Bundesamt für Sicherheit im Gesundheitswesen
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The COMBINE project: **Interface between medicines and medicinal products**

Enpr-EMA 2 October 2024, presented by Dr. Marianne Lunzer

AGES MEA, Department Clinical Trials

Background

- 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.

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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 project (long-term): clarify and work towards aligning the interface between clinical trials of investigational medicinal products, performance studies of in vitro diagnostics and clinical investigations of medical devices.
- 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.

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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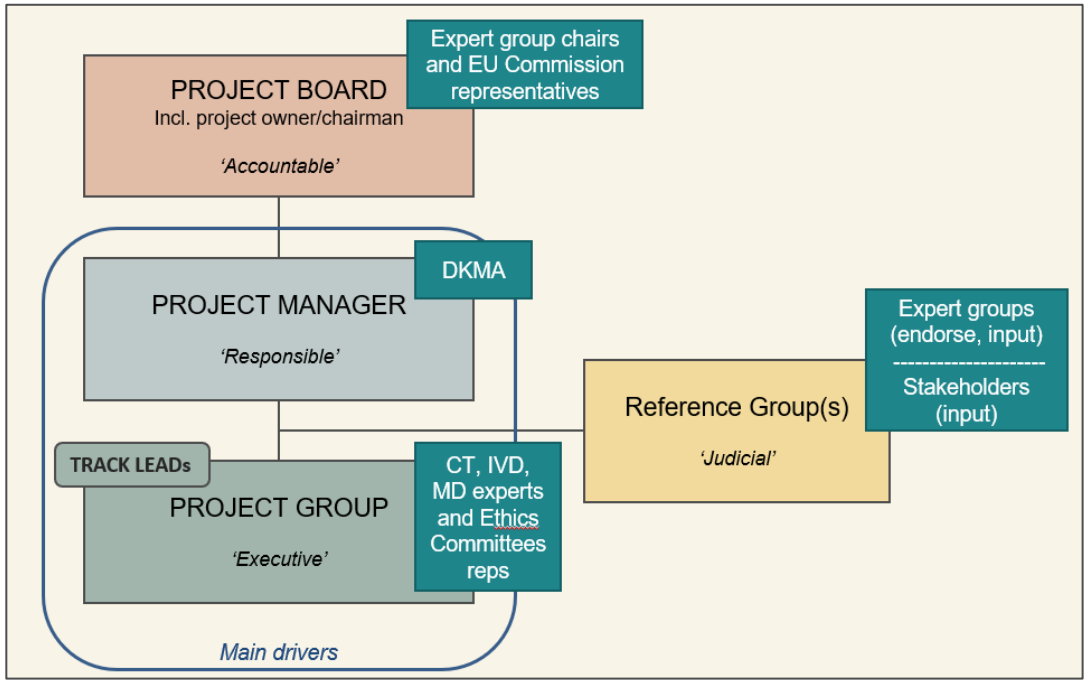
Actors involved - strategy project approach



- **Project group** involving **competent authorities from CT, MD and IVD field**, **medical research ethics committee** representatives and the **EMA**
  - **Mandate:** Outcomes to be endorsed by the **relevant EU authority groups** (MDCG, CIE WG, IVD WG, CTAG, CTCG, MedEthicsEU)
  - **Stakeholder input: Stakeholder reference group** spanning CT, MD and IVD sectors, patients and clinical professionals.
  - **Steering board** of competent authorities and European Commission – **expert group chairs.**

15 MS, 55+ experts 4 functional areas

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‘COMBINE’ project group – cross-functional/MS

Project group	EU group representative	Country
Ugur Erman	CIE WG; IVD WG	DK
Nebojsa Serafimovic (Nebo	CIE WG	AT
Benedicte Nuyttens - altern	CIE WG	BE
Steve Eglem	CIE WG	BE
Kristin Jøranli Astrup	CIE WG	DK
CIE expert	CIE WG	ES
Gearóid O'Connor	CIE WG	IE
CIE expert	CIE WG	PT
CIE expert	CIE WG	PT
Mariana Madureira	CIE WG; IVD WG	PT
Jeroen Poels - Ranya Mouda	IVD WG	BE
Laura van Diepen	IVD WG	DE
Ulf Schriever	IVD WG	DE
Morten Sichlau Bruun	IVD WG	DK
IVD expert	IVD WG	ES
IVD expert	IVD WG	ES
Sarah Madrieres	IVD WG	FR
Philip Kelly	IVD WG	IE

Project group	EU group representative	Country
Michelle Fonteyne	Ethics Committees	BE
Helle Christiansen	Ethics Committees	DK
Solveig Nordahl Jacobsen	Ethics Committees	DK
Ethics Committee member	Ethics Committees	ES
Janica Juvonen	Ethics Committees	FI
Jean-Marc Davy	Ethics Committees	FR
Pierre-Henri Bertoye	Ethics Committees	FR
Ethics Committee member	Ethics Committees	FR
Virginie Rage-Andrieu	Ethics Committees	FR
Chita Murray	Ethics Committees	IE
Laura Mackey	Ethics Committees	IE
Louise Houston	Ethics Committees	IE
Ethics Committee member	Ethics Committees	NO
Helena Kames Kjeldgaard	Ethics Committees	NO
Marianne Carson	Ethics Committees	NO
Tina Majonen	Ethics Committees	SE
Jadranka Boturović Ponikva	Ethics Committees	SI
Marjeta Zorman Terčelj	Ethics Committees	SI
Ethics Committee member	Ethics Committees	DE
Guido Grass	Ethics Committees	DE
Wolfgang Berdel	Ethics Committees	DE
Lucía Arellano	Ethics Committees	ES
Eunika Książkiewicz	Ethics Committees	PL
Maria Alexandra Ribeiro	Ethics Committees	PT
Ethics Committee member	Ethics Committees	RO

Project group	EU group representative	Country
Anne Lenaers	CTCG	BE
Hilke Zander	CTCG	DE, PEI
Jörg Engelbergs	CTCG	DE, PEI
Lene Grejs Petersen	CTCG	DK
Marita Kailajärvi	CTCG	FI
Corinne Kiger	CTCG	FR
Francisca Menezes	CTCG	PT
Gunilla Andrew-Nielsen	CTCG	SE
Stina Löfling	CTCG	SE
Monique Al	CTCG, MedEthicsEU	NL
Ilona Reischl	CAT chair	AT
Noemie Manent	EMA	EMA
Stiina Aarum	EMA	EMA

15 MS,
55+ experts
4 functional areas

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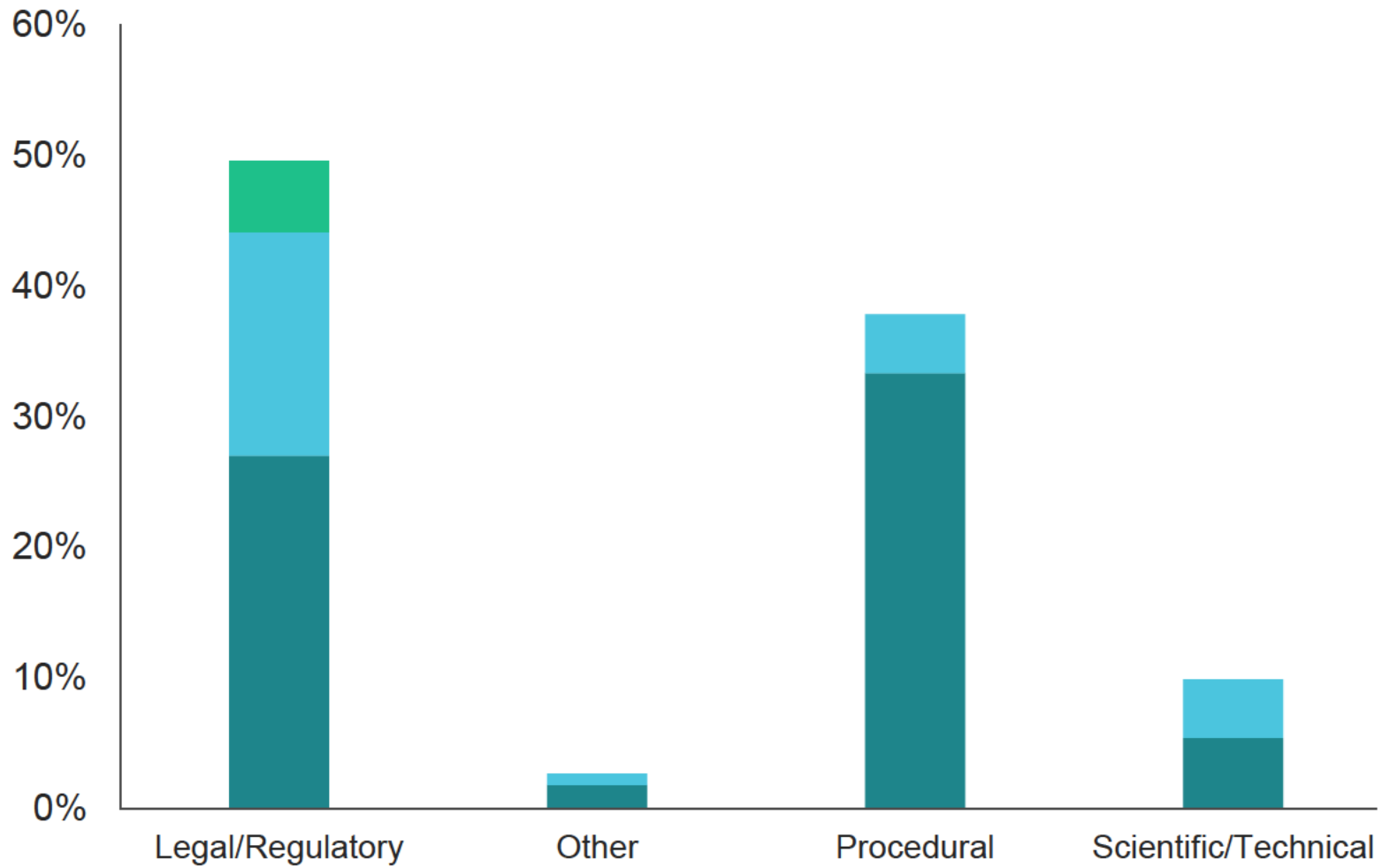
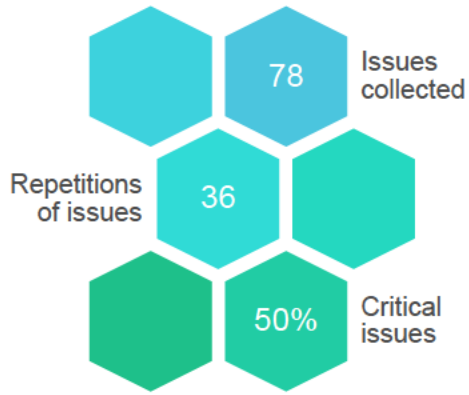
Stakeholder reference group

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 – Nature of issues



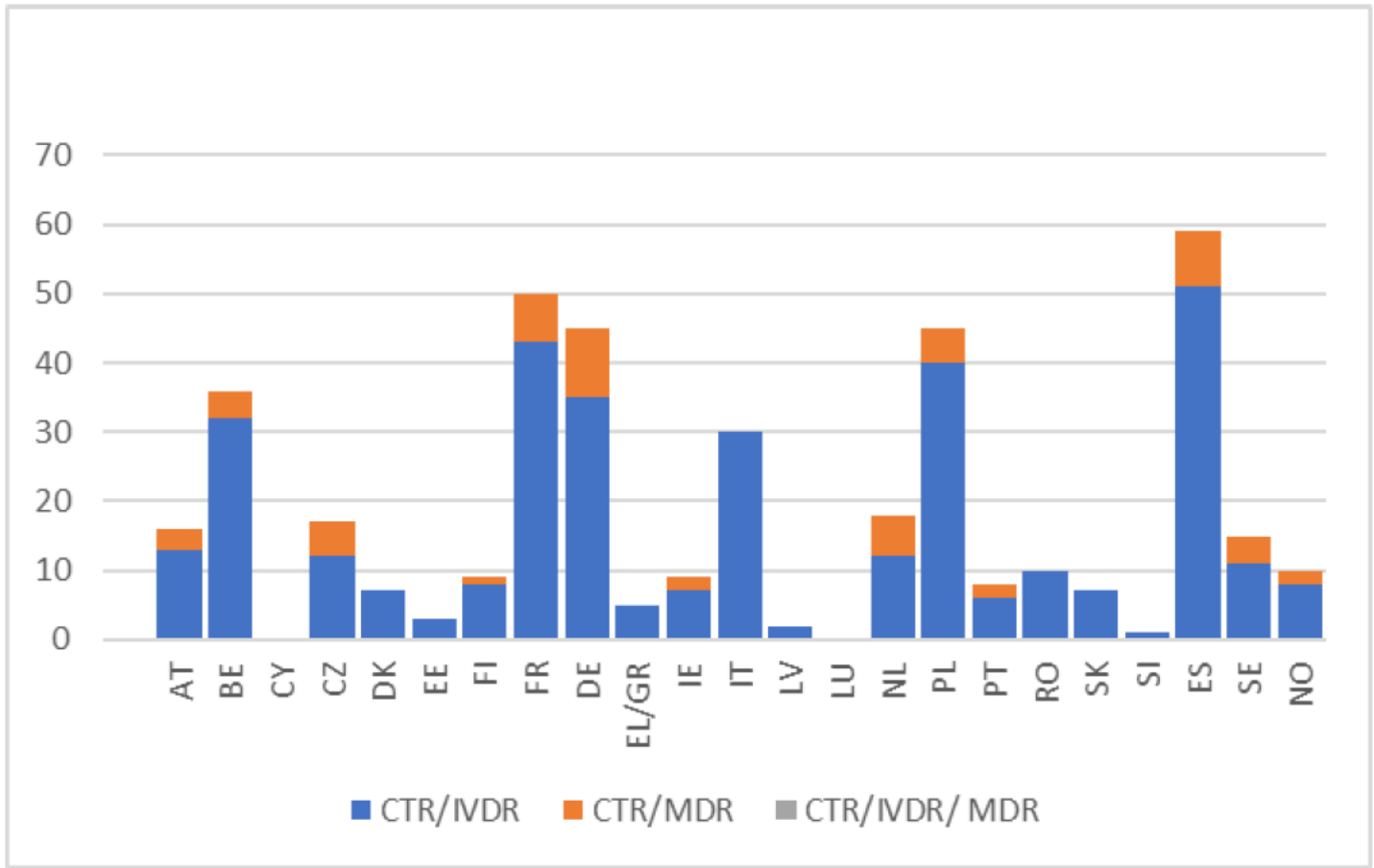


→ Multifaceted challenges

→ Predominantly major/critical

Total combined studies applications per year

Total: 402



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

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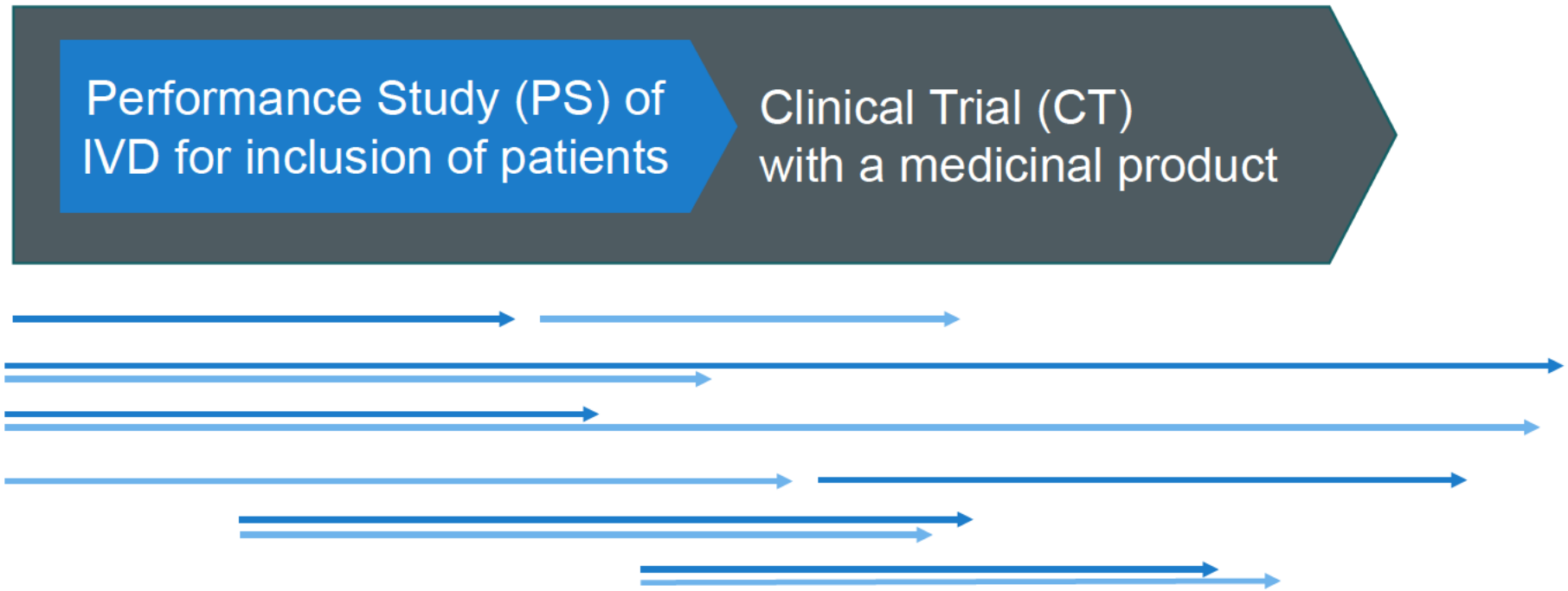
Survey highlights

- The same regulator deals with CI's, CT's and PS's 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.

Group	#	Item
Coordinated Assessment	1.1	CI/PS Competent Authority Coordinated Assessment
	1.2	Aligning Ethics Assessment Procedures (Member State level)
	1.3	Coordination between CTR & CI/PS Competent Authority Assessment
	1.4	IT Infrastructure (interim as well as long-term)

Example of multinational combined study (CT/PS) in 6 Member States:



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

PS/CIE: National procedures by competent authorities (CAs) and ethics committees – currently no coordination

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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.

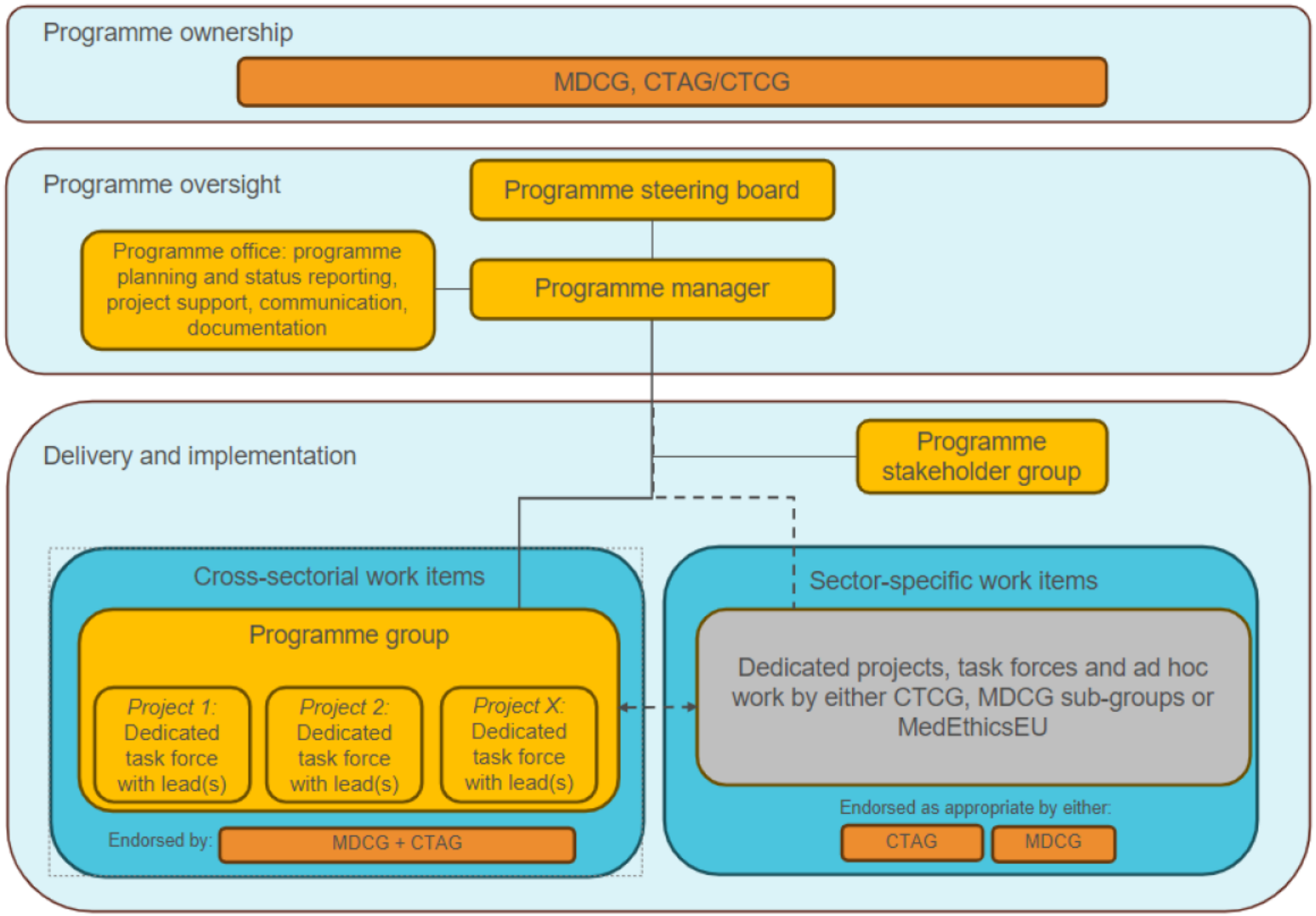
Analysis | Plan | Development of solution | Step-wise approach | Implementation

Too much work to manage in one project – recommend step-wise approach

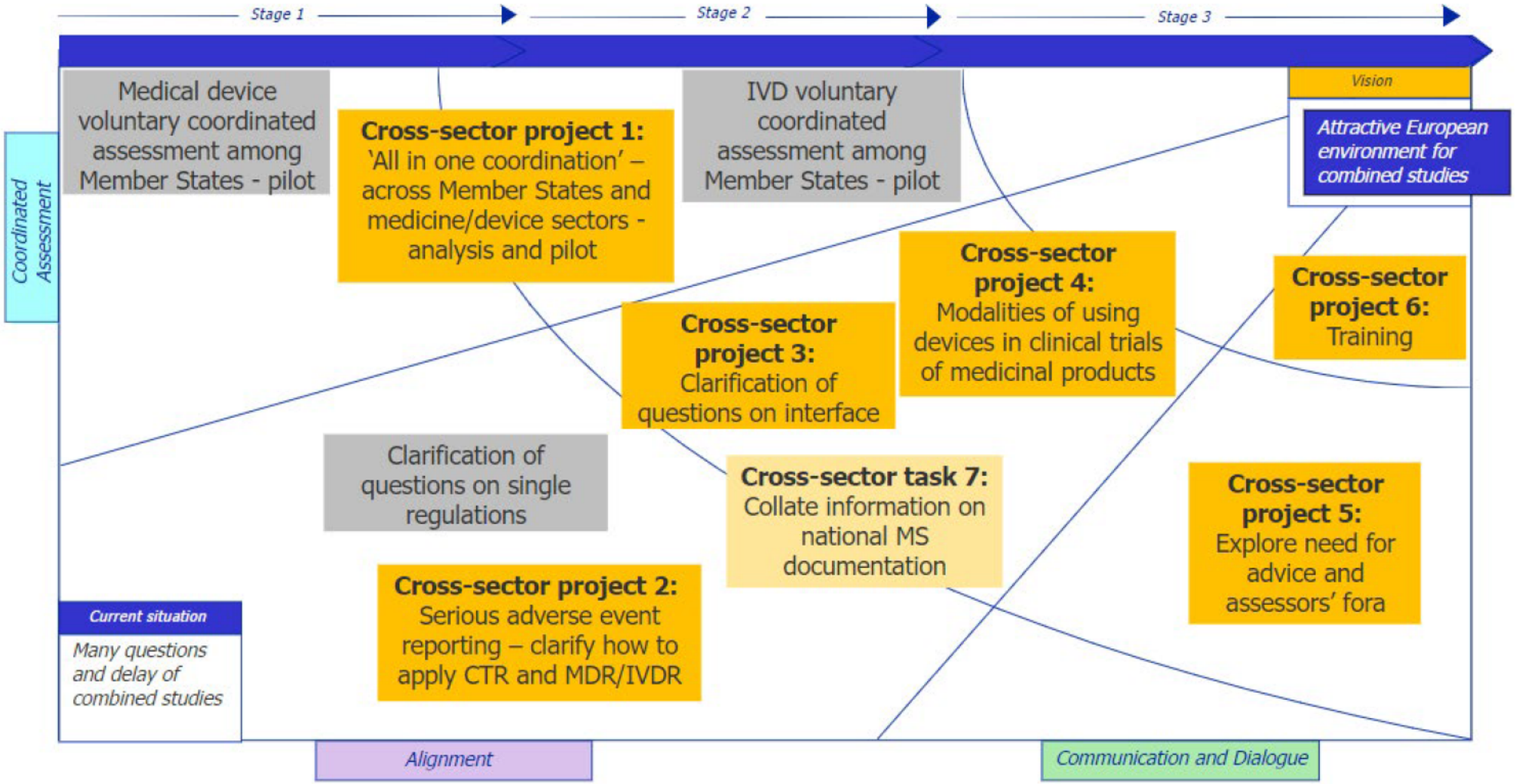
DRAFT programme organisation

Still leverage stakeholder input

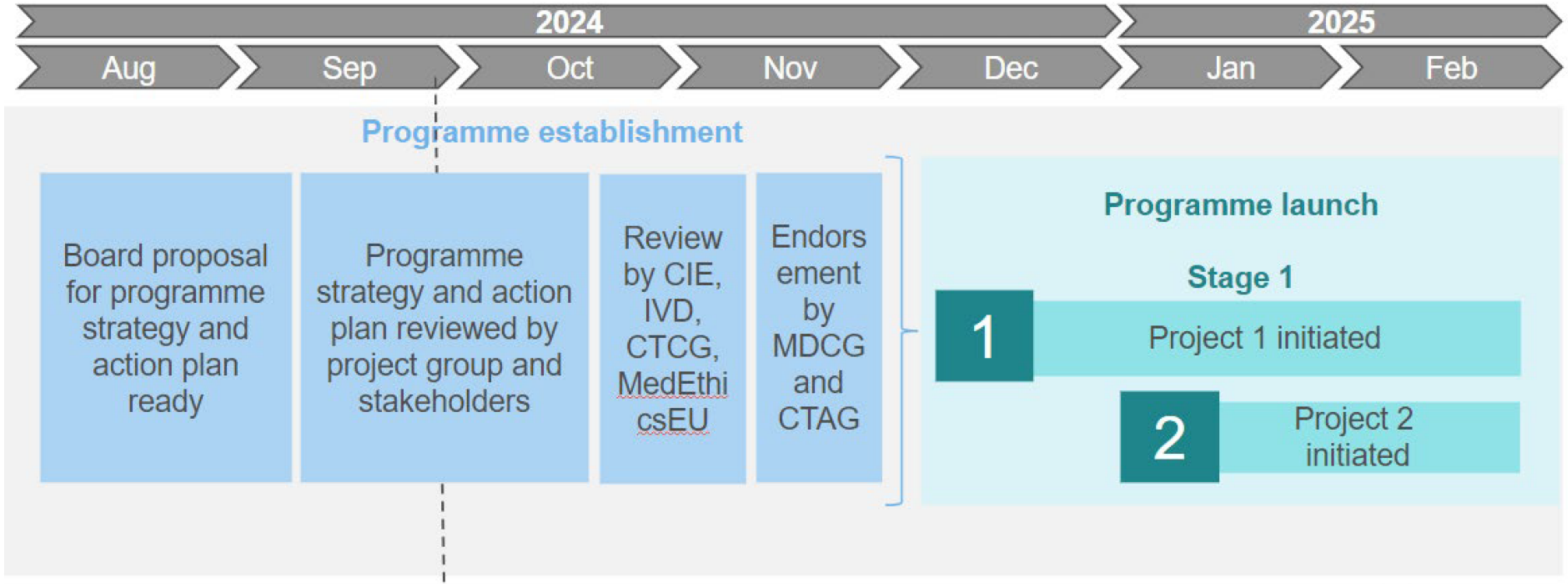
Work split into ‘cross-sector’ and ‘sector-specfic’



DRAFT overview of action plan



High-level timeline



Next steps for ‘COMBINE’

- Currently reshaping collaboration into step-wise program approach
  - to be agreed and endorsed by the expert groups (Expected launch: Dec).

More information and analysis report on ‘COMBINE’ webpage: [Combined studies - European Commission (europa.eu)]

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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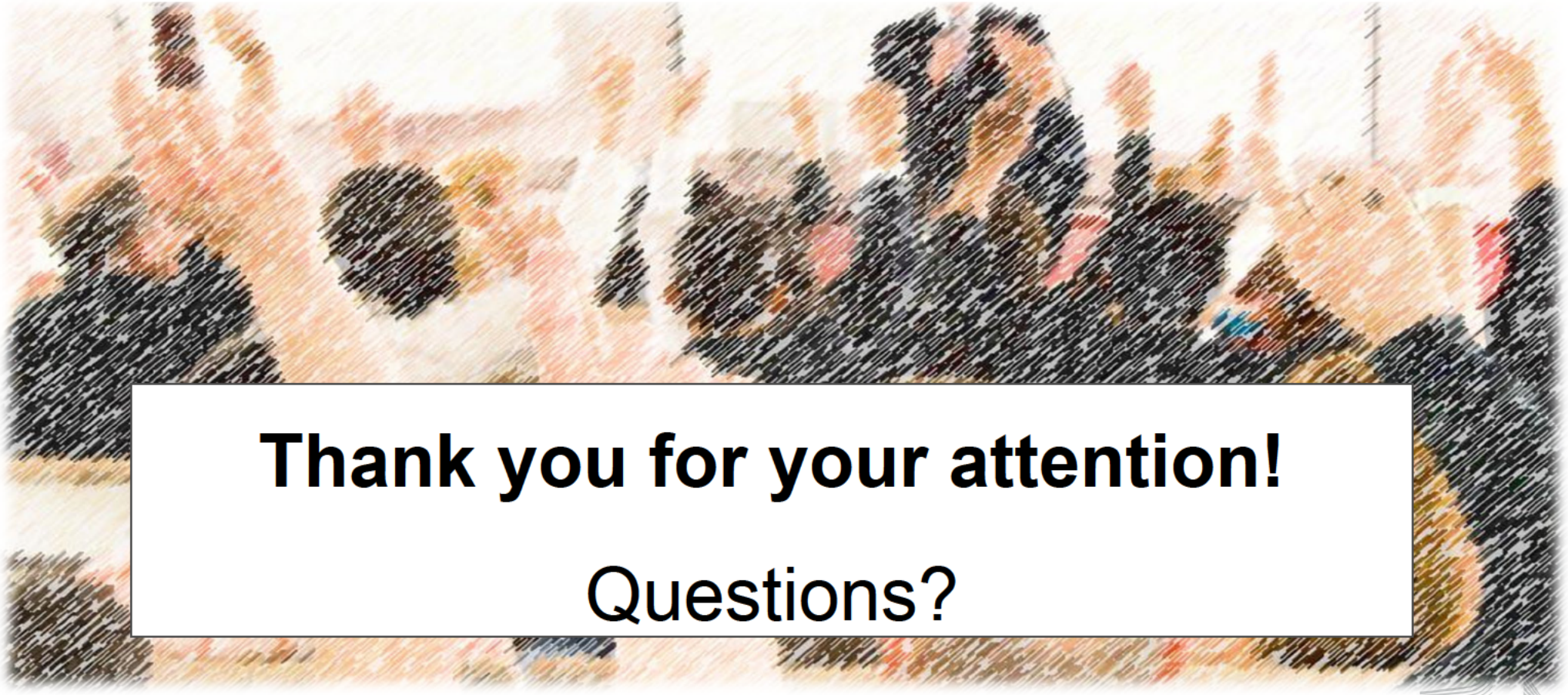
Thanks to the European Commission for supporting the presentation with the core slide deck and the programme office for additional input



Thank you for your attention!

Questions?

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