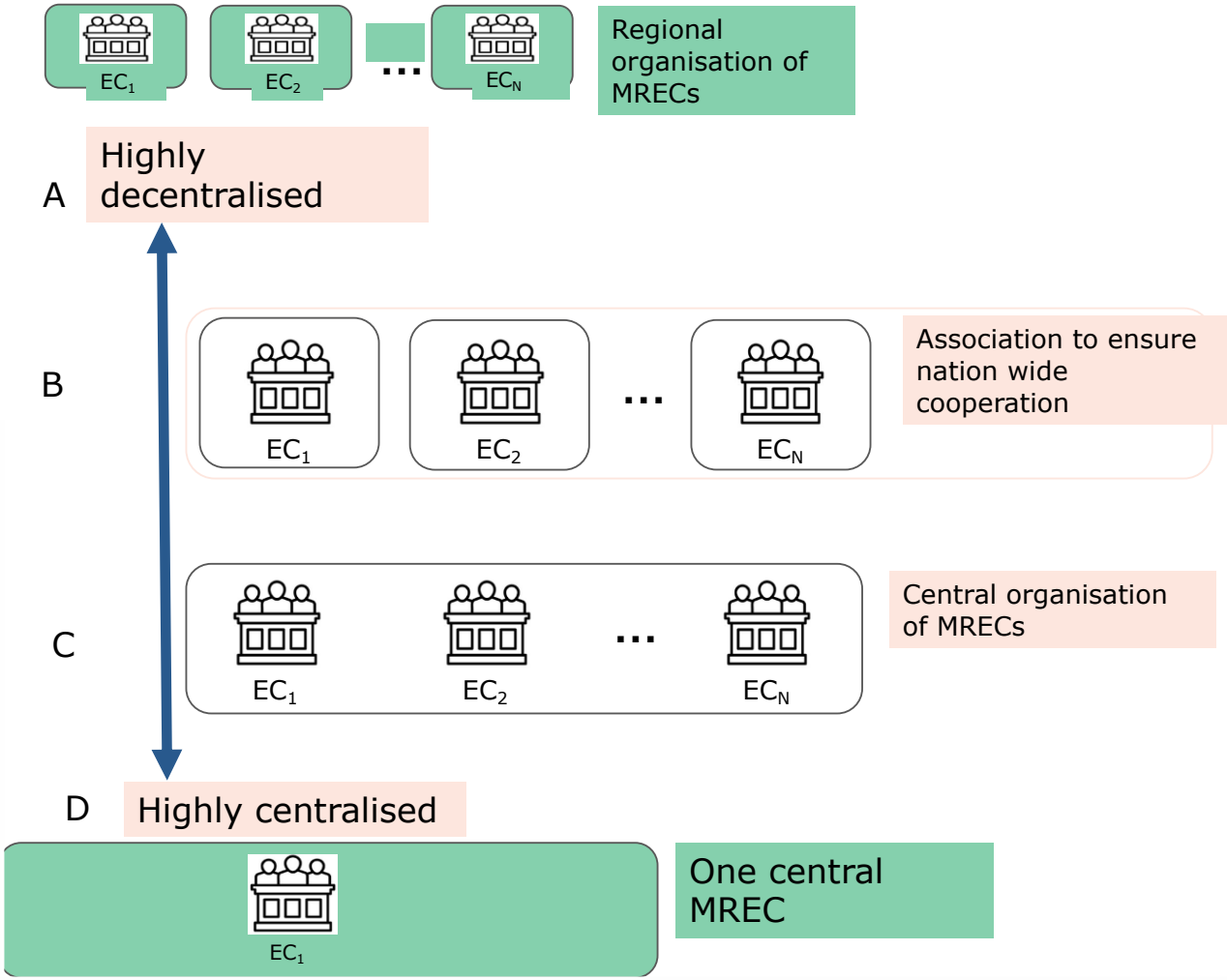
•Identify effective models, challenges, and innovations under **CTR/MDR/IVDR**.

Approach:

•**Qualitative semi-structured interviews** with representatives from national authorities, REC secretariats, coordinators, and experts.

•Participants mapped their national systems using a **schematic "tree structure."**

•Explored differences in review tracks for clinical trials, medical devices, and IVDs.


EC1
EC2
...
ECN
Regional organisation of MRECs
A
Highly decentralised
B
EC1
EC2
...
ECN
Association to ensure nation wide cooperation
C
EC1
EC2
...
ECN
Central organisation of MRECs
D
Highly centralised
EC1
One central MREC

EU RMECS COMPARATIVE INTERVIEWS

UNDERSTANDING ETHICS COMMITTEE STRUCTURES ACROSS THE EU: PILOT INTERVIEW STUDY

Topics covered:

1. Full ethics review pipeline (submission → decision).
2. Roles of admin, legal, and scientific staff; handling of RFIs (Part I & II).
3. Composition, appointment, training, remuneration, and expert use.
4. Funding and structural support for review capacity.
5. Ongoing reforms, innovation, and lessons learned.

EU MRECS COMPARATIVE INTERVIEWS

UNDERSTANDING ETHICS COMMITTEE STRUCTURES ACROSS THE EU: PILOT INTERVIEW STUDY

Common Challenges:

- Classifying device/AI studies under MDR/IVDR.
- Variable RFI management and decision-making styles.
- Limited harmonisation of training and guidance.

EU MRECS COMPARATIVE INTERVIEWS

UNDERSTANDING ETHICS COMMITTEE STRUCTURES ACROSS THE EU: PILOT INTERVIEW STUDY

Good Practices Identified:

•**Primary-reviewer model** feeding multidisciplinary discussion.

•Formal mandates for **scientific & administrative experts** (Ireland, Denmark).

•Preference for conditional approval rather than outright rejection (Ireland).

Training & Harmonisation Needs:

•Develop **EU-wide ethics training module** adaptable to national law.

•Strengthen cross-committee knowledge transfer and interpretation alignment.

EU Harmonisation & Remaining Divergences:

•Persistent national differences in GDPR interpretation, paediatric placebo use, and consent formats.

•Networks like **MedEthics EU** and **CTR Collaborate** promote exchange, but participation remains limited to a few experts.

KEY FINDINGS

KEY FINDINGS

WHERE WE FALL SHORT OF EU OBJECTIVES

1. Harmonisation Not Achieved

- Identical cases receive **different outcomes** across MRECs — "**Ethics Lottery**." (also in EU?)
- Persistent **interpretative disparities**.

2. Transparency Gaps

- **CTIS and EUDAMED** underused for learning and feedback; limited access for MRECs.
- Sponsors and MRECs operate in **information silos**

3. Efficiency and Innovation Barriers

- Ethics review remains **redundant and slow**
- Procedural focus on **format and wording** over substantive ethics delays approvals.
- Complex trials (e.g. AI, decentralised, or SaMD) face **regulatory uncertainty** and fragmented oversight.

4. Ethics and Protection under Strain

- Ethical reflection often reduced to **compliance checking**.
- Unequal expertise on **data protection**, **vulnerable groups**, and **digital trials** across MRECs.
- No consistent **training or quality monitoring** to ensure participant-centred review.

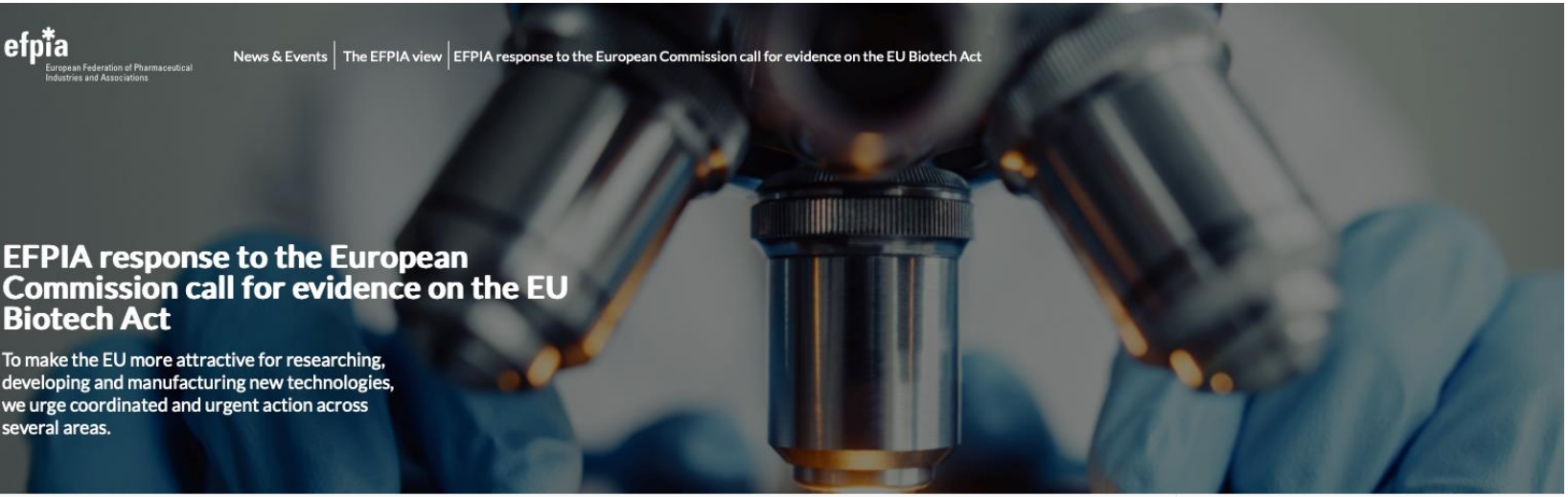
FUTURE LEGISLATION?

REVIEW OF CTR AND MDR/IVDR

CTR AND THE EU BIOTECH ACT

PLANNED DIRECTIONS OF CHANGE

- Reduce administrative burden and procedural
- Improve the practical functioning of CTIS
- Increase flexibility in trial design, including adaptive trials and complex innovative study designs
- Clarify and streamline requirements for multinational trials, particularly where current CTR processes cause delays
- Strengthen EU competitiveness by **accelerating trial start-up times** *without lowering safety or ethical standards*
- Improve coordination between regulatory authorities, ethics committees, and other oversight bodies
- Better align CTR implementation with other EU frameworks relevant to biotech research, including MDR/IVDR, data legislation, and future AI rules

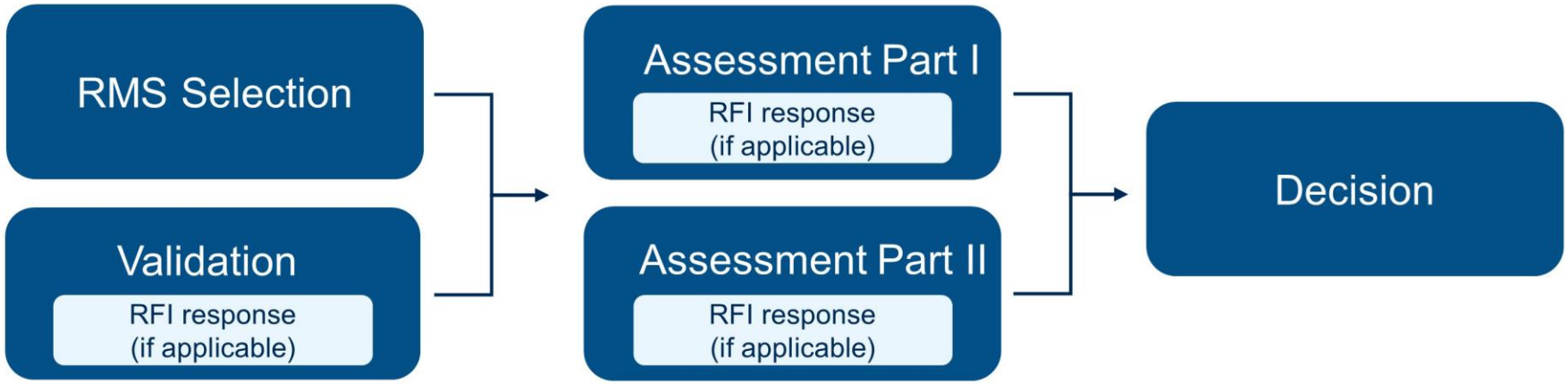


EFPIA response to the European Commission call for evidence on the EU Biotech Act

- Simplify, speed up and harmonise the **EU framework for clinical trials.**

This might mean: pragmatic implementation of the Clinical Trials Regulation avoiding requirements beyond its scope; faster, harmonised, and coordinated processes for multi-country trials, including ethics reviews, with the use of reliance mechanisms; enabling parallel submissions of substantial modifications; resources and a dedicated platform for continued regulator/innovator dialogue beyond Clinical Trials Information System (CTIS), and a shift towards a product-based approach that optimises efficiency. Regulatory pathways should be aligned across frameworks such as Medical Device Reguation/In Vitro Diagnostics Regulation/Genetically Modified Organisms legislation/etc to reduce duplication.

Initial application for approval of a clinical trial pursuant to Regulation EU 536/2014



Member States' responsibilities
Sponsor's responsibilities

RFI = Request for Information
RMS = Reference Member State

THE PACE PROBLEM: LAW, TIME & SCOPE

SPEED CAN ERODE REFLECTION.

- The CTR, MDR, IVDR has been fully in force for *only three years* → adaptation is still ongoing.
- Europe is attempting to harmonise 27 culturally rooted ethics systems + 27 legal systems

We can and must be more efficient → but not at the cost of reflection or participant protection.

Bridging the translation gap!

- **Sponsors and researchers** benefit from submitting *fully complete, high-quality dossiers* : *reducing unnecessary back-and-forth*.
- **MRECs** often say they lack time: but if that's true, why would they waste effort writing *non-critical* remarks?

--> Reviewers are volunteers


If harmonisation means becoming faster, we should ask ourselves: does faster really mean better? Or stronger?

UNDERSTANDING BEFORE HARMONISING

EFFICIENCY REQUIRES MUTUAL UNDERSTANDING.

- How can we reach efficiency if **we don't understand each other's systems?**
- We need deeper comparative insight: surveys, interviews, pilot studies across Member States.
  - *Pilot study: 4 MS*

  Example: *when a country says, "one central ethics committee," does it mean one legal entity or an administrative hub supporting several ECs?*
- Workshop Pharma.be "Sponsor feedback":

  "We receive contradictory GDPR questions → but are they really contradictions, or different ethical interpretations of data risk?"
- We have the data in CTIS we must structure and analyse it before drawing conclusions.
- Legislative reform should be thoughtful, not legislative "plumbing" —> tightening pipes without rethinking design.

ETHICS OR COMPLIANCE?

ETHICS CREEP OR COMPLIANCE CREEP?

- Our study: Many RFIs over-apply or misinterpret legal provisions.
- Ethics committees need legal support, not more legal work.
- Suggested reform:
  - Pre-check for administrative and regulatory compliance.
  - Ethics phase for substantive interdisciplinary reflection and dialogue on participant protection, autonomy, and proportionality.

Ethics as partnership, not paperwork

A EUROPEAN REFLECTION SPACE

HARMONISATION THROUGH DIALOGUE, NOT UNIFORMITY

- We need more shared knowledge on EU MREC functioning and RFI patterns: why EU ethics committees ask what they ask.
- Are differences due to dossier quality, or legitimate ethical interpretation?
- Templates like the ICF help, but flexibility remains essential.

Cultural pluralism in the ethics review is a strength, *not an obstacle*, for ethical oversight in Europe but there must be transparancy on each MS

HARMONISATION SHOULD NEVER MEAN HOMOGENISATION

CLOSING VISION

ETHICAL OVERSIGHT AS EUROPE'S INNOVATION ADVANTAGE

- No ethics washing!

We can streamline without simplifying ethics:

- The future lies in efficiency with reflection: allow (time for) discussion
- Ethics protects people, by people, and is therefore subjective, but profoundly valuable.
- Ethics must remain interdisciplinary, rooted in local culture, and open to dialogue between experts and non-experts.

It takes reflective time → not a checklist, not an AI.


Ethics is not a pause in innovative progress → it is what keeps progress human

THANK YOU!

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THE WORLD NEEDS YOU

THINKING NEVER SUBMITS, NEITHER TO A DOGMA, NOR TO A PARTY, NOR TO A PASSION, NOR TO AN INTEREST, NOR TO A PRE-JUDICE, NOR TO ANYTHING, BUT ONLY TO THE FACTS THEMSELVES, FOR MAKING IT SUBJUGATE MEANS THE END OF ALL THINKING

Henri Poincaré (1912-1854)