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# COMBINE - Update and Outcomes

Cancer Drug Development Forum – 4 Feb 2025

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**Danish Medicines Agency (DKMA)**

# Agenda

- Background of COMBINE
- Short summary of analysis phase
- Major focus on programme approach and projects in pipeline

# Implementing 3 regulations together…

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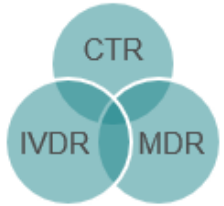
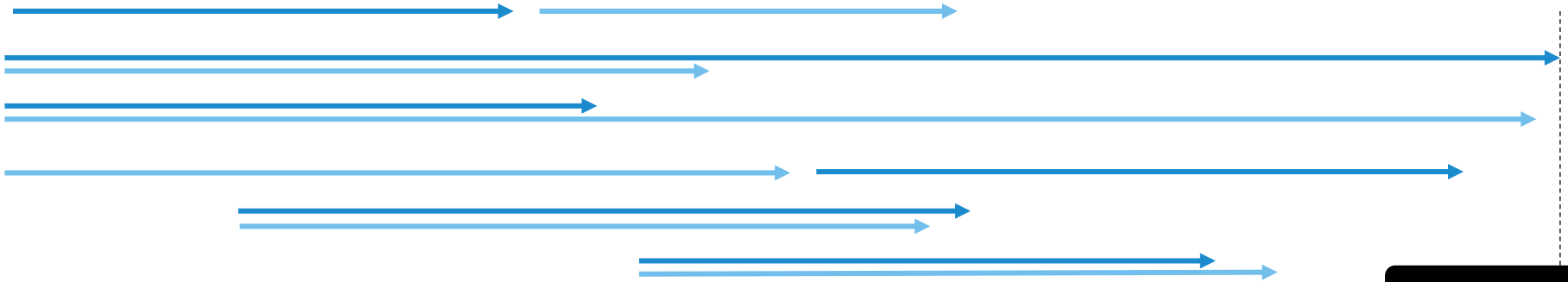
- CTR applicable since 21 January 2022: **Coordinated in CTIS**
- MDR applicable since 21 May 2021: **Not yet coordinated**. Eudamed for national CA 2027. For MS CA coordinated process 2029 (not ethics)
- IVDR applicable since 21 May 2022:





CT: CTIS – one entry with coordinated CA and ethics assessments



PS/CIE: National procedures by competent authorities (CAs) and ethics committees

*delay of CT initiation*

# Scope of ‘COMBINE’ Project

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**Combined study** (informal definition): clinical trial of a medicinal product together with a performance study of an IVD or a clinical investigation of a medical device

- The MDR, IVDR and CTR contain requirements for the respective individual authorization for clinical investigation, performance studies or clinical trials processes.

**1** **Analysis** (Sep 2023-May 2024): understand challenges and obstacles at the interface between MDR, IVDR, CTR that overlap in combined studies and propose solutions.

**2** **Development of solutions** (May 2024-): to clarify and work towards aligning the interface between clinical trials of investigational medicinal products, performance studies of in vitro diagnostics and clinical trials.

➡ Programme approach established Dec 2024

# EU Groups involved

Broad framework for collaboration across EU landscape: Commission and EU Expert groups of national competent authorities

## Clinical trials of medicines

- Clinical Trials Advisory Group (CTAG)
- Clinical Trials Coordination Group (CTCG)

## Medical devices

- Medical Device Coordination Group (MDCG)
- 2 of its 13 subgroups: IVD and CIE

## Ethics

- MedEthics EU - Voluntary coordination between national ethics committees

# Stakeholder reference group

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ACRO (Association of Clinical Research Organizations)
AMDM (Association of Medical Diagnostics Manufacturers)
Biomedical Alliance in Europe
COCIR
Conect4Children Stichting
EAN (European Academy of Neurology)
EATRIS (European Infrastructure for Translational Medicine)
ECRIN (European Clinical Research Infrastructure Network )
EUCOPE
EuropaBio
EAAR (European Association of Authorised Representatives)
EFPIA (European Federation of Pharmaceutical Industries and Associations)
EHA (European Hematology Association)
EORTC (European Organisation for Research and Treatment of Cancer)
ESMO (European Society for Medical Oncology)
MedTech Europe
MPP Association
NBCG-Med (Notified Body Coordination Group)
TEAM-NB (European Association for Medical Devices of Notified Bodies)
VE (Vaccines Europe)

# Phase 1 – Analysis of challenges

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1

## Issue List — BE

Clarify challenges that cause delays in combined studies in terms of 'scientific, procedural, legal' issues – with input from stakeholders

2

## Mapping of EU Landscape — IE

Mapping of competent authority landscape for the different regulations on MS level and parameters relevant to the CT/PS/CI application processes

3

## SE — Mapping of Relevant Activities

Mapping of work potentially related to the MDR/IVDR/CTR interface

4

## IE — Proposals for Solutions

Proposals for solutions that could address identified issues, taking into account the mapping of landscape and ongoing work

*15 MS,*
*55+ experts*
*4 functional areas*

Analysis report at Website:
Combined studies - European Commission

# Track 1 – Clusters of issues

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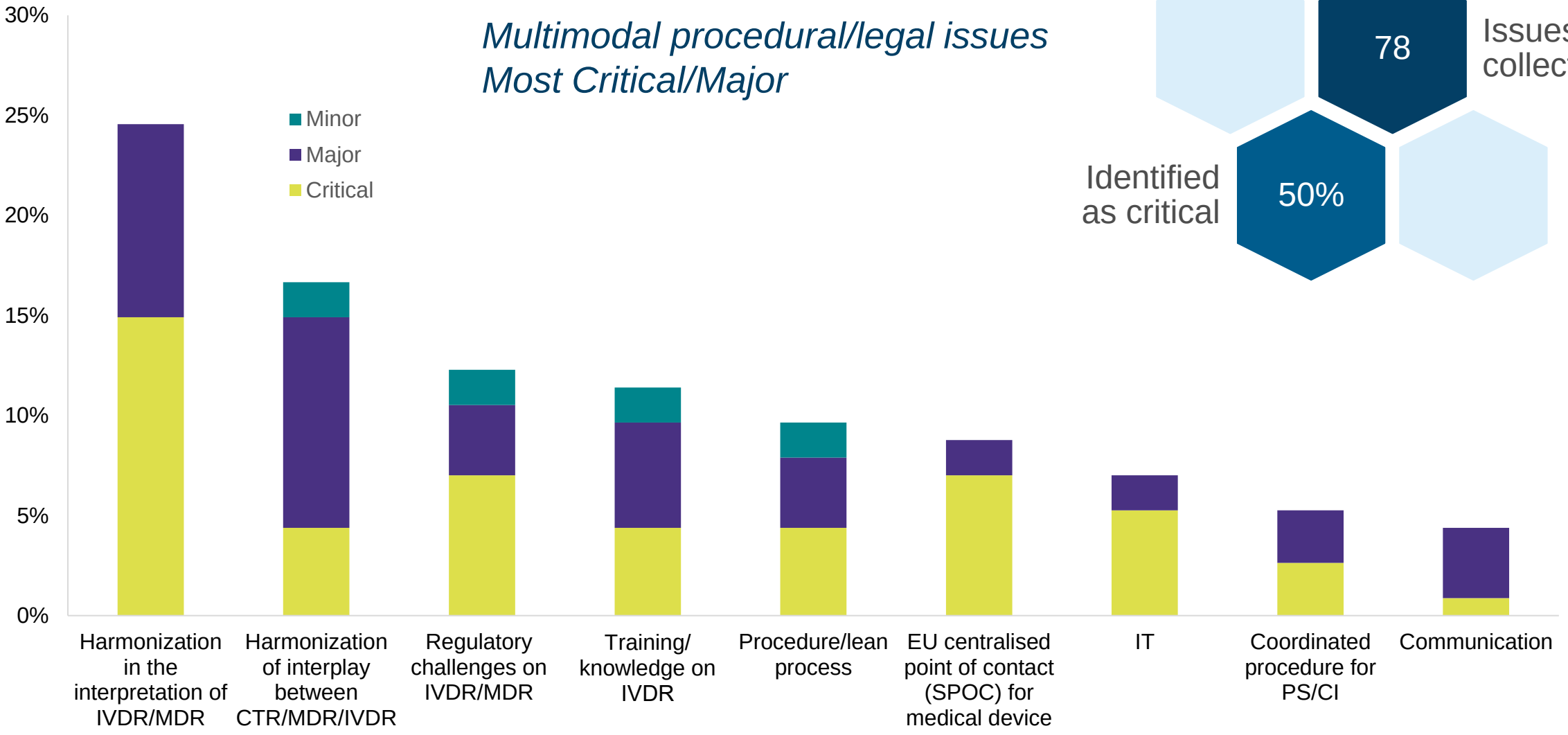
*Multimodal procedural/legal issues*
*Most Critical/Major*



# Combined study applications per year

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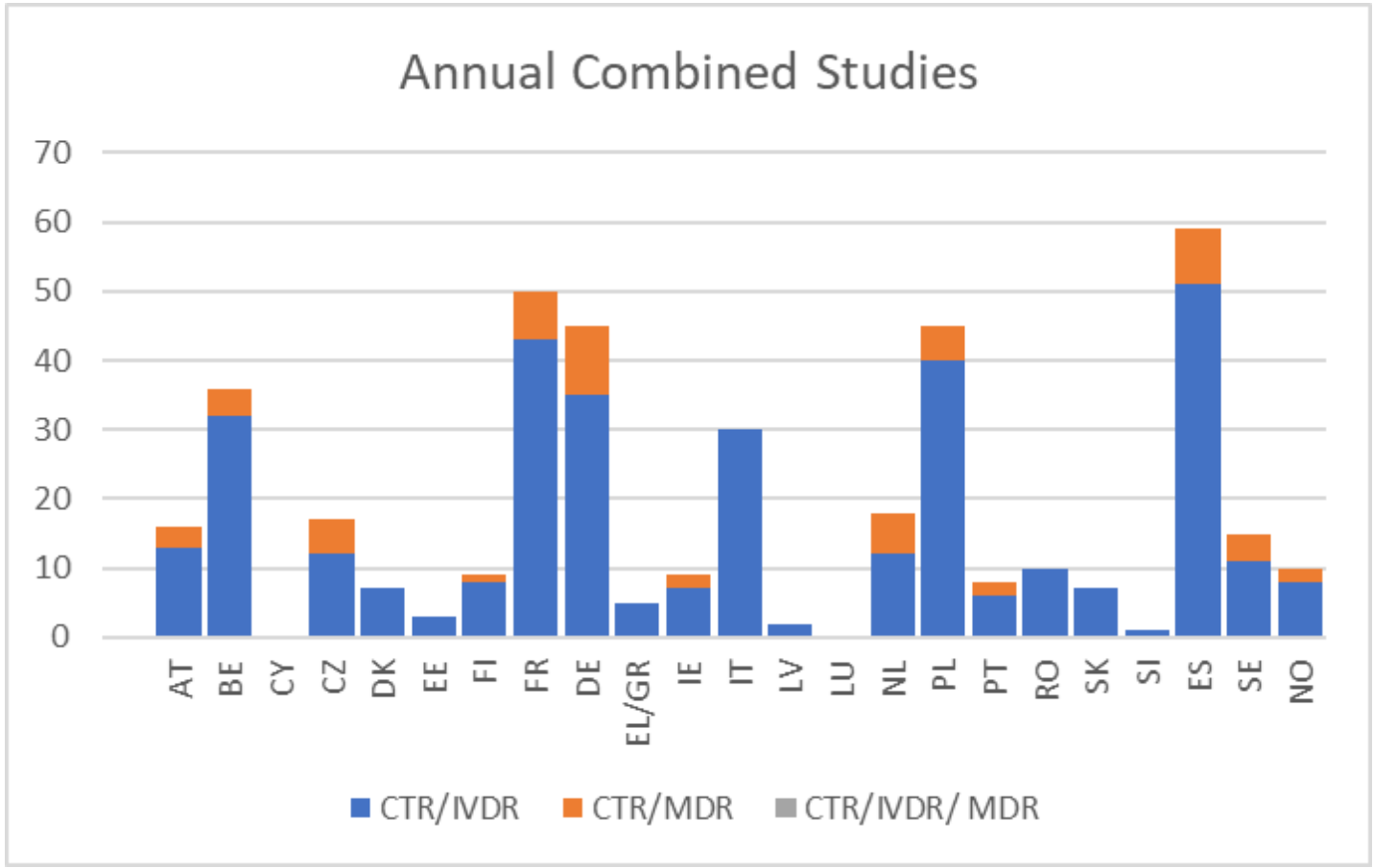
**Total: 402**




## Most combined studies and greatest overlap with CTR/IVDR

About ¾ of all performance study applications for an IVD are combined with a CT of a medicine – much less for clinical investigations for a medical device.

Most combined studies are multinational:

- CTR/IVDR: 96%
- CTR/MDR: 88%

TABLE 5: SUMMARY OF PROPOSED WORK ITEMS TO ADDRESS ISSUES FOR COMBINED STUDIES.

| Group | # | Item |
|---|---|---|
| **Coordinated Assessment** | 1.1 | CI/PS CA Coordinated Assessment |
| | 1.2 | Aligning Ethics Assessment Procedures (MS level) |
| | 1.3 | Coordination between CTR & CI/PS CA Assessment (Single Application) |
| | 1.4 | IT Infrastructure |
| **Alignment** | 2.1 | Align MS positions |
| | 2.2 | Develop Understanding |
| | 2.3 | Improve Sponsor awareness |
| **Guidance & Clarity** | 3.1 | IVDR/MDR Topics |
| | 3.2 | Common Topics |
| | 3.3 | CTR Topics |
| **Communication & Dialogue** | 4.1 | Scientific/Technical Advice |
| | 4.2 | Open dialogue/ exchange of best practice |
| | 4.3 | Training Initiatives |
| | 4.4 | Encourage creation of cross functional national teams at a member state level (CT/CI/PS) |

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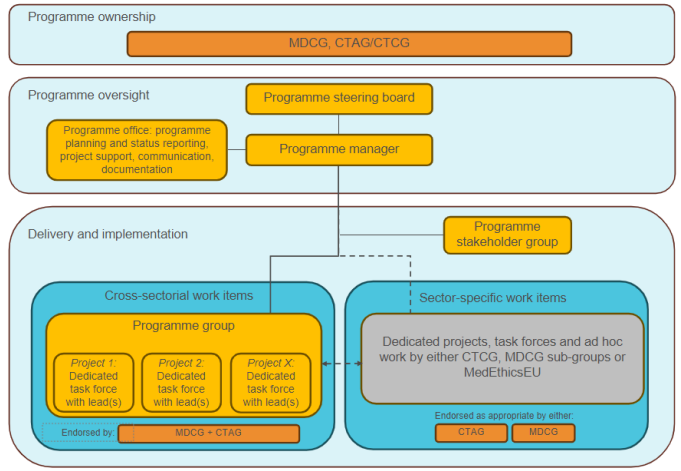
# Track 4 - proposals

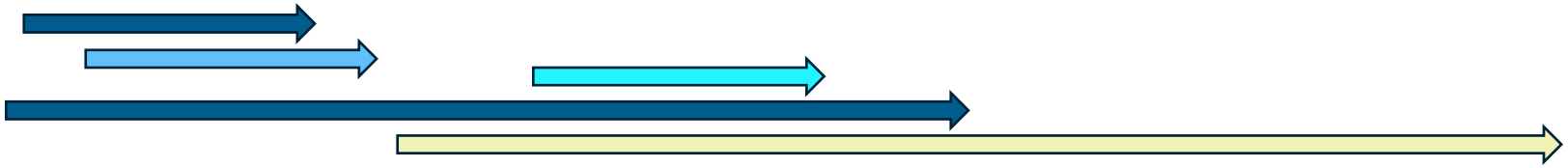
Ideas for solutions that would address most of identified issues – more than 50 individual actions proposed.

# Approach for phase 2: from project to programme




- Reorganised 51 work items into **6 cross-sector projects and 1 task + sector-specific work**
- Framework for **working across fields** with established groups where projects specific to the interface can be conducted jointly
- Continuous involvement of **stakeholder group** throughout project development
- **Stepwise progress**, checkpoints and stock-taking together as we go
- Overview of all ongoing work

## Inclusive, pragmatic, staggered



# ‘COMBINE’ programme kick-off Dec 2024

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The COMBINE programme seeks to make the European Union an attractive region to conduct combined studies, envisioning a clear and smoothly functioning regulatory environment for combined studies through broad involvement of regulators, ethics committees and all impacted stakeholders, with the ultimate goal to support availability of innovative treatments for patients.

If you want to go fast, go alone
If you want to go far, go together

Analysis report and programme strategy at Website: Combined studies - European Commission

# Transformation diagram of projects

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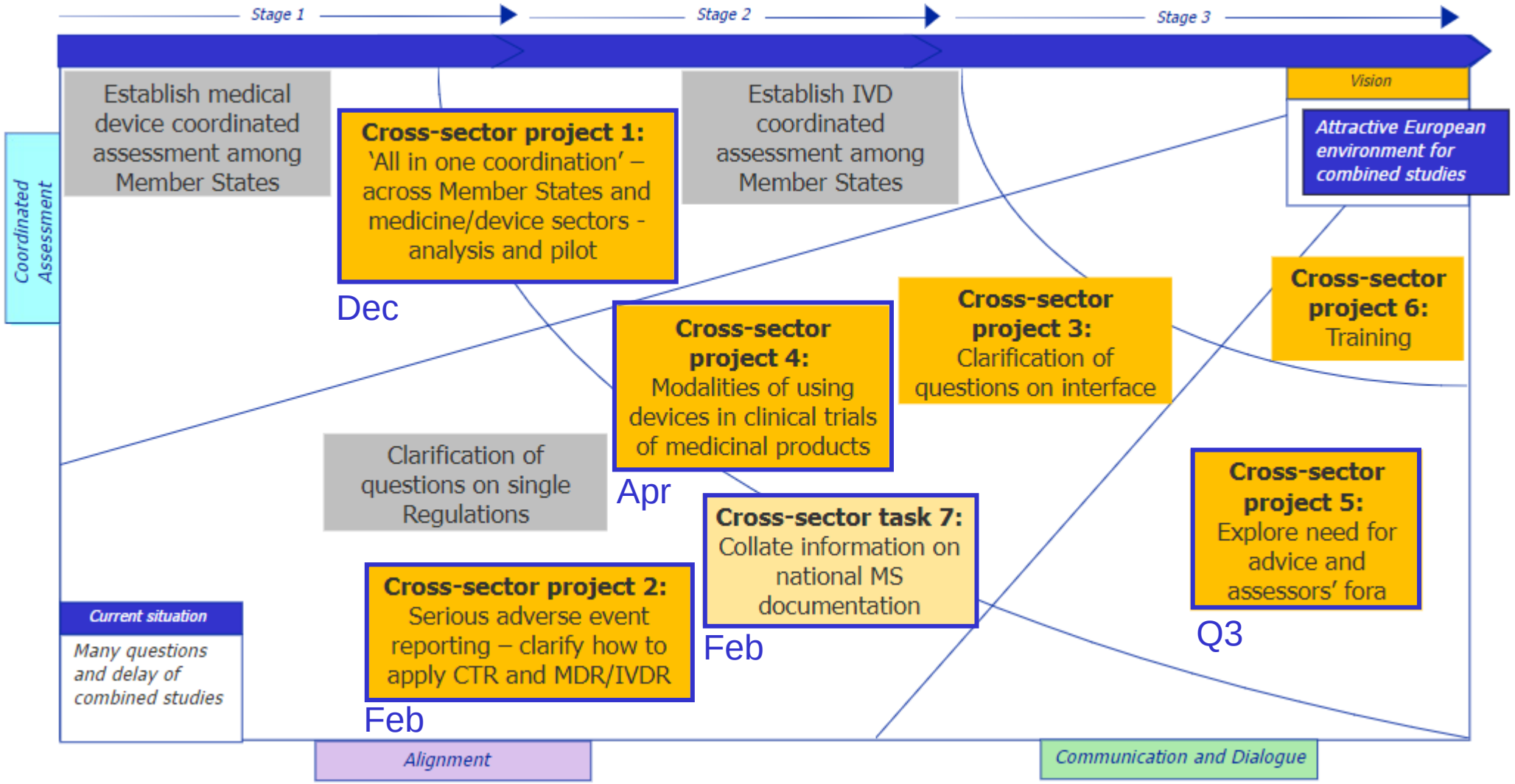


# Project 1: ‘All in one’ assessment under CTR/IVDR/MDR

**Cross-sector project 1:**
‘All in one coordination’ – across Member States and medicine/device sectors - analysis and pilot

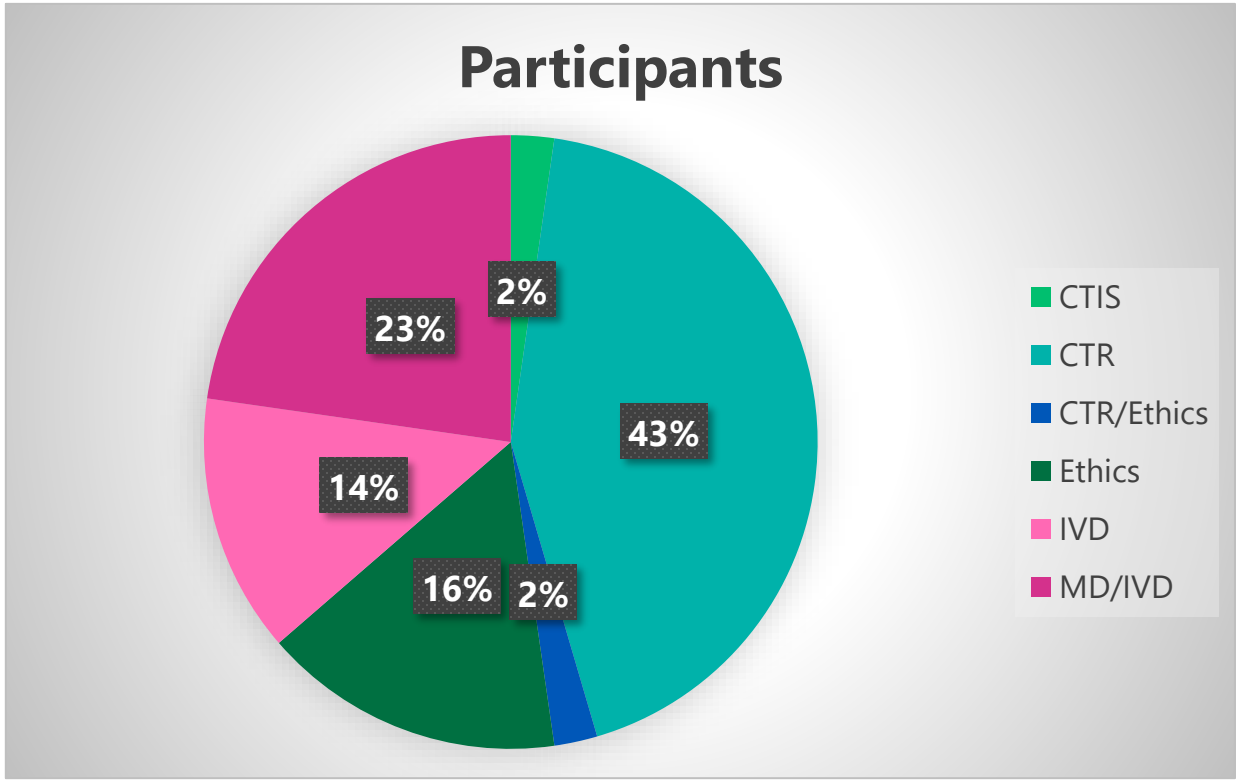
**Purpose:** to explore coordinating Member State assessments of applications for combined studies by competent authorities and ethics committees across CTR/IVDR/MDR.
Focus on most common type of combined study: CT of a medicinal product combined with PS of a companion diagnostic IVD.

- **Expected deliverables:**
  - Analyse possibilities for a voluntary multi-Member State CT/PS single procedure
  - Propose outline of a single procedure pilot
  - Establish and run pilot
  - Evaluate the results of the pilot and draw up recommendation for a voluntary single procedure for CT/PS and CT/CI combined
  - Convey learnings on IT business procedures

Project initiated Dec 2024

# Project 1

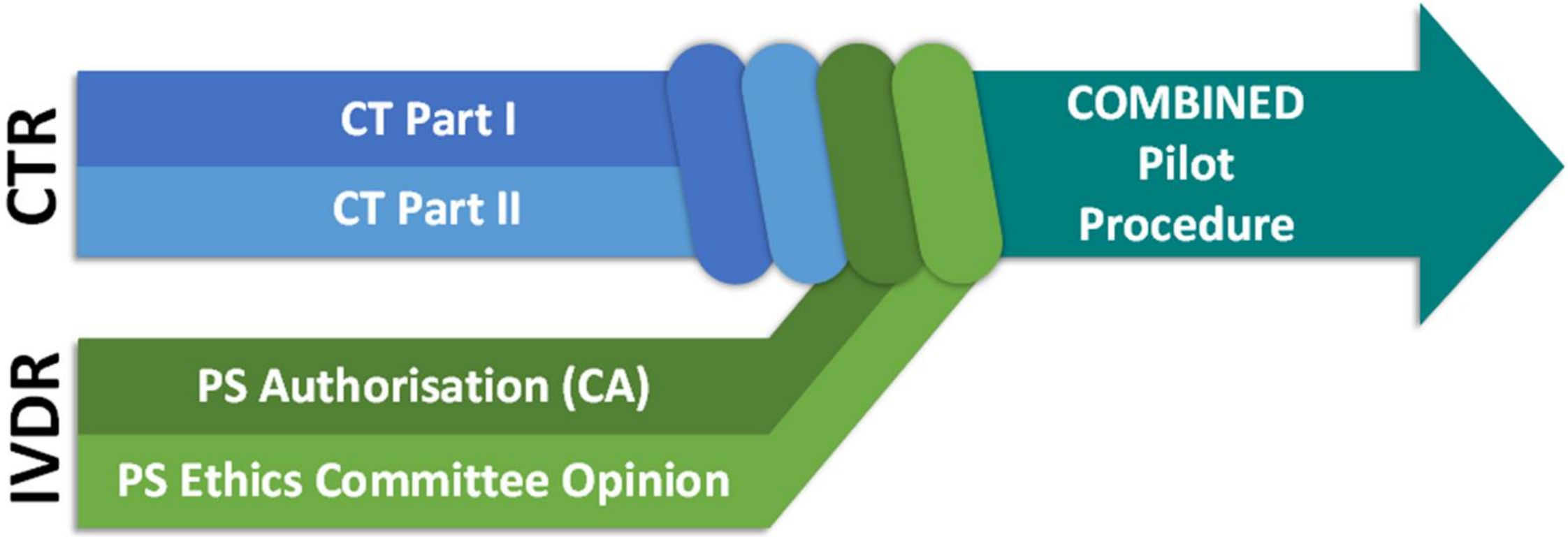
- Launched in December 2024
- Analysis work underway since Q2 2024.
- Discussions to date explored
  - Legal frameworks and current practice for CTR/IVDR
  - Similarities and differences
  - What could a pilot look like?
  - Challenges and aspects for clarification




Project 1 Group as of 24/01/25

- 44 participants
- 14 MS + EMA

# Targeted Approach



# Project 2: ‘Serious adverse event reporting across CTR/IVDR/MDR’

**Cross-sector project 2:** Serious adverse event reporting – clarify how to apply CTR and MDR/IVDR

**Purpose:** to clarify how to apply the CTR, MDR and IVDR requirements on serious adverse event reporting in combined studies

- **Expected deliverables:**
  - Comparison of safety reporting procedures under each of the three legal frameworks
  - Understand practical experience and challenges from stakeholders.
  - Suggestion for solution of identified issues e.g. a guidance document text.

Project initiated Feb 2025

# Project 4: ‘Modalities of using devices in clinical trials of medicinal products’

**Cross-sector project 4:** Modalities of using devices in clinical trials of medicinal products

**Purpose:** to explore different modalities of using medical devices and IVDs in clinical trials of medicinal products, in order to clarify applicable regulatory context for those devices and IVDs.

- **Expected deliverables:**
  - A set of scenarios for using and/or investigating medical devices and IVDs in clinical trials of medicinal products.
  - Clarification of the regulatory framework applicable to each scenario.

If appropriate, a guidance document or similar tool to clarify the regulatory context for some or all of those scenarios. One possibility is the update and expansion of MDCG 2022-10.

Project initiated Apr 2025

# Task 7: ‘Info on national requirements’

**Cross-sector task 7:** Collate information on national MS documentation

**Purpose:** to 1) take stock of feedback from stakeholders on different Member State practices for documentation requirements and 2) to develop understanding of national requirements for applications by facilitating sponsor access to this information.

**Expected deliverables:**

- Collation of feedback from stakeholders gathered during analysis on different Member State practices on documentation, sharing with relevant Member State expert groups.
- Communication to Member States to encourage to make information available to sponsors on national requirements that impact combined studies.
- Collection and publication of a set of links to national websites with requirements for combined studies

Task initiated Feb 2025 by Commission

# Project 5: ‘Explore need for advice and assessors’ fora’

**Cross-sector project 5:**
Explore need for advice and assessors’ fora

**Purpose:** to explore needs and opportunities for offering advice to sponsors and for exchange of best practice among assessors.

**Expected deliverables:**

- Clarify sponsor needs for advice, assessment of which elements of those needs are covered by existing mechanisms for advice, and proposals for how gaps could be addressed.

- Clarification of competent authority and ethics committees’ needs for fora to exchange experience and best practices as regards combined studies, assessment of which elements of those needs are covered by existing fora and proposals for how gaps could be addressed.

Project initiated Q3 2025

# Outlook - programme approach

- Brings parties together across sectors
- Active participatory roles, intended to address needs
- Aims to facilitate implementation
- Tests new ways of working
- Will inform possible future policy development

*More information:*

*Combined studies - European Commission (europa.eu)*

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# Thank you
# Any questions?

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