‘COMBINE’ project

- analysing the regulatory landscape for combined studies on the IVDR/MDR/CTR interface

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SANTE D.2 Unit Medical Products

SANTE D.3 Unit Medical Devices

Last update: March 2024

Abbreviations key

- CTR – Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use
- MDR – Regulation (EU) 2017/745 on medical devices
- IVDR – Regulation (EU) 2017/746 on *in vitro* diagnostic medical devices
- MD – medical device
- IVD – *in vitro* diagnostic medical device
- CT – clinical trial (of a medicinal product)
- CI – clinical investigation (of a medical device)
- PS – performance study (of an *in vitro* diagnostic medical device)
- MS – Member State of the European Union
- CA – competent authority (of a Member State)

Background

- Competent authorities in the field of clinical trials are receiving an increasing number of questions on how to handle the design and the submission of clinical trials involving candidate investigational medicinal products and medical devices/IVDs.
- Competent authorities for medical devices have been receiving analogous questions.
- Several stakeholder organisations have reached out to the European Commission with concerns regarding delays in conducting combined studies in the EU due to the complexity of the regulatory interplay among the Clinical Trials Regulation (CTR) and either the In Vitro Diagnostics Regulation (IVDR) or the Medical Device Regulation (MDR).
- The topic was identified as a priority during the ACT EU multistakeholder platform workshop held on 22-23 June 2023.

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.

Scope of ‘COMBINE’ Project

- The MDR, IVDR and CTR contain requirements for the respective individual authorization for clinical investigation, performance studies or clinical trials processes.
- Combined studies are commonly conducted and are important to ensure that innovative treatments are available to patients. The interaction of procedures is posing a challenge and smoother interplay between these Regulations would reduce burden on sponsors.
- Scope of analysis phase: understand challenges and obstacles on the way to alignment of the three frameworks (MDR, IVDR, CTR) that overlap in combined studies and propose solutions.
- Scope of project (long-term): clarify and align interface between clinical trials of investigational medicinal products, performance studies of in vitro diagnostics and clinical investigations of medical devices.

1	**Analysis of the challenges** at the interface between MDR, IVDR, CTR
2	**Possible development of solutions** that aim to align the interface

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Analysis phase - understanding challenges and obstacles

1

Issues List

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

2

Mapping of EU Landscape

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

3

Mapping of Relevant Activities

Mapping of work potentially related to the MDR/IVDR/CTR interface
(e.g. poss. update of Q&A on interface IVDR/CTR (DK)
devt of Q&A on performance studies (lead: SE), etc.)

4

Proposals for Solutions

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

The outcome of the analysis phase will be a document describing the three analysis elements and the proposed solutions.

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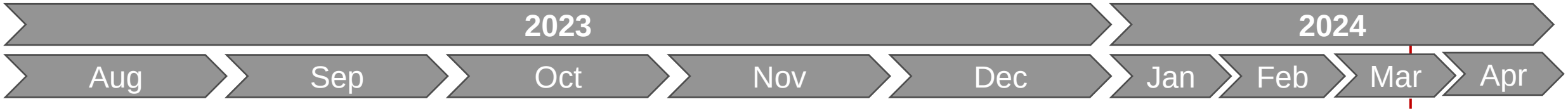
High-level timeline for analysis phase



PHASE 1

1. Issue list
2. Mapping of IVDR/MDR/CTR EU landscape
3. Mapping of relevant activities
4. Proposals for solutions

Deliverable: document describing 3 analysis elements & proposed solutions

Preparation for phase 2

Planning for possible development of solutions

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Actors involved

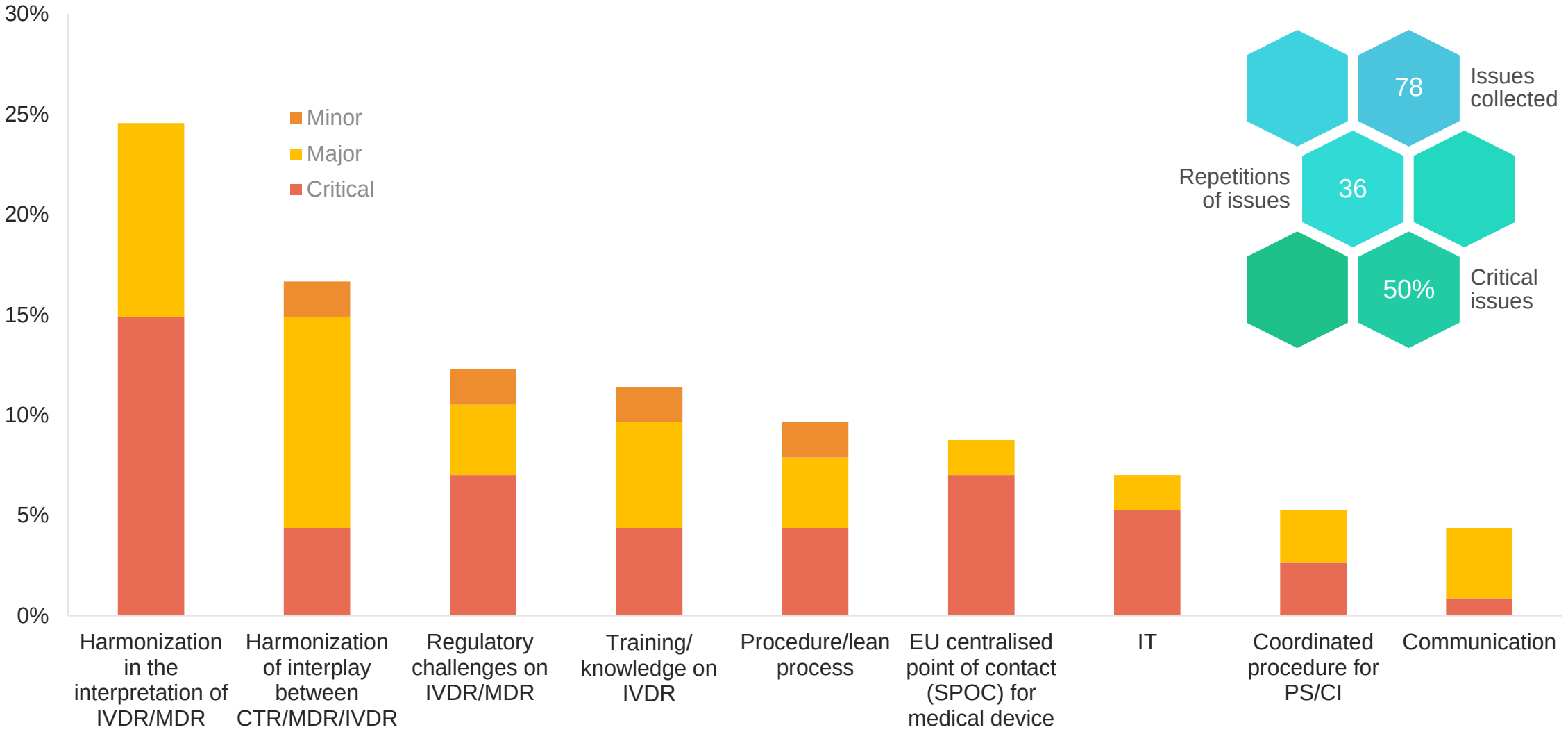
15 countries,
55+ experts
4 functional areas

- Project group involving competent authorities from CT, MD and IVD field, medical research ethics committee representatives and the EMA
- Stakeholder reference group spanning CT, MD and IVD sectors, patients and clinical professionals.
- Steering board of competent authorities and European Commission
- Outcomes to be endorsed by the relevant authority groups (Medical Device Coordination Group, relevant Clinical Trials groups)

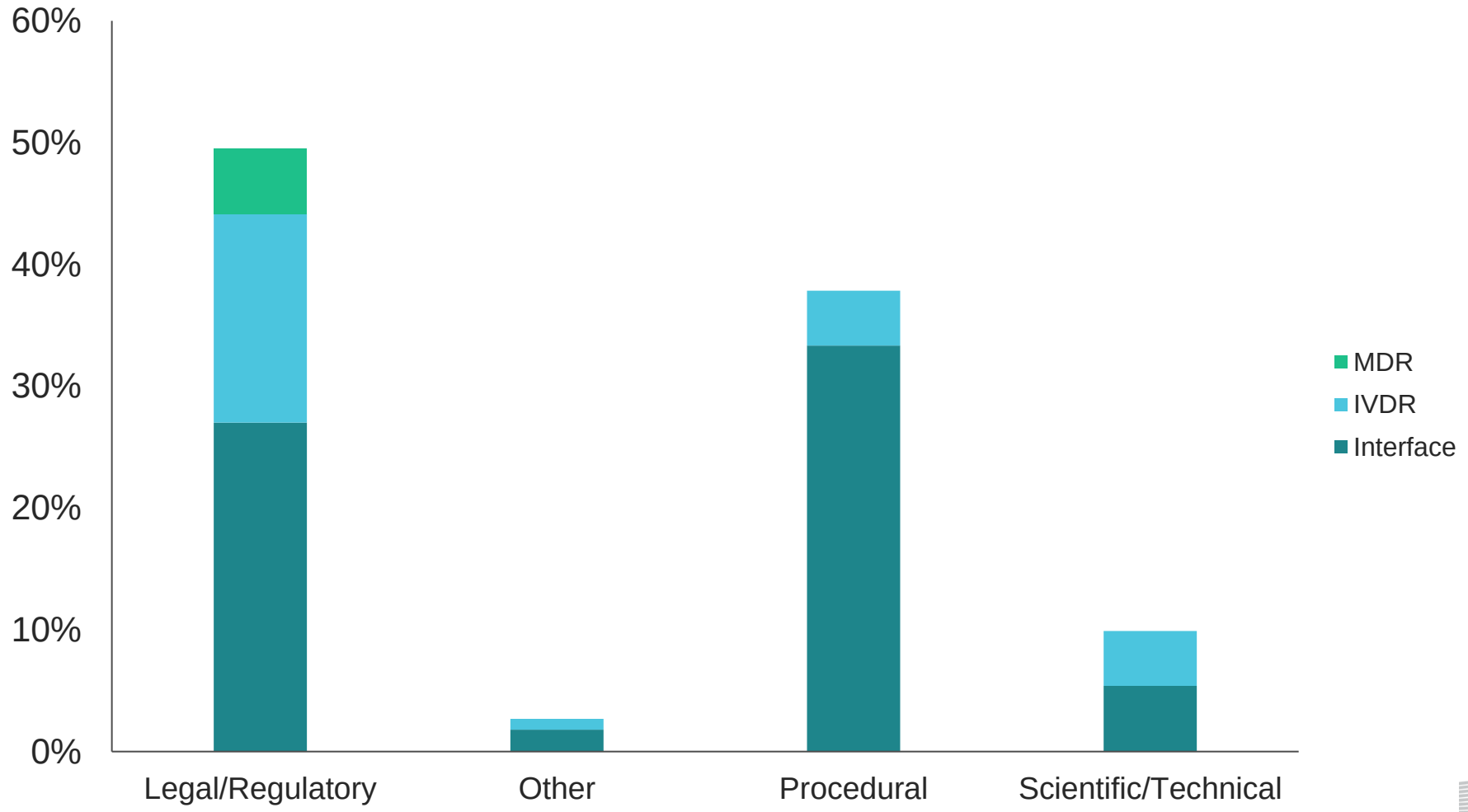
Stakeholder reference group

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)
EPF (European Patients' Forum)
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)

Track 1 – Outcome – Clusters of reported issues



Track 1 – Outcome – Nature of reported issues



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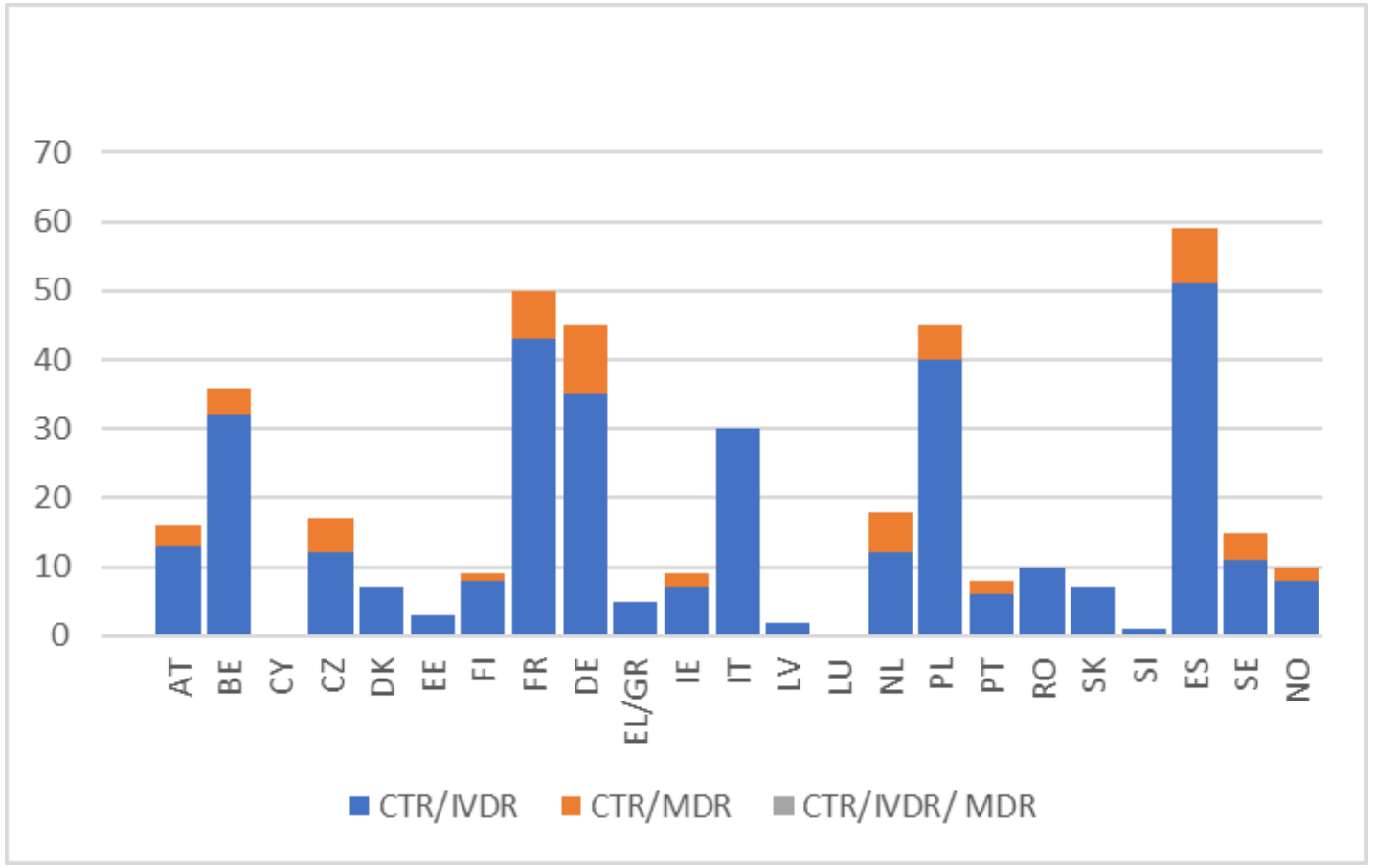
Track 2 – Mapping EU landscape

- Map competent authority landscape for the different regulations on MS level and parameters relevant to the CT/PS/CI processes
- 21 Questions, 3 further questions
- 5 Major themes
    - Competent Authorities
    - Ethics committees
    - Processes in each MS
    - National legislation
    - Communication between sponsors/CA's/ethics and indication of volume of studies
- 24 countries replied

Total combined studies applications per year

(collected in late 2023)

Total: 402



≠ number of combined studies – many studies are multi-country

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Track 2 - Survey highlights

- The same regulator deals with clinical trials of medicines, clinical investigations of medical devices and performance studies of IVDs in **61%** of responding Member States.
- Similarly, **61%** of Member States have established at least one ethics committee entity that can give an opinion on all three types of study.
- **57%** of Member State competent authorities offer advice to sponsors of combined studies prior to application.
- **36%** of Member States competent authorities offer pre submission meetings prior to the application of combined studies (**70%** of these free of charge)
- A single ethics application can be made for combined studies involving clinical trials in **14%** of responding Member States.
- Currently **no** Member State accepts a single competent authority application for combined studies which involve a clinical trial.

Track 3 – Mapping existing work

- Objective to map existing and ongoing work potentially related to the MDR/IVDR/CTR interface
  - List created with published or draft official documents, from EU groups or national member states, that could be relevant to combined studies.
    - Some general guidance about CTR, MDR & IVDR respectively + material that relates to combined studies
    - Including relevant material from external stakeholders.
  - In English language only.

Track 4 – Analysis and proposals for solutions

Draft COMBINE Analysis Report

- Introduction
- Track 1: Issues
- Track 2: EU Mapping
- Track 3: Mapping relevant activities
- Track 4: Analysis
- Proposed Direction
- Annexes
- Appendix: Issues List

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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)

These are ideas for solutions that would address most of identified issues.

To be addressed **after** the analysis phase:
- prioritisation
- selection
- concrete plans for implementation

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Next steps for ‘COMBINE’

<u>Scope of analysis:</u> understand enough about issues to set direction for project plans to solve the issues.

Challenging to manage many work items in one project – recommend stepwise approach

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Next steps for ‘COMBINE’

- Analysis phase report to be endorsed by Member States and published on Commission webpage in April 2024
- Preparation and planning of next phase (in the form of a stepwise approach) - to be agreed and endorsed by Member States (~Q2 2024).

→ **Plan** to provide overview of ongoing activities and basis for prioritization and coordination of new activities in the area of combined studies across expert groups.

→ **Framework to collaborate** across stakeholders leveraging the established structure in the ‘COMBINE’ project ensuring multi-stakeholder input to solutions.

More information on ‘COMBINE’ webpage :
Combined studies - European Commission (europa.eu)

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