COMBINE

CTR-IVDR-MDR

ANALYSIS PHASE REPORT

Further information on the Health and Food Safety Directorate-General is available on the internet at: http://ec.europa.eu/dgs/health_food-safety/index_en.htm

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Abbreviations

ACT EU: Accelerating Clinical Trials in the EU

CIE: Clinical Investigation & Evaluation Working Group

CI: Clinical Investigation

CT: Clinical Trial

CTAG: Clinical Trials Coordination and Advisory Group

CTCG: Clinical Trials Coordination Group

CTEG: Expert Group on Clinical Trials Expert Group on Clinical Trials

CTR: Clinical Trials Regulation[1]

EMA: European Medicines Agency

HMA: Heads of Medicines Agency

IMP: investigational medicinal product

IVD(s): In vitro diagnostic medical device(s)

IVDR: In-Vitro Diagnostic Medical Devices Regulation[2]

IVDWG: In Vitro Diagnostic Medical Devices Working Group

MDCG: Medical Devices Coordination Group

MDR: Medical Devices Regulation[3]

PS: Performance study

[1] Regulation (EU) 2014/536 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 (OJ L 158, 27.5.2014, p. 1).

[2] Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU (OJ L 117, 5.5.2017, p. 176).

[3] 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 (OJ L 117, 5.5.2017, p. 1).

1. Foreword

The COMBINE project was initiated in response to the growing number of challenges identified when conducting combined studies[4] in Europe. In addition to challenges identified by competent authorities for medicines and medical devices a number of organisations representing interests across the healthcare sector voiced concerns regarding the complexity experienced when navigating multiple Regulations simultaneously. Notably this could create delays in starting clinical research and if left unresolved could impact innovation, availability of novel therapeutics and health care products for patients within Europe.

In response to these concerns the 'COMBINE' project was initiated with the goal to make EU more attractive to conduct and participate in combined studies by facilitating innovation while ensuring safety and wellbeing of study participants as well as generation of reliable and robust data. Achieving this goal promotes public health through ensuring safe and effective medicinal products and safe and performant devices for patients.

The first phase involved analysing the issues impacting combined studies. This initial approach explored the interface between clinical trials (CT) of investigational medicinal products (IMP), performance studies (PS) of In-Vitro Diagnostic Medical Devices (IVDs) and clinical investigations (CI) of medical devices (MDs). The goal was to understand the issues facing combined studies and provide a direction for future work which could address these underlying challenges. This document describes the activities undertaken during the analysis phase, culminating in a proposed direction for future work on this topic aimed at improving the EU landscape for combined studies going forward.

2. Scope of Analysis Phase

The scope of this analysis phase was to investigate and highlight future work which could address the challenges which arise when conducting clinical research for studies which combine multiple health care products under different regulatory frameworks. Specifically, this project looked at products regulated by the Clinical Trials Regulation (CTR), Medical Devices Regulation (MDR) and *In-Vitro* Diagnostic Medical Devices Regulation (IVDR). This first phase focused on clarifying and capturing the issues, mapping the regulatory landscape at the Member State level, understanding ongoing activities related to regulatory interfaces, and

[4] For the purpose of this document combined studies can be understood as studies that involves the simultaneous investigation of a medicinal product, an IVD and/or MD which are subject to the requirements of the CTR, IVDR and/or MDR.

- A clinical trial of a medicinal product in parallel with a performance study of an in vitro diagnostic medical device.
- A clinical trial of a medicinal product in parallel with a clinical investigation of a medical device.
- A clinical investigation of a medical device in parallel with a performance study of an in vitro diagnostic medical device.
- A clinical trial of a medicinal product in parallel with a performance study of an in vitro diagnostic medical device and a clinical investigation of a medical device (in practice, no such studies were recorded; see Figure 9).

ultimately exploring what future work could improve the framework and enhance the overall efficiency of combined studies in the European Union.

3. Introduction

This project represents a pivotal initiative aimed at addressing and refining the intricate landscape surrounding combined studies that involve investigational medicinal products alongside medical devices or in vitro diagnostics within the European regulatory framework. The three Regulations (CTR, IVDR, MDR) contain requirements for the respective individual authorization for clinical trials, performance studies or clinical investigations. Combined studies are often conducted, providing important platforms to enable the availability of innovative and personalised treatments for patients in Europe. The multidimensional nature of such studies poses inherent challenges, including scientific intricacies, procedural complexities, ethical and legal considerations. This project involved cross-functional collaboration at an EU level, involving experts from different EU governance structures.

Medical devices are governed at a European level by the EU Commission expert groups, organised under the Medical Device Coordination Group (MDCG)(see Figure 1). For this project, experts from the clinical investigation and evaluation working group (CIE WG) and in vitro diagnostic medical devices (IVD WG) formed part of the project group.

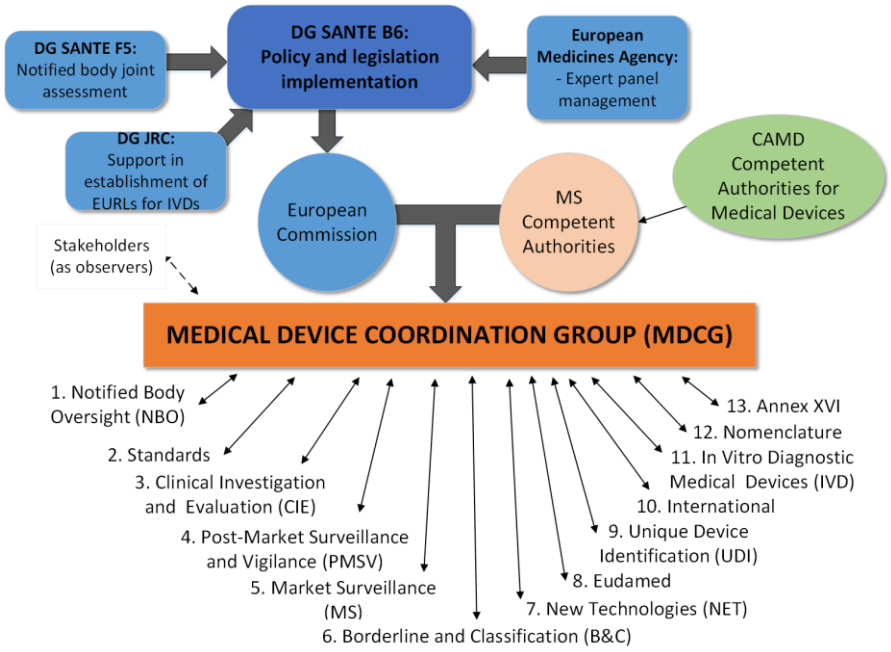

FIGURE 1: STRUCTURE OF EU MEDICAL DEVICES GOVERNANCE

Medicines are governed by the three pillars the Heads of Medicines Agency (HMA), the EU Commission and the European Medicines Agency (EMA). Within the medicines area, the topic of clinical trial authorisation by NCAs is governed by the following two EU groups: Clinical Trials Coordination Group (CTCG) at the HMA and the Clinical Trials Coordination and Advisory Group (CTAG) at the EU Commission as depicted below. The CTCG is co-sponsoring the

COMBINE project providing the infrastructure for the collaboration and experts are part of the project group. The CTAG brings together national contact points of each Member State for endorsement of documents and strategies.

The Ethics Committees system is made up of national Research Ethics Committees (RECs) for both medicines and devices, sometimes the same Committees cover both aspects and sometimes the Committees are separate. Ethics Committee experts were initially invited to COMBINE through both the Expert Group on Clinical Trials (CTEG)) at the EU Commission and through the MDCG. During the project, the MedEthicsEU forum has been established representing Ethics Committees of both medicines and medical devices (including IVDs). Many members from the MedEthicsEU forum were already actively contributing to COMBINE as part of the project group and as such MedEthicsEU was included for input during the review phase.

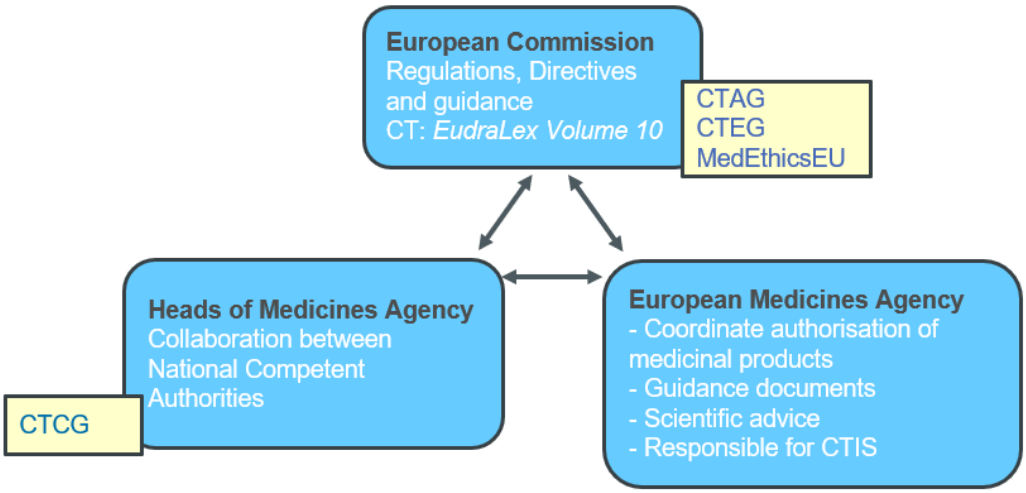

FIGURE 2: STRUCTURE OF EU MEDICINES GOVERNANCE.

The COMBINE project was steered by a project board consisting of the chairs from the IVD-WG, CIE, CTCG, CTAG alongside the European Commission (Annex A Table A1) and overseen by Project Management (Annex A Table A2). The core project group delivering the work was formed from approximately 60 experts including representatives from competent authorities and ethics committees involved in the CTR, MDR and IVDR and the EMA; representing a significant body of sectoral knowledge and practical experience (Annex A Table A3).

An external stakeholder reference group provided continuous input to the project and consisted of 21 EU associations representing a wide range of stakeholders from industry, patients, academic research groups, health care professionals, clinicians and notified bodies; see Annex A Table A4 for a full list. This external stakeholder group contributed significantly to this work sharing their understanding and practical experience by identifying issues and presenting case studies to highlight the challenges facing combined studies in Europe.

The project took a deep dive into the identification and clarification of issues contributing to delays in the initiation of combined studies. This initial project phase explored these challenges systematically by employing a four-track approach that encompasses issue collection, mapping, analysis and proposal of solutions.

Track 1 sought to capture and categorise the issues which involve a mix of scientific, technical, procedural and legal aspects. Recognizing the value in understanding the diverse range of perspectives in Europe; stakeholder engagement was a critical component of this phase. By engaging in targeted workshops, a holistic understanding of challenges reflecting the experience from entire regulatory ecosystem was collected. An overview of key work and outputs from track one can be found in section 4 and Annex D.

Track 2 set out to map the current regulatory landscape across Member States. This involved examining the infrastructure in each Member State in terms of their application processes for clinical trials, performance studies, and clinical investigations. By creating a detailed overview of the regulatory environment at a national level this track looked to identify similarities, synergies and opportunities for improvement which alongside the issues raised could inform potential solutions. An overview of the outputs of this work can be found in section 5 with supporting data available in Annex B and Annexes E and F.

Track 3 formed another integral aspect of the project which mapped published guidance and ongoing activities currently related to the CTR, MDR and IVDR to provide an objective overview of the state of play, highlighting where existing work items may be leveraged for further efficiency. Section 6 describes work conducted in Track 3 with the completed list provided in Annex C.

Track 4, the final track of this analysis phase was dedicated to consolidating the information gained and capture the project group's reflections on possible solutions. Building upon the insights gathered from stakeholder engagement, regulatory mapping, and ongoing activities, this track aimed to structure and collate the information and data from tracks 1-3 and work towards proposed actions which could address the challenges identified. The ultimate goal was to provide a roadmap for future work which could enhance the efficiency of combined studies, reduce delays, and foster a more harmonized and streamlined regulatory framework for these complex investigations within the European Union. See section 7 for further details on this work with the outputs provided in section 8.

Figure 3 shows an overview of the timelines for initiation and completion of the various tracks.

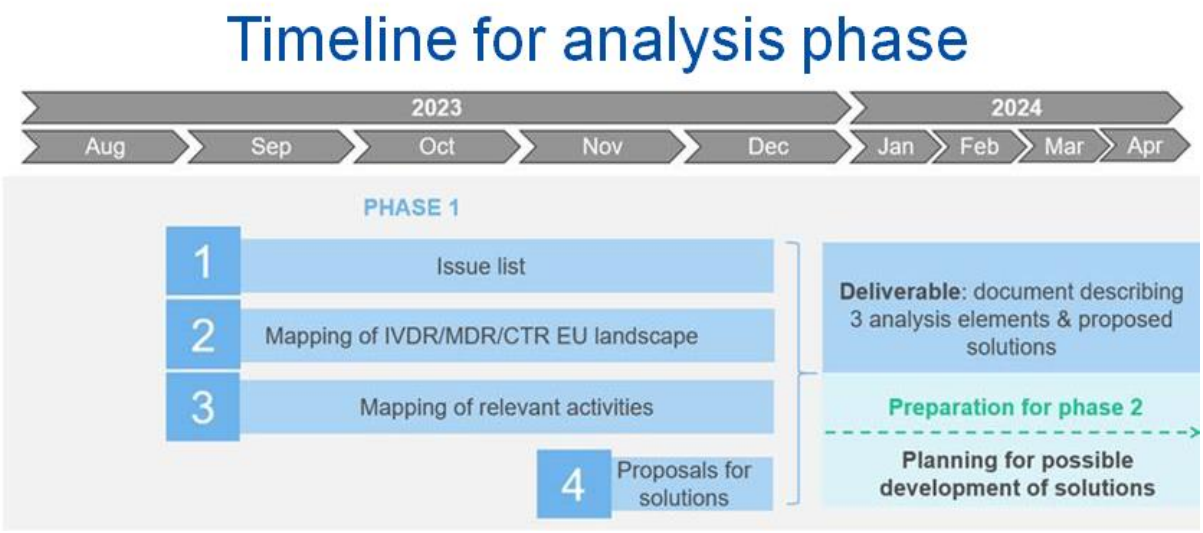

FIGURE 3: TIMELINE FOR THE COMBINE ANALYSIS PHASE.

4. Track 1: Issues

4.1 Objective

The focus of Track 1 was the collection of issues which related to initiating and conducting combined studies.

4.2 Workflow

The first step for Track 1 was the creation of a template to facilitate the collection of issues. This process included agreeing on the key information to be captured which included; capturing a description of the issue, consequence of the issue and information on the nature of the issue, i.e. whether it was a technical, ethical or legal issue and whether more than one Regulation was implicated. In addition, qualitative parameters such as grading (Table 1) and an initial categorisation (Table 2) were defined to assess the issues. Once drafted and after suitable consultation with the project group the template was endorsed by the Project Board.

1 **TABLE 1: DESCRIPTION OF GRADING**

Grading	Description
Minor	Workaround possible or solution needed later
Major	Possible risks, should be discussed, solutions needed at mid-term (e.g. delays for start of the combined study)
Critical	Impact on decision on the combined study, impact on the risks for the subjects, competitiveness of EU

TABLE 2: DESCRIPTION OF CATEGORIES

Category	Description
Legal/ Regulatory	e.g. timelines as set in the legislation, terminology, lack of mature regulatory system
Scientific/ Technical	e.g. assessment, impact of benefit - risk ratio , consolidation at study level
Procedural	e.g. IT system, parallel submissions, consolidated decision
Other	Other

Track 1 hosted five dedicated workshops in total, with the initial three focusing on the issues experienced by representatives of the of the project group. These workshops collated issues from the perspective of Ethics Committees, National Competent Authorities for CTR, IVDR & MDR and the European Medicines Agency. A further two workshops were held with representatives of the external stakeholder groups to ensure all perspectives were captured. The issues were collected live during the workshops allowing the opportunity to discuss and capture the cause of the issues, consequence, and potential scoring.

For each workshop, a dedicated excel worksheet was used to record the issues raised following the endorsed template. The workshops were divided into two parts. In the first part volunteers were asked to present case studies or examples of issues experienced. The second part opened up the floor to collect and discuss issues from the workshop attendees. Before the external stakeholder workshops, working versions of the issue lists were circulated in advance to enable a reflection on the current issues captured. Stakeholders were encouraged to focus on identifying issues which had not already been captured.

Following each workshop Track 1 consolidated the issues; grouping them where the same issues were repeated multiple times. After the final workshop was concluded the issues were further organised by assigning clusters to give an overview of the topics covered, and number of issues captured in each cluster. Figure 4 provides an overview of the timeline for key activities from Track 1.

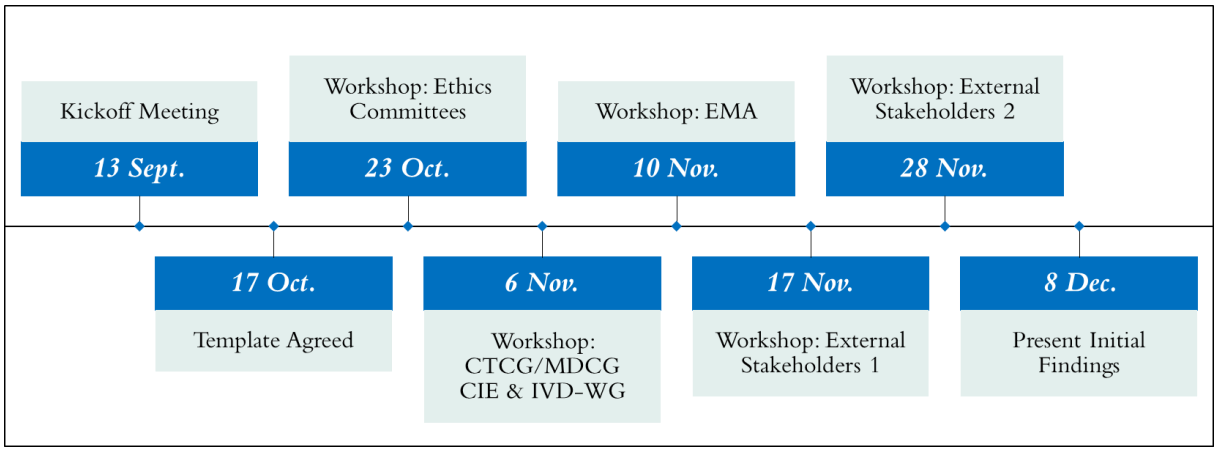

FIGURE 4: TRACK 1 TIMELINE HIGHLIGHTING KEY MILESTONES

4.3 Output

In total 114 Issues were collected including 78 unique issues with 36 issues considered 'repetitions' of unique issue. A full list of issues is provided in Annex D: Issue list. The total number of issues raised across all workshops can be seen in Figure 5. The majority of issues (>85%) belonged to the categories legal/regulatory and procedural. In addition, the majority of issues (>90%) were graded as major or critical and ~66% occurred frequently (see Figure 6).

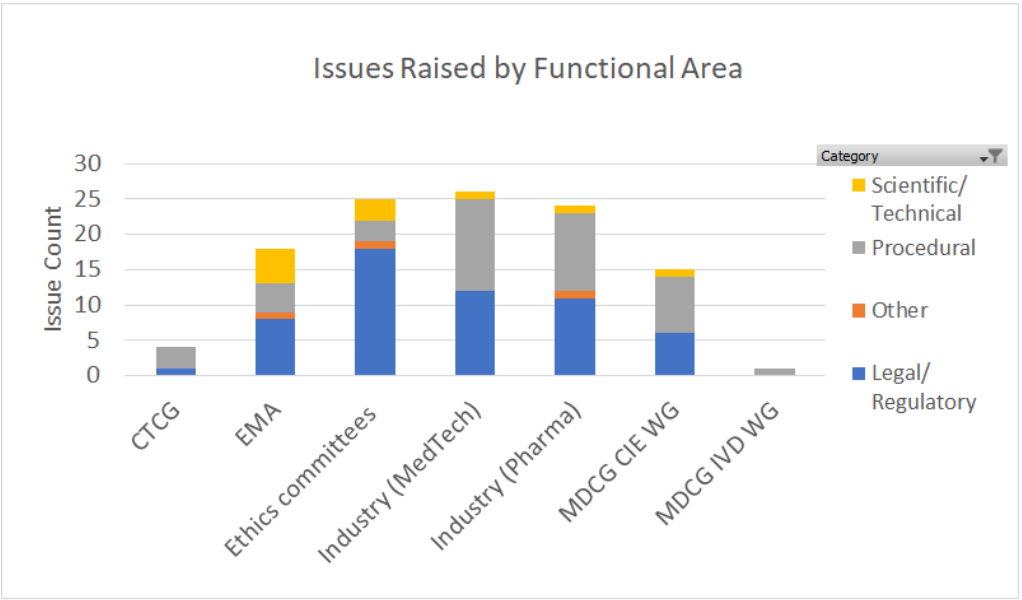

FIGURE 5: TOTAL NUMBER OF ISSUES RAISED BY FUNCTIONAL AREA.

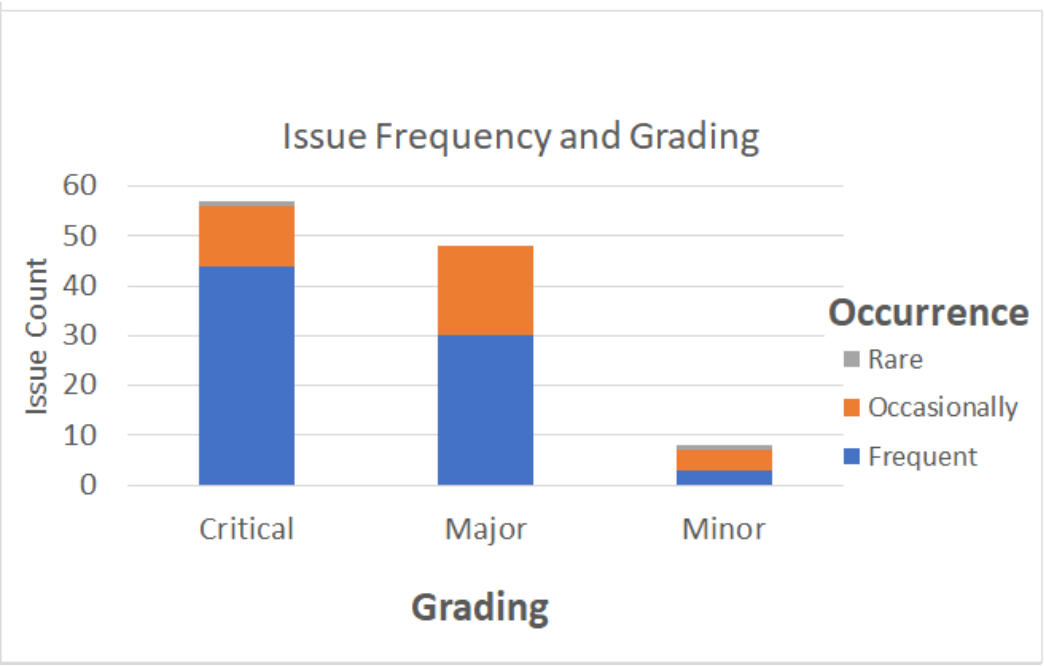

FIGURE 6: GRADING AND OCCURRENCE FOR ALL ISSUES RAISED.

As the workshops progressed the number of unique issues decreased, with a corresponding increase in repetitions, highlighting that the unique issues identified were common to multiple stakeholders. By the end of the fifth workshop a limited number of additional unique issues were identified providing confidence that the core issues had been identified and captured.

The different issues were clustered by track 1 as follows.

- Harmonization of interplay between CTR/MDR/IVDR
- Harmonization in the interpretation of IVDR/MDR
- Procedure/lean process
- IT
- Communication
- Coordinated procedure for PS/CI
- Training/ knowledge on IVDR
- Regulatory challenges on IVDR/MDR
- EU centralised point of contact for medical device

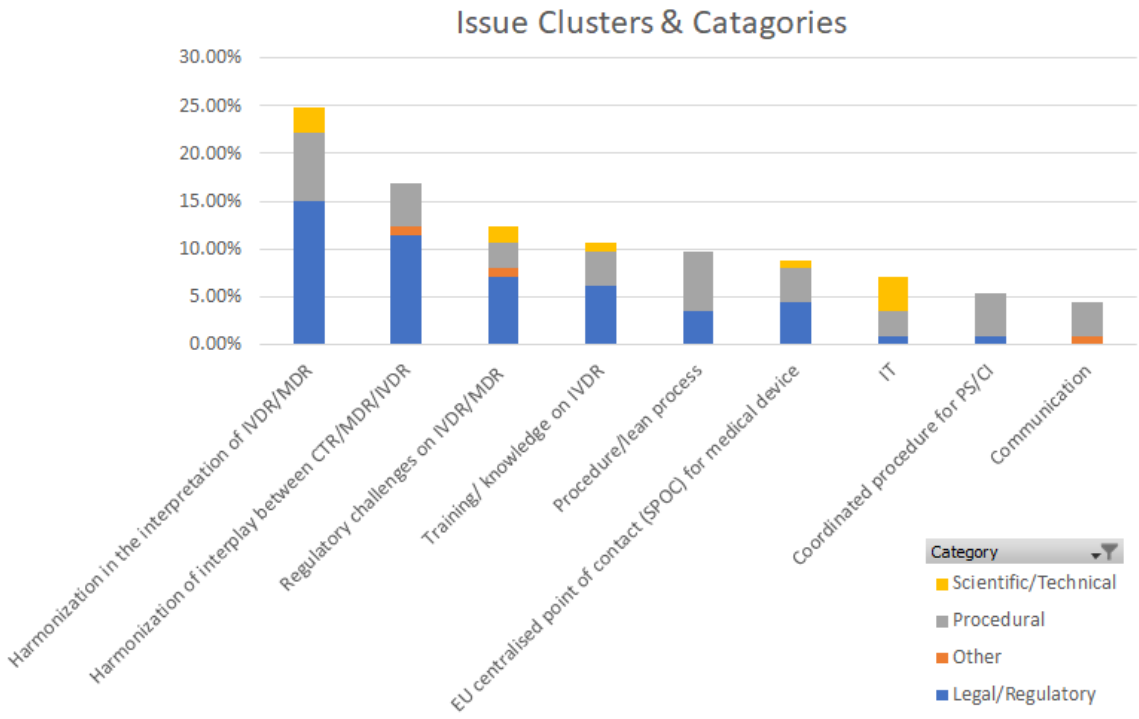

FIGURE 7: CATEGORISATION AND CLUSTERING OF ISSUES.

Figure 7 shows all issues broken down by category and cluster. Clusters are shown on the x axis and were created to show an overview of the types of issues experienced in a more granular fashion than could be seen using category alone. Each issue was assigned to a single cluster however it is worth noting that some issues could span multiple clusters. For example, issues involving coordinated assessment could also be considered under the harmonisation categories. Similarly, solutions to the underlying issues for each cluster would likely address issues in other clusters as well. The interdependence and overlap of issues formed a key consideration when structuring the analysis in Track 4.

4.4 Summary of issues

A large number of issues were identified as part of activities led by Track 1 (114 issues in total with 78 unique issues identified). Owing to their diverse and detailed nature, it is challenging to accurately summarise the full scope of issues here. In order to provide context, some of these issues are discussed further below. Please note this is not an exhaustive discussion and is not intended to provide a comprehensive summary of the issue list. For a full list of the captured issues please see Annex D.

At its core, the problems facing combined studies stem from a lack of alignment between the CTR, IVDR and MDR. Each of these Regulations are relatively recent and still undergoing their own implementation. Between the Regulations there are different rules and criteria which apply to clinical research of their respective health products; for example, there are different considerations to apply when determining if a CT, CI or PS is required. In addition, the requirements, documentation, timelines and processes, as envisaged by the regulations, vary significantly between the CTR, IVDR and MDR. Conducting a combined study involves navigating all the requirements of each applicable Regulation and reconciling the differences between the same.

Applications for CI/PS are submitted and assessed nationally, in each concerned member state. The lack of coordinated assessment for CI/ PS increases the total number of applications required and can impact the turnaround time for regulatory approval of combined studies. In contrast with the CTR where coordinated assessment procedures are already running, CI's and PS's are authorised on a national basis, with coordinated assessment delayed due to the development timelines for key IT infrastructure (EUDAMED). Understanding and navigating this complex regulatory landscape poses significant challenges for sponsors where uncertainty in the requirements can lead to delays and where it is not always clear the best route to seek clarity on regulatory, scientific or technical questions. There may also be a national legislation or interpretation of the regulations which can lead to Member State specific requirements, protocol amendments, positions and application processes which add to the complexity in conducting, in particular, multinational combined studies. However, as indicated previously the underlying legal, regulatory, technical and procedural particulars, which result in the issues identified, are more complex than can be reflected in this simple summary.

5. Track 2: Mapping EU Landscape

5.1 Objective

Map at a Member State level the EU ethics committee and competent authority landscape for parameters relevant to combined studies under the CTR/IVDR/MDR.

5.2 Workflow

Track 2 determined that the most appropriate way to map the EU landscape for combined studies would be to survey Member States. In addition, mapping work conducted by stakeholders which could complement this activity would be considered. Stakeholders were invited to submit any reports or contributions for consideration. Two contributions were submitted by MedTech Europe (Annex E) and EFPIA (Annex F).

The draft Member State survey was compiled and circulated to the project group for comment. After feedback was considered, the survey was finalised and circulated to Member States using the CTAG expert group. CTAG was chosen in order to coordinate the input from various entities and provide one single contribution per Member state. Once issued, Member States had over 2 weeks to complete the survey and respond. To encourage responses, the survey was discussed at a stakeholder meeting and at multiple EU working groups. A reminder was circulated to Member States who had not replied through the CTAG secretariat before officially closing the survey.

The survey consisted of 27 questions exploring how combined studies are dealt with on a Member State level. Included in the survey were questions on the number of combined studies each Member State has received. Overall, the survey aimed to cover six major themes.

1. Competent Authorities
2. Ethics committees
3. Processes in each Member State
4. National legislation
5. Communication between sponsors/CAs/ethics
6. Indication of volume of applications

Figure 8 provides an overview of key activities conducted for this survey. A copy of the survey questions is provided in Annex B Table B1.

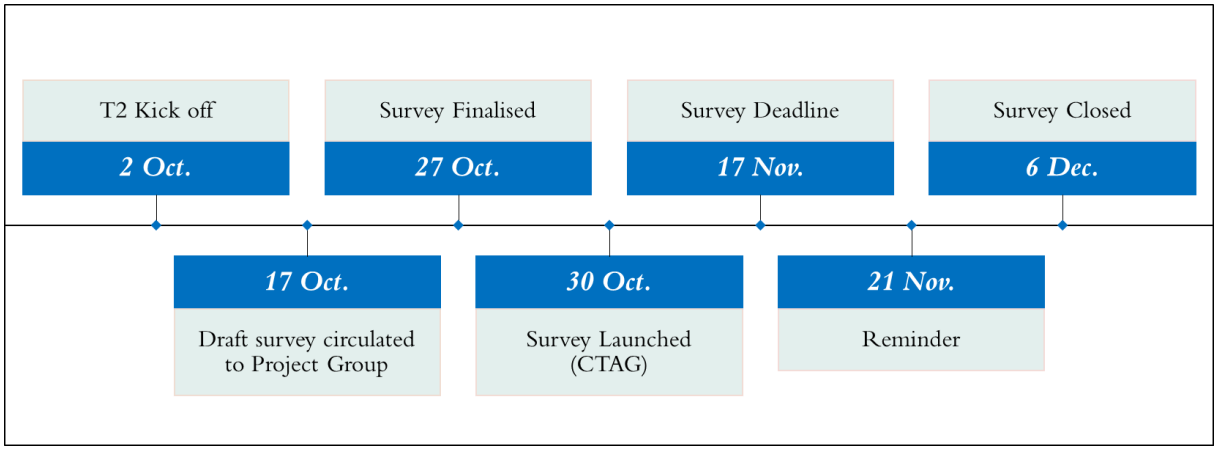

FIGURE 8: TRACK 2 TIMELINE HIGHLIGHTING KEY MILESTONES

5.3 Output

5.3.1 Track 2 Survey

A high survey response rate was achieved with responses received from 24 out of 28 Member States (EU + NO). The aggregate survey results are provided in Annex B Table B2. The data includes all Member States surveyed meaning across all questions the information is unknown for at least 4/28 (14%) Member States.

Notable results include.

- Questions 1 and 7 show that the same regulator deals with CI's, CT's and PS's in 61% of 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. This shows there is a good basis for potential improvements to the system.
- Questions 2 and 3 show that 57% of Member State competent authorities offer advice to sponsors of combined studies prior to application. However, only 11% offer national scientific advice which includes aspects other than the clinical trials.
- Questions 4 and 5 show that, in total, 36% of Member States competent authorities offer pre submission meetings prior to the application of combined studies. These meetings are provided without a fee in 70% of those Member States where they are offered.
- Question 10 showed that a single ethics application can be made for combined studies involving clinical trials in 14% (4/28) of Member States.
- Question 12 showed that currently no Member State accepts a single competent authority application for combined studies which involve a clinical trial.

Responses to questions 22 to 27 provided information on the annual number of applications Member States received (Annex B Table B3). Figure 9 shows the number of applications received for the different types for combined studies. In total the average number of studies received per Member State was 17 with a range from 0 to 59. Notably no applications had been received for studies involving all three Regulations together. In the case of multinational combined studies individual applications are submitted for IVDR/MDR. As such a single combined study may be represented multiple times in Figure 9. Finally, Table 3 provides an overview of how many of these studies were multinational. For a full breakdown per Member State please see Annex B Table B4 & B5.

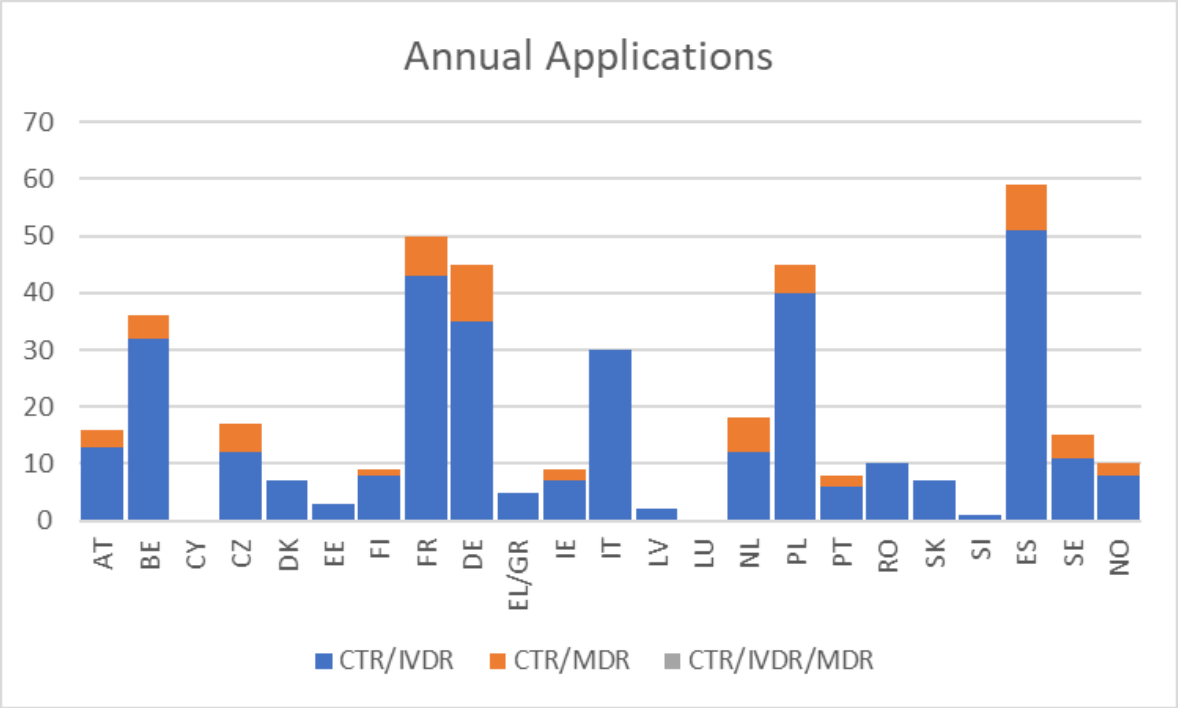

FIGURE 9: CHART SHOWING THE NUMBER OF APPLICATIONS RECEIVED PER MEMBER STATE FOR COMBINED STUDIES.

TABLE 3: NUMBER OF STUDY APPLICATIONS RECEIVED ACROSS ALL MEMBER STATES INCLUDING INFORMATION ON THE NUMBER AND % OF STUDIES WHICH WERE MULTINATIONAL. FOR A BREAKDOWN BY COUNTRY SEE ANNEX B TABLE B5

Combined Study	Number of Applications	Multinational	% Multinational
CTR/IVDR	343	296	86%
CTR/MDR	59	43	73%
CTR/IVDR/MDR	0	0	-

In general, the data shows that there is a high degree of heterogeneity in how Member States approach combined studies. In addition, multiple applications are needed for combined studies in the majority of cases increasing the administrative burden for all stakeholders. On a more positive note, most Member States who responded have consolidated (CTR/IVD/MDR) ethics committees (17/22) and competent authorities (17/20) for all study types, suggesting that potential improvements are achievable.

5.3.2 Stakeholder Contributions

In addition to information gained from the survey, stakeholders also provided an overview of activities conducted to understand the EU landscape for combined studies.

MedTech Europe conducted a survey looking at the impact of IVDR on combined studies. This survey showed a desire for improved coordination and harmonisation between and within Member States, more access to information regarding study approval processes, improved

communication between sponsors and authorities, reduced time and administrative burden, reduced costs of application and a simplification of the combined study submission process. According to data from MedTech Europe the mean time from submission to approval of performance studies was 137 days, with a range of 45-267 days (see Annex E).

The European Federation of Pharmaceutical Industries and Associations (EFPIA) conducted a survey on the impact of IVDR on combined studies also. They estimated that, due to a lack of a centralised procedure for authorising performance studies there would be between 1,992 and 3,275 performance studies submissions based on 849 clinical trial submissions expected to be made over the next 3 years (see Annex F).

The stakeholder analyses were conducted without input or verification from the authorities. The timelines are expected to be affected by multifactorial elements also including quality of the submitted files and sponsor's response time. The stakeholder analyses support a need for broad collaboration to solve the multifactorial challenges mapped in the COMBINE issue analysis (see section on track 1).

6. Track 3: Mapping Relevant Activities

6.1 Objective

Mapping of existing and ongoing work related to combined studies

6.2 Workflow

Track 3 compiled an initial list of documents including final (published) or draft EU level documents from EU Commission, EMA, EU-groups such as CTCG, MDCG IVD, MDCG CIE and global documents that could be relevant for combined studies. The list includes information on the type of product(s) concerned (medicinal products, medical devices or in-vitro diagnostics), status of the document and links to where the documents can be found.

The list focused on gathering documents which relate to combined studies with information relevant across Europe, however additional key documents from each of the three Regulations were also included in the list to highlight relevant information. The type of documents included in the list include guidance documents, Q&A documents, and relevant standards.

After finalisation, the draft list was reviewed by the project group and an updated proposal was circulated to the external stakeholder group for input. In particular external stakeholders were asked if they were aware of other material which should be included in the list.

6.3 Output

The list of activities/documents is presented in Annex C Table C1

Very few documents were found to include information related to all three Regulations. Though one activity within the ongoing initiative Accelerating Clinical Trials in the EU (ACT EU) is considering piloting regulatory advice on combined studies and involve regulatory expertise within CTR, MDR and IVDR. Relevant documents currently under development are mainly within MDR and IVDR.

7. Track 4: Analysis

7.1 Objective

The primary objective of Track 4 was to consolidate and analyse the outputs from Tracks 1-3, to facilitate translation of the work of this analysis phase into a roadmap for future work and to produce this output document.

7.2 Process for solution generation & refinement.

Following completion of the issues list by Track 1 a 'Solutions Workshop' was organised with the project group. For this workshop the Issue list was separated into the clusters identified in Track 1 (see Figure 7). These issue clusters were mapped to quasi-objective statements with a view to facilitating refinement of the objective statements for the next phase of COMBINE. The project group was split into 4 breakout rooms to reflect on the issues contained within the assigned clusters and to discuss potential solutions. Following the breakout session, the proposed solutions were captured under each cluster. Any additional notes, considerations or objective statements were also captured and used in future steps.

This resulted in collections of potential solutions assigned under each cluster with some solutions repeated across the categories. A number of steps were then taken to translate this initial group into the direction outlined in section 8 of this document. The first step was to review and group the solutions based on themes of common activities. The issue list from Track 1 (Annex D) was reviewed and the issues mapped to a potential work item. It is worth noting that some issues could be addressed by multiple items either directly or indirectly. Each issue was mapped to the item which could best address the underlying concern, however implementing some items may also address in part or in whole other issues not listed under that proposal group.

7.3 Overview of proposed work

The collection and refinement of solutions resulted in groups of work items with the underlying issues mapped to that item or group. The proposals were then further reviewed, consolidated and aligned, factoring in synergies and dependencies resulting in four high level groups. Figure 10 provides a visual representation of these groups including the issue numbers covered by each group. Section 8 explores these items in further detail.

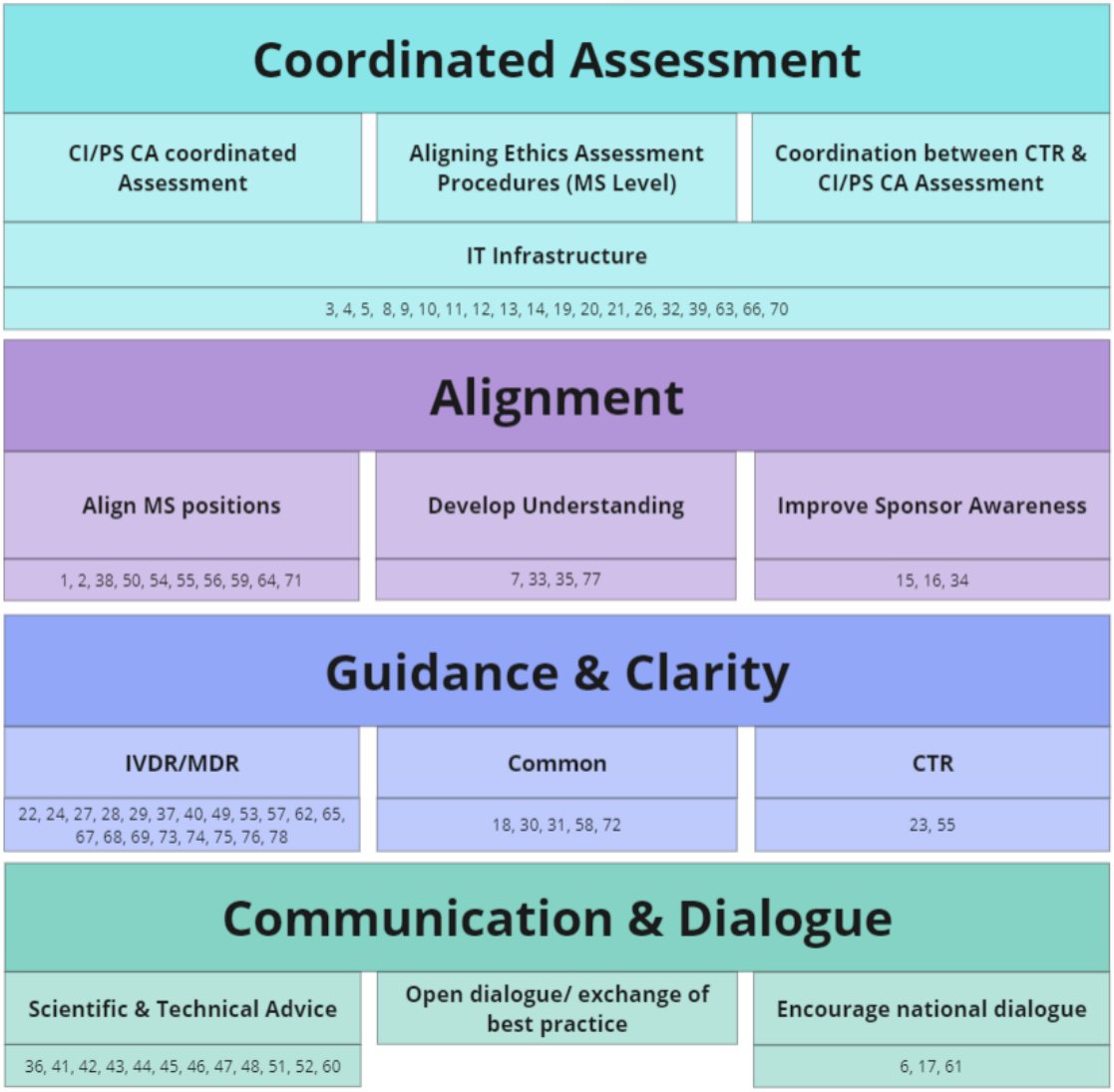

FIGURE 10: OVERVIEW OF PROPOSED WORK GROUPS TO ADDRESS THE UNDERLYING ISSUES IDENTIFIED IN TRACK 1. NUMBERS LISTED UNDER EACH HEADING REFER TO SPECIFIC ISSUE NUMBER IN ANNEX D.

Once the groups had been identified, further analysis was conducted to assist in translating the issue analysis (Section 5) to the proposed direction. Specifically, the grading, frequency and number of the underlying issues for each item/group was used to help illustrate the landscape of proposed work. Briefly the grading and occurrence for each issue/ repetition was given a numerical score (see Table 4).

TABLE 4: NUMERICAL VALUES ASSIGNED TO THE GRADING / OCCURRENCE OF EACH ISSUE FOR THE PURPOSES OF UNDERSTANDING THE OVERALL GRADING / OCCURRENCE OF THE SEPARATE WORK ITEMS OR GROUP.

Grading	Score	Occurrence	Score
Minor	1	**Rare**	1
Major	2	**Occasionally**	2
Critical	3	**Frequent**	3

For each item or group the following was then determined.

- The number of issues including repetitions contributing to the group.
- The average 'Grading' for the group (values between 1-3).
- The average 'Occurrence' for the group (values between 1-3).

Figure 11 shows a bubble plot of average grading vs average occurrence with the size of the bubbles representing the number of issues and repetitions in each group. From this figure it can be seen that work items with the largest number of issues cluster in positions with high average grading and occurrence. As each issue was assigned to one group only, items which overlap may share common elements. For example, the issues underpinning coordinated assessment, guidance/clarity for IVDR/MDR topics and alignment do share overlapping and common elements, however it is worth noting that this analysis is intended to be illustrative.

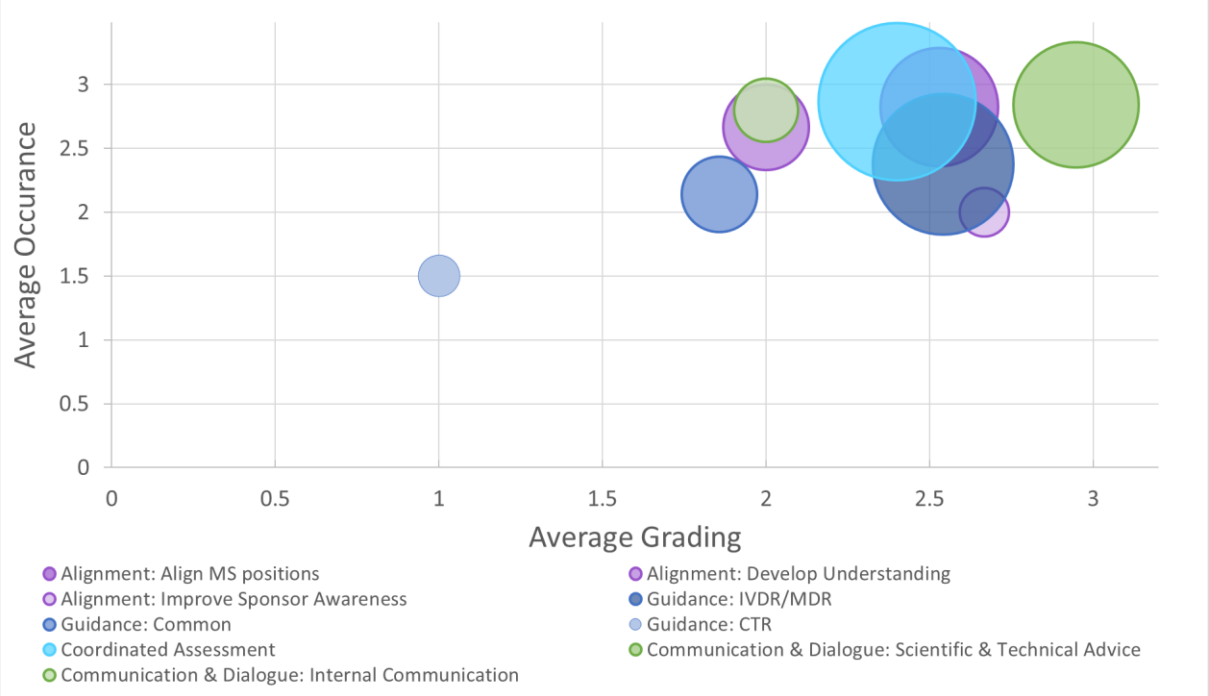

FIGURE 11: BUBBLE PLOT SHOWING THE AVERAGE GRADING AND OCCURRENCE FOR ISSUES UNDERPINNING THE WORK GROUPS ABOVE. THE SIZE OF THE BUBBLE REPRESENTS THE NUMBER OF ISSUES (INCL. REPETITIONS) CONTRIBUTING TO EACH WORK GROUP. OF NOTE THE LARGEST BUBBLE REPRESENTING THE HIGHEST NUMBER OF UNDERPINNING ISSUES RELATES TO COORDINATED ASSESSMENT.

8. Proposed Direction

8.1 Discussion

This section outlines the proposed work that is deemed important to address the collected issues. The outline of the proposed work is based on the 'Solutions Workshop' held on December 15th with the COMBINE project group. The proposed work has been developed with the COMBINE vision in mind to make EU more attractive to conduct and participate in combined studies by facilitating innovation while ensuring safety and wellbeing of study participants as well as generation of reliable and robust data. These proposals are aimed at facilitating EU alignment, simplifying the framework for combined studies and optimising the use of resources and infrastructure for all parties involved (NCAs, ECs, CT sponsors and manufacturers).

Following the 'Solutions Workshop' all proposed solutions were reviewed alongside the 78 unique issues from the issue list (Annex D). The proposed direction was then refined and organised by Track 4 with a final review by the entire project group and board together with stakeholders. Each issue was mapped to a work item ensuring that no issues had been missed. Work items were grouped into the categories below:

1. Coordinated Assessment
2. Alignment
3. Guidance & Clarity
4. Communication & Dialogue

For many of the work items, there are several options for how to conduct and organise the specific work. For instance, an external guidance or internal best practice document might be one approach, however other activities might achieve the same goal. The list of proposed work thus serves as the direction, providing an overview of work which could address the underlying issues The reflection on how to best conduct the work will be done in the next steps of planning that will also organise the work to accommodate feasibility and use of resources. The reflection on the next steps needs to be done by the Governance structures described in section 3.

Without prejudice to the planning activities required to translate these proposals into a work plan and with due consideration on the interdependency of underlying issues, when considering these proposals coordinated assessment stood out as a firm priority. For example, there is currently no coordinated assessment for CI/PS leading to a large number of applications required in order to proceed with multinational combined studies.

On review of the issues and proposed work it was clear that implementation across member states of a procedure for coordinated assessment of a CI/PS application represents a critical step in improving the system for combined studies in the EU (See Section 8.2.1). From Figure 11 it can be seen that the largest number of issues are directly linked to the need for coordinated assessment. Many additional issues could be indirectly addressed in whole or in part by implementing coordinated assessment for CI/PS. For example, a large number of issues seek additional alignment and harmonisation of requirements and clarity of interpretation. By introducing a coordinated assessment procedure for CI/PS many issues related to, for example, divergent interpretations, lack of harmonisation or clarity of requirements for CI/PS may be addressed through the act of collaborative working. In

summary introducing a coordinated assessment for CI/PS has the greatest potential impact on issue list as a whole. In practice once implemented coordinated assessment would reduce the total number of applications sponsors have to make for multinational studies, reducing duplication of effort, administrative burden and provide procedural certainty.

The lack of synchronisation between the three regulations CTR/IVDR/MDR has resulted in a number of issues which were captured by Track 1. Further aligning the regulatory framework for clinical research in order to facilitate innovation and clinical progress with the EU should also be considered.

The remaining work identified in the document provide a means to address underlying issues for combined studies and should be prioritised in light of all factors including, where applicable, available resources to progress the work items.

Numbers in parentheses throughout this section refer to the issue numbers collected as a result of the Track 1 workshops (Annex D).

8.2 Work Items

TABLE 5: SUMMARY OF WORK ITEMS ADDRESSING ISSUES FOR COMBINED STUDIES.

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
Alignment	2.1	Align Member State 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 national dialogue

8.2.1 Coordinated Assessment

(3, 4, 5, 8, 9, 10, 11, 12, 13, 14, 19, 20, 21, 26, 32, 39, 63, 66, 70)

This group looks at the options available and steps that could be taken to improve the coordination of the assessment for combined studies.

8.2.1.1 CI/PS Competent Authority Coordinated Assessment

This item refers to Competent Authority coordinated assessment for CI/PS as outlined in Article 74 (IVDR) Article 78 (MDR); which involves a coordinating Member State and common review of a CI or PS. The IVDR/MDR provides for a coordinated assessment procedure contingent on the availability of EUDAMED. It is worth exploring if these articles can be utilised in advance of EUDAMED through alternative technical solutions or otherwise. This could involve:

I. Exploring the legal basis for coordinated assessment with alternative technical solutions.
II. Deciding and structuring the means of coordination.
III. Piloting the coordinated process
IV. Review effectiveness of pilot and propose long term solutions.

8.2.1.2 Aligning Ethics Assessment Procedures (MS level)

This item involves working towards aligning the ethics assessment procedures at a Member State level. For example, under CTR the output is a national evaluation and for IVDR/MDR the output is typically a decision letter. This item would explore aligning the ethics assessment such that the procedures could run at the same time, where the conclusion(s) of the ethics review remains valid for both sides of the combined study. Such work could include:

I. Exploring whether there are any barriers to this at a national or EU level. Consider why current options are being used?
II. Work towards aligned Ethics procedures (per MS) for a combined study.
III. Alignment of documentation/ best practice for ethics reviews.

8.2.1.3 Coordination between Competent Authority CTR & CI/PS Assessment

This item aims to bring the coordinated assessment from the CTR and the coordinated assessment from IVDR/MDR together, to combine overlapping steps and explore where efficiencies can be gained. This would involve coordinating both the Competent Authority reviews in the same process for combined studies. This could include leveraging the aligned ethics procedures at a Member State level resulting from work in 8.2.1.2. In practice this would mean the Competent Authority and Ethics Committee reviews for both the clinical trial aspects and CI/PS aspects would be assessed in tandem. This solution would be dependent and build on work from items 8.2.1.1 & 8.2.1.2. Such work could include:

I. Exploring coordinated Competent Authority review/ single decision
II. Leveraging work from 8.2.1.1 & 8.2.1.2 to establish and pilot a single application/ single decision process.
III. Review effectiveness of pilot and propose long term solutions.

8.2.1.4 IT Infrastructure

The item looks at examining potential short and long-term options to improve the IT systems for combined studies, which could include:

I. Exploring the possibility of alternative/interim technical solutions. This item seeks to look into the possibility of shorter-term options which could facilitate coordinated assessment for combined studies in advance of EUDAMED (Linked to 8.2.1.1). This item could seek to explore: -
    a. If alternative/interim technical solutions could be used for IVDR Article 74/ MDR Article 78 assessments?
    b. If alternative/interim technical solutions could be used for coordinated assessment of CT/CI/PS
    c. If alternative/interim technical solutions could include ethics.
    d. What alternative technical solutions are potentially available and would be suitable to support one or more interim/pilot procedure(s) (See 8.2.1.1 - 8.2.1.3)?
    e. Barriers to Implementing of any alternative/interim technical solutions identified.

II. Integration of IT systems for combined studies.
    a. Share learnings from CTIS implementation.
    b. Explore Integration/ IT communication between CTIS and EUDAMED,

    Explore possibilities for single application for combined studies considering respective timelines.

8.2.2 Alignment

The work items explored in this group involve reaching a common understanding and finding common approaches and improving understanding and certainty overall.

8.2.2.1 Align Member State Positions

To reduce divergence, this work item looks at aligning (where possible) Member States opinion, interpretation and requirements which impact combined studies. In particular the following areas for alignment were identified:

I. Differing opinions/interpretations (1, 2, 50)
II. Different documentation requirements (38, 54, 55, 59, 64)
III. How to handle the early termination of combined studies (56)
IV. The requirements for performance studies involving testing sites only (71)

Where alignment is reached such solutions could be implemented in, for example, an internal best practice or external document. In general, consideration should be given to publishing and clarifying the aligned positions where possible.

8.2.2.2 Develop Understanding

Where alignment is not practical it is important the differing views and approaches are easily understood by all stakeholders and that a framework is created to facilitate continuous learning and knowledge exchange with the aim to work towards alignment. For this goal, the following approach could be considered.

I. Clarify National provisions (where applicable) (7,77) This would involve making information on, for example, national requirements which impact combined studies available in an easy to access and understand format.
II. Improve Competent Authority understanding of other Member State approaches to combined studies. (follow on to 8.2.2.1) (33)
This includes both an understanding reached through activities in 8.2.2.1 and sharing of information (linked to 8.2.4.2)
III. Creation of best practice documents and shared learning from the assessment of CI/PS. (35)

8.2.2.3 Improve Sponsor Awareness

Activities to improve sponsor awareness could include:

I. Improving the awareness of the requirements for combined studies (34)
II. Providing practical advice in relation to the quality of applications and expectations by CA's / EC's (15).
Developing tools to ensure dossiers are complete including tools to help structure or navigate the documentation. For example, this could take the form of a proposed document structure or checklist mapping the requirements to the documentation provided. This would also assist in Member State assessment of large volumes of documentation. (16)

8.2.3 Guidance & Clarity

A number of issues raised are seeking clarity on several topics. This clarity may be reached through guidance documents, formal positions or by other means. It is worth noting that while a topic may involve predominantly one Regulation, where representatives may serve to lead development of the proposed clarification, a cross functional review of the proposals and involvement of stakeholders would bring additional benefit. This could include taking into account practical constraints, and additional relevant factors arising from the involvement of multiple Regulations. Such broad input and review could be facilitated by the COMBINE organisational structure.

8.2.3.1 IVDR/MDR Topics

Some of the topics listed here may already be addressed by the ongoing work of the IVD-WG PS Q&A taskforce which is currently under development, or other activities. Such topics include:

I. When is a PS or CI needed? (22, 40, 49, 67, 68, 69, 74, 76, 78)
II. IVDR Article 58(2)[5] and the definition of left over sample (24)
III. Studies with no benefits for minors (28)
IV. IVDR Article 58(1a)[6] surgically invasive sample taking (37)
V. Non-CE-marked devices used in clinical trials and in house devices (29, 65, 75)
VI. Rare diseases (53)
VII. Exploratory biomarker requirements / prototype devices (57, 62)
VIII. IVDs in multiple trials (27)
IX. Multiple IVDs in a single trial (73)

8.2.3.2 Common Topics

Some of the topics raised were not linked to a specific Regulation. Such topics include:

I. The responsibilities of investigators and sponsors (18, 72)
II. Terminology (31)
III. Safety events (58)
For example, the different definitions for safety events. How to practically manage the definitions. How should parties approach the assessment and logistics for the safety events resulting as part of a combined study.
IV. Substantial modifications (30)
For example, substantial modifications may impact one of more side of a combined study, substantial modifications may result in a new assay being introduced. How can substantial modifications be managed in an efficient way?

[5] IVDR Article 58(2) describes the requirements for studies involving companion diagnostics including a notification for studies involving companion diagnostics using only left over samples.

[6] IVDR Article 58(1a) specified that any performance study in which surgically invasive sample-taking is done only for the purpose of the performance study shall, in addition to meeting the requirements set out in Article 57 and Annex XIII, be designed, authorised, conducted, recorded and reported in accordance with this Article and Articles 59 to 77 and Annex XIV.

8.2.3.3 CTR Topics

One CTR specific topic was identified.

I. What are the requirements for combined studies transitioning to the CTR? (23, 25) Are CI/PS applications needed?

8.2.4 Communication & Dialogue

The proposals under communication & dialogue are aimed at promoting exchange of information. Some of these proposals speak about coordinating exchange of information at an EU level, ensuring the right actors are involved in disseminating information and exploring the structures which can facilitate this exchange. Other items look at fostering dialogue at a national level encouraging close alignment, exchange of information and mutual coordination nationally.

8.2.4.1 Scientific & Technical advice.

(36, 41, 42, 43, 44, 45, 46, 47, 48, 51, 52, 60)

Whilst some options are available to receive scientific/technical advice, the issues highlight challenges faced by sponsors and manufacturers in getting advice, consistency of advice and reliability of advice. Some of the suggestions on how to improve this are given below.

I. A forum to discuss scientific/technical advice.
II. Explore having the right expertise contributing to Scientific Advice for combined studies.
III. Consider how to raise awareness of the available routes for scientific & technical advice. Consider interface with other EU initiatives.

8.2.4.2 Open dialogue/exchange of best practice

I. A forum for exchange of information was suggested. In general, this item seeks to explore how best to facilitate dialogue at an EU level on combined studies.
II. Exchange of information/best practice amongst Ethics Committees.

8.2.4.3 Training Initiatives

Consider how best training initiatives could be run for combined studies, which platforms to use, content speakers etc. Consider link with other EU initiatives. Consider the training needs for stakeholders.

8.2.4.4 Encourage national dialogue

(6, 17, 61)

The aim is for Member States to foster internal dialogue and open communication channels as work towards coordinated assessment and review proceeds. This could include:

I. Encourage the creation of national teams with representatives from the different areas.

Examples of how some Member States have achieved good internal communication or best practice guidelines could assist in this regard.

II. Encourage exchange of information between Assessors who assess different aspects of combined studies within the same Member State.

III. Encourage Member States to offer pre-submission meetings or information.

IV. Encourage communication between Competent Authority and Ethics Committees, including a reflection on what information is key to exchange? Is there an optimal time to exchange information? Is a best practice guide needed?

9. Conclusion

This initial work of the COMBINE project set out to understand the combined studies landscape, map challenges and propose future work that could help make improvements for combined studies going forward. Through a series of workshops led by the Track 1 team a total of 78 unique issues were identified across a broad spectrum of categories. It was noted that a large number of issues were common to many stakeholders meaning we shared similar challenges.

Track 2 compiled and ran a survey of Member States to capture a snapshot of the current EU landscape for combine studies. This survey achieved a high response rate with 24 out of 28 competent authorities responding, providing a meaningful insight into current practices. Overall, a high degree of heterogeneity was observed in how Member States approach combined studies, noting room for improvement. Data provided by the external stakeholder group indicated that for a potential 849 clinical trial submissions between 1,992 – 3,275 performance study submissions would be needed based on the current system. In addition, the average time from submission to approval for a performance study was seen to be 137 days with a range from 45-267 days.

Through the work of Track 3 a list of ongoing work and relevant published documents was compiled to serve as a basis for understanding work already conducted; enabling a reflection on how best to move towards future work.

Finally, the project group in conjunction with track 4 participated in a workshop to translate the issues identified in Track 1 into potential solutions. These solutions were refined into proposed direction including work items which could provide a means to address the challenges facing combined studies in Europe.

The benefit of this COMBINE analysis phase can be clearly seen as the comprehensive review of the issues and potential solutions, which was created through dialogue with relevant experts and stakeholders across Europe, provides confidence that the core issues have been identified; allowing a reflection on the optimal direction. Whilst all the proposed actions are expected to yield benefits, in particular, it is clear that improving coordinated assessment in a strategic and stepwise fashion will likely result in a meaningful improvement for combined studies in the EU and act to resolve a large number of issues both directly and indirectly.

In conclusion the output of the COMBINE analysis phase can serve as a basis for planning and implementing future work to address these ongoing challenges in a structured and strategic manner. The next steps will be elaborated by the relevant Member State expert groups with the support of Commission and involvement of all relevant stakeholders.

10. Annex

Annex A: Project group & Stakeholder representatives

TABLE A1: COMBINE PROJECT MANAGEMENT

Name	Country
Ditte Zerlang Andersen	DK
Päivi Susanna Worsøe	DK

TABLE A2: COMBINE PROJECT BOARD

EU Commission		
Isabelle Clamou - SANTE.D2 - CTEG/CTAG		
Olga Tkachenko - SANTE.D3 - MDCG/IVD WG/CIE WG		
Louise Schluter - SANTE.D3 – MDCG/IVD WG/CIE WG		
Paul Piscoi - SANTE.D3 - MDCG/IVD WG/CIE WG		
Name	**Country**	**EU group**
Gaëlle Le Brun	FR	IVD WG co-chair
Marianne Lunzer	AT	CTCG chair
Monique Al	NL	CTCG vice-chair
Elin Karlberg	SE	CIE WG co-chair

TABLE A3: COMBINE PROJECT GROUP

Name	Country	Domain	Track 1	Track 2	Track 3	Track 4
Nebojsa Serafimovic	AT	CIE WG				
Benedicte Nuyttens	BE	CIE WG	✓			
Steve Eglem	BE	CIE WG	Lead			
Jeroen Poels	BE	IVD WG				
Laura van Diepen	DE	IVD WG				
Ulf Schriever	DE	IVD WG				
Ugur Erman	DK	CIE & IVD WG				
Kristin Jøranli Astrup	DK	CIE WG			✓	
IVD expert	DK	IVD WG				
CIE expert	ES	CIE WG				
IVD expert	ES	IVD WG				
IVD expert	ES	IVD WG				
Sarah Madrieres	FR	IVD WG	✓			✓
Gearóid O'Connor	IE	CIE WG		Lead		
Philip Kelly	IE	IVD WG	✓			Lead
CIE expert	PT	CIE WG				
Mariana Madureira	PT	CIE & IVD WG				
CIE expert	PT	CIE WG				
Ilona Reischl	AT	CAT chair				
Anne Lenaers	BE	CTCG	Lead			
Lene Grejs Petersen	DK	CTCG		✓		✓
Marita Kailajärvi	FI	CTCG				
Corinne Kiger	FR	CTCG		✓		
Monique Al	NL	CTCG vice-chair				
Stina Löfling	SE	CTCG			Lead	
Francisca Menezes	PT	CTCG				

Name	Country	Domain	Track 1	Track 2	Track 3	Track 4
CTCG Expert	SE	CTCG				
Michelle Fonteyne	BE	Ethics Committees	Lead			
Ethics Representative	BE	Ethics Committees	✓			
Wolfgang Berdel	DE	Ethics Committees				✓
Guido Grass	DE	Ethics Committees				
Ethics Representative	DE	Ethics Committees				
Helle Christiansen	DK	Ethics Committees		✓		
Solveig Nordahl Jacobsen	DK	Ethics Committees				
Lucía Arellano	ES	Ethics Committees				
Ethics Representative	ES	Ethics Committees				
Janica Juvonen	FI	Ethics Committees				
Ethics Representative	FR	Ethics Committees				✓
Pierre-Henri Bertoye	FR	Ethics Committees	✓		✓	
Virginie Rage-Andrieu	FR	Ethics Committees				
Jean-Marc Davy	FR	Ethics Committees				
Laura Mackey	IE	Ethics Committees		✓		
Louise Houston	IE	Ethics Committees				
Chita Murray	IE	Ethics Committees		✓		
Marianne Carson	NO	Ethics Committees	✓			
Ethics Representative	NO	Ethics Committees	✓			
Helena Kames Kjeldgaard	NO	Ethics Committees			✓	
Eunika Książkiewicz	PO	Ethics Committees				
Maria Alexandra Ribeiro	PT	Ethics Committees				
Ethics Representative	RO	Ethics Committees				
Tina Majonen	SE	Ethics Committees				
Jadranka Boturović Ponikvar	SI	Ethics Committees				
Marjeta Zorman Terčelj	SI	Ethics Committees				
Noemie Manent	EMA	EMA		✓		
Stiina Aarum	EMA	EMA	✓			

Stakeholder Representatives

TABLE A4: LIST OF ORGANISATIONS INCLUDED IN THE 'COMBINE' STAKEHOLDER REFERENCE GROUP

'COMBINE' stakeholder reference group
ACRO (Association of Clinical Research Organizations)
AMDM (Association of Medical Diagnostics Manufacturers)
Biomedical Alliance in Europe
COCIR (European Coordination Committee of the Radiological, Electromedical and Healthcare IT Industry)
Conect4Children Stichting
EAN (European Academy of Neurology)
EATRIS (European Infrastructure for Translational Medicine)
ECRIN (European Clinical Research Infrastructure Network)
EUCOPE (European Confederation of Pharmaceutical Entrepreneurs)
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 (Medtech & Pharma Platform) Association
NBCG-Med (Notified Body Coordination Group)
TEAM-NB (European Association for Medical Devices of Notified Bodies)
VE (Vaccines Europe)

Annex B: Track 2 Survey

Survey Questions

TABLE B1: TRACK 2 COMBINED STUDIES SURVEY TO MEMBER STATES

Q	Question	Answer	Comments
	Competent Authorities		
1	With regards to the competent authority which is responsible for CT's/CI's/PS's in you Member State, which of the following applies:	i. CI/CT/PS regulator is one entity, even if this is different departments. " ii. CT/PS regulator is one entity, CI regulator is a different entity. " iii. CI/CT regulator is one entity, PS regulator is a different entity. " iv. CI/PS regulator is one entity, CT regulator is a different entity. " v. CI/CT/PS are regulated by three different entities." vi. CI/CT/PS are regulated by more than three different entities (i.e., more than one entity regulates CI's or CT's or PS's). If this is the case, provide more details in the comments box. "	
2	Does your Member State offer any advice to sponsors of combined studies prior to application?	Yes / No	
3	If "Yes" to Q2, is national scientific advice for combined studies offered (only for the clinical trial aspects of the study)?	Yes / No / Not applicable	
4	If "Yes" to Q2, are pre submission meetings offered prior to the application of combined studies?	Yes / No / Not applicable	
5	If "Yes" to Q4, is there a fee for pre submission meetings?	Yes / No / Not applicable	

Q	Question	Answer	Comments
	Ethics Committees		
6	Does your Member State have a dedicated ethics committee to review CI's or PS's (not combined studies)?	Yes / No	
7	With regards to ethics committee opinions for CT's/CI's/PS's in your Member State, which of the following applies:	i. There is at least one ethics committee entity which can give opinions for CI's, CT's and PS's. " ii. There is at least one ethics committee entity which can give opinions for CT's and PS's, but will not review CI's." iii. There is at least one ethics committee entity which can give opinions for CI's and CT's, but will not review PS's." iv. There is at least one ethics committee entity which can give opinions for CI's and PS's, but will not review CT's. " v. CI/CT/PS must be reviewed by different ethics committee entities."	
8	Where at least one ethics committee entity in your Member State will give an opinion for more than one study type (answers i-iv in Q7), the study will be subject to:	i. A single ethics committee review with a single opinion being provided at the end of the process. ii. A separate ethics committee review for each of the study types, with a single opinion being provided at the end. iii. A separate ethics committee review for each of the study types, with separate opinions being provided at the end.	
9	Is it a requirement to obtain ethics approval prior to Competent Authority submission of CI and PS in your Member State?	Yes / No	

Q	Question	Answer	Comments
	Processes		
10	For which of the following can a sponsor submit a single application for ethics approval in your MS, even if this is composed of multiple forms:	i. CT/PS combined studies only ii. CI/CT combined studies only iii. CI/PS combined studies only iv. CI/CT/PS combined studies v. None of the above - separate applications must be made for each	
11	If answer i-iv is selected for Q10, can this application be made on a single application form?	Yes / No / Not applicable	
12	For which of the following can a sponsor submit a single application for Competent Authority approval in your Member State, even if this is composed of multiple forms:	i. CT/PS combined studies only ii. CI/CT combined studies only iii. CI/PS combined studies only iv. CI/CT/PS combined studies v. None of the above - separate applications must be made for each	
13	If answer i-iv is selected for Q12, can this application be made on a single application form?	Yes / No / Not applicable	
14	For which of the following can a sponsor submit a single application for both ethics and Competent Authority approval in your Member State, even if this is composed of multiple forms:	i. CT/PS combined studies only ii. CI/CT combined studies only iii. CI/PS combined studies only iv. CI/CT/PS combined studies v. None of the above - separate applications must be made for each	
15	If answer i-iv is selected for Q14, can this application be made on a single application form?	Yes / No / Not applicable	

Q	Question	Answer	Comments
	Legislation		
16	Does your Member State have national legislation, including requirements on ethics committees, for studies conducted under IVDR:	Yes / No	
17	Does your Member State have national legislation, including requirements on ethics committees, for studies conducted under MDR:	Yes / No	
	Resources/Communication		
18	In your Member State, do ethics committees communicate their final decisions to the relevant Competent Authorities?	i. Yes in all cases ii. Yes in some cases iii. No in all cases	
19	In your Member State, do Competent Authorities communicate their final decisions to the relevant ethics committees?	i. Yes in all cases ii. Yes in some cases iii. No in all cases	
20	Is there a national public portal for the submission of ethics applications for studies under IVDR?	Yes / No	
21	Is there a national public portal for the submission of ethics applications for studies under MDR?	Yes / No	
22	How many combined study applications which fall under CTR and IVDR have your Member State received per year since IVDR came into force?	#	
23	How many studies referred to in Q22 have been multinational?	#	
24	How many combined study applications which fall under CTR and MDR have your Member State received per year since MDR came into force?	#	
25	How many studies referred to in Q24 have been multinational?	#	
26	How many combined study applications which fall under CTR, IVDR and MDR have your Member State received per year since IVDR came into force?	#	
27	How many studies referred to in Q26 have been multinational?	#	

Aggregate Survey Results

In total 24 / 28 Member States replied to the survey. For individual questions, where it is indicated that a certain number of Member States did not provide a response, this includes the four Member States that did not respond to the survey.

TABLE B2: AGGREGATE SURVEY RESULTS FOR QUESTIONS 1-21.

	Competent Authorities		
Q1	**With regards to the competent authority which is responsible for CT's/CI's/PS's in you Member State, which of the following applies:**	**n**	**%**
	CI/CT/PS regulator is one entity.	17	61%
	CI/PS regulator is one entity; CT regulator is a different entity.	3	11%
	No Response or did not respond to survey	8	29%
Q2	**Does your Member State offer any advice to sponsors of combined studies prior to application?**	**n**	**%**
	Yes	16	57%
	No	7	25%
	No Response or did not respond to survey	5	18%
Q3	**If "Yes" to Q2, is national scientific advice for combined studies offered (only for the clinical trial aspects of the study)?**	**n**	**%**
	Yes	12	43%
	No	3	11%
	Not applicable	7	25%
	No Response or did not respond to survey	6	21%
Q4	**If "Yes" to Q2, are pre submission meetings offered prior to the application of combined studies?**	**n**	**%**
	Yes	10	36%
	No	6	21%
	Not Applicable	7	25%
	No Response or did not respond to survey	5	18%
Q5	**If "Yes" to Q4, is there a fee for pre submission meetings?**	**n**	**%**
	Yes	2	7%
	No	7	25%
	No Response or did not respond to survey	19	68%

	Ethics		
Q6	**Does your Member State have a dedicated ethics committee to review CI's or PS's (not combined studies)?**	**n**	**%**
	Yes	12	43%
	No	12	43%
	No Response or did not respond to survey	4	14%
Q7	**With regards to ethics committee opinions for CT's/CI's/PS's in your Member State, which of the following applies:**	**n**	**%**
	At least one Ethics Committee can give opinions for CI's, CT's and PS's	17	61%
	At least one Ethics Committee can give opinions for CI's and PS's, but will not review CT's	4	14%
	CI's, CT's and PS's must be reviewed by different EC's	1	4%
	No Response or did not respond to survey	6	21%
Q8	**Where at least one ethics committee entity in your Member State will give an opinion for more than one study type (answers i-iv in Q7), the study will be subject to:**	**n**	**%**
	A single ethics committee review with a single opinion being provided at the end of the process.	13	46%
	A separate ethics committee review for each of the study types, with separate opinions being provided at the end.	8	29%
	Not Applicable	1	4%
	No Response or did not respond to survey	6	21%
Q9	**Is it a requirement to obtain ethics approval prior to Competent Authority submission of CI and PS in your Member State?**	**n**	**%**
	Yes	10	36%
	No	13	46%
	No Response or did not respond to survey	5	18%

	Processes		
Q10	**For which of the following can a sponsor submit a single application for ethics approval in your MS, even if this is composed of multiple forms:**	**n**	**%**
	CI/PS combined studies only	4	14%
	CI/CT/PS combined studies	4	14%
	None of the above - separate applications must be made for each	15	54%
	No Response or did not respond to survey	5	18%

Q11	If answer i-iv is selected for Q10, can this application be made on a single application form?	n	%
	Yes	5	18%
	No	1	4%
	No as separate ethics applications must be made for each study type	15	54%
	No Response or did not respond to survey	7	25%
Q12	**For which of the following can a sponsor submit a single application for Competent Authority approval in your Member State, even if this is composed of multiple forms:**	**n**	**%**
	CI/PS combined studies only	2	7%
	None of the above - separate applications must be made for each	20	71%
	No Response or did not respond to survey	6	21%
Q13	**If answer i-iv is selected for Q12, can this application be made on a single application form?**	**n**	**%**
	Yes	2	7%
	Not Applicable	20	71%
	No Response or did not respond to survey	6	21%
Q14	**For which of the following can a sponsor submit a single application for both ethics and Competent Authority approval in your Member State, even if this is composed of multiple forms:**	**n**	**%**
	CI/PS combined studies only	2	7%
	None of the above - separate applications must be made for each	20	71%
	No Response or did not respond to survey	6	21%
Q15	**If answer i-iv is selected for Q14, can this application be made on a single application form?**	**n**	**%**
	Yes	2	7%
	Not applicable	20	71%
	No Response or did not respond to survey	6	21%

	Legislation		
Q16	**Does your Member State have national legislation, including requirements on ethics committees, for studies conducted under IVDR:**	**n**	**%**
	Yes	19	68%
	No	5	18%
	No Response or did not respond to survey	4	14%
Q17	**Does your Member State have national legislation, including requirements on ethics committees, for studies conducted under MDR:**	**n**	**%**
	Yes	22	79%
	No	2	7%
	No Response or did not respond to survey	4	14%

	Resources/ Communication		
Q18	**In your Member State, do ethics committees communicate their final decisions to the relevant Competent Authorities?**	**n**	**%**
	Yes in all cases	14	50%
	Yes in some cases	6	21%
	No in all cases	4	14%
	No Response or did not respond to survey	4	14%
Q19	**In your Member State, do Competent Authorities communicate their final decisions to the relevant ethics committees?**	**n**	**%**
	Yes in all cases	9	32%
	Yes in some cases	6	21%
	No in all cases	8	29%
	No Response or did not respond to survey	5	18%
Q20	**Is there a national public portal for the submission of ethics applications for studies under IVDR?**	**n**	**%**
	Yes	6	21%
	No	18	64%
	No Response or did not respond to survey	4	14%

Q21	Is there a national public portal for the submission of ethics applications for studies under MDR?	n	%
	Yes	7	25%
	No	17	61%
	No Response or did not respond to survey	4	14%

TABLE B3: SURVEY RESULTS BY MEMBER STATE FOR Q22-27

Annual Combined Studies						
Country Code	CTR/IVDR	Multinational CTR/IVDR	CTR/MDR	Multinational CTR/MDR	CTR/IVDR/MDR	Multinational CTR/IVDR/MDR
AT	13	13	3	1	0	0
BE	32	30	4	4	0	0
CY	0	Not applicable	0	Not applicable	0	Not applicable
CZ	12	7	5	3	0	Not applicable
DK	7	7	0	0	0	0
EE	3	3	0	0	0	0
FI	8	8	1	1	0	0
FR	43	43	7	8	0	Not applicable
DE	35	No response given	10	No response given	0	0
EL/GR	5	5	0	0	0	0
IE	7	6	2	2	0	0
IT	30	30	Unknown exactly (<30)	Unknown	Unknown (<10)	Unknown
LV	2	2	0	0	0	0
LU	0	N/A	0	N/A	0	N/A
NL	12	12	6	3	0	0
PL	40	40	5	5	none	Not applicable
PT	6	6	2	2	0	0
RO	10	10	0	0	0	Not applicable
SK	7	7	0	0	0	0
SI	1	1	0	0	0	0

ES	51	47	8	8	0	0
SE	11	11	4	4	0	Not applicable
NO	8	8	2	2	0	0

Member State Survey Responses

TABLE B4: CONSOLIDATED MEMBER STATE RESPONSES FOR Q1-19. IN GREEN THE MEMBER STATE RESPONSES WERE MODIFIED AS THE ANSWER WAS DEPENDANT ON THE PRECEDING QUESTION, FOR EXAMPLE Q5 ONLY APPLIES IF THE ANSWER TO Q4 WAS YES.

MS Response	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Q17	Q18	Q19
AT	i.	Yes	No	Yes	No	Yes	i.	i.	Yes	iii.	Yes	iii.	Yes	v.	N/A	Yes	Yes	i.	iii.
BE	i.	Yes	Yes	No	N/A	No	i.	iii.	No	v.	N/A	v.	N/A	v.	N/A	Yes	Yes	i.	i.
BG																			
HR																			
CY	iv.	No	N/A	N/A	N/A	Yes	i.	i.	No	iv.	Yes	v.	N/A	v.	N/A	No	No	i.	ii.
CZ	NR	Yes	Yes	Yes	NR	Yes	v.	N/A	Yes	v.	N/A	v.	N/A	v.	N/A	Yes	Yes	ii.	iii.
DK	i.	Yes	Yes	Yes	Yes	Yes	i.	iii.	No	v.	N/A	v.	N/A	v.	N/A	Yes	Yes	i.	i.
EE	iv.	No	N/A	N/A	N/A	Yes	NR	NR	NR	NR	NR	v.	N/A	v.	N/A	Yes	Yes	iii.	iii.
FI	i.	Yes	Yes	No	N/A	No	iv.	i.	Yes	iv.	Yes	v.	N/A	v.	N/A	Yes	Yes	ii.	iii.
FR	NR	Yes	No	Yes	No	No	i.	i.	No	v.	N/A	v.	N/A	v.	N/A	Yes	Yes	i.	i.
DE	i.	Yes	Yes	No	N/A	Yes	iv.	iii.	Yes	iii.	No	v.	N/A	iii.	yes	yes	Yes	i.	i.
EL/GR	i.	No	N/A	N/A	N/A	No	i.	i.	No	v.	N/A	v.	N/A	v.	N/A	Yes	Yes	i.	iii.
HU	i.	Yes	Yes	No	N/A	Yes	iv.	iii.	Yes	v.	N/A	v.	N/A	v.	N/A	Yes	Yes	i.	i.
IE	i.	Yes	Yes	Yes	No	Yes	i.	iii.	No	v.	N/A	v.	N/A	v.	N/A	Yes	Yes	i.	i.
IT	iv.	No	N/A	N/A	N/A	No	NR	i.	Yes	v.	N/A	v.	N/A	v.	N/A	Yes	Yes	i.	i.
LV	i.	Yes	No	No	N/A	Yes	i.	i.	Yes	iv.	NR	NR	NR	NR	NR	Yes	Yes	ii.	ii.
LT																			
LU	i.	Yes	N/A	N/A	N/A	Yes	i.	i.	no	iv.	NR	NR	NR	NR	NR	Yes	Yes	i.	i.
MT																			
NL	i.	NR	NR	NR	NR	No	i.	i.	No	iii.	Yes	iii.	Yes	iii.	Yes	Yes	Yes	i.	NR
PL	NR	No	N/A	N/A	N/A	No	iv.	NR	Yes	v.	N/A	v.	N/A	v.	N/A	Yes	Yes	i.	iii.
PT	i.	No	N/A	N/A	N/A	No	i.	i.	No	v.	N/A	v.	N/A	v.	N/A	No	Yes	ii.	ii.
RO	i.	Yes	NR	Yes	No	No	i.	i.	Yes	v.	N/A	v.	N/A	v.	N/A	No	Yes	iii.	ii.
SK	NR	No	Yes	Yes	Yes	No	i.	i.	Yes	v.	N/A	v.	N/A	v.	N/A	Yes	Yes	iii.	iii.
SI	i.	Yes	Yes	Yes	No	No	i.	i.	No	v.	N/A	v.	N/A	v.	N/A	No	No	iii.	iii.
ES	i.	Yes	Yes	No	N/A	No	i.	iii.	No	v.	N/A	v.	N/A	v.	N/A	No	Yes	ii.	ii.
SE	i.	Yes	Yes	Yes	No	Yes	i.	iii.	No	v.	N/A	v.	N/A	v.	N/A	Yes	Yes	ii.	ii.
NO	i.	Yes	Yes	Yes	No	Yes	i.	iii.	No	iii.	Yes	v.	N/A	v.	N/A	Yes	Yes	i.	i.

	Response Pending	**N/A**	Not Applicable
	Dependant on another Q	**NR**	No Response

TABLE B5: CONSOLIDATED MEMBER STATE RESPONSES FOR Q20-27

MS Response	Q20	Q21	Q22	Q23	Q24	Q25	Q26	Q27
AT	No	No	13	13	3	1	0	0
BE	No	No	32	30	4	4	0	0
BG								
HR								
CY	No	No	0	N/A	0	N/A	0	N/A
CZ	No	No	12	7	5	3	0	N/A
DK	No	No	7	7	0	0	0	0
EE	No	No	3	3	0	0	0	0
FI	No	No	8	8	1	1	0	0
FR	Yes	Yes	43	43	7	8	0	N/A
DE	Yes	Yes	35	NR	10	NR	0	0
EL/GR	No	No	5	5	0	0	0	0
HU	Yes	Yes	NR	NR	NR	NR	NR	NR
IE	No	No	7	6	2	2	0	0
IT	No	No	30	30	Unknown exactly (<30)	Unknown	Unknown (<10)	Unknown
LV	No	No	2	2	0	0	0	0
LT								
LU	No	No	0	NA	0	NA	0	NA
MT								
NL	Yes	Yes	12	12	6	3	0	0
PL	No	No	40	40	5	5	none	N/A
PT	No	Yes	6	6	2	2	0	0
RO	No	No	10	10	0	0	0	N/A
SK	No	No	7	7	0	0	0	0
SI	No	No	1	1	0	0	0	0
ES	No	No	51	47	8	8	0	0
SE	Yes	Yes	11	11	4	4	0	N/A
NO	Yes	Yes	8	8	2	2	0	0

Response Pending

N/A Not Applicable

NR No Response

Annex C: Track 3 list of ongoing work

TABLE C1: TRACK 3 OUTPUT SHOWING A LIST OF ONGOING AND FUTURE DOCUMENTS RELATED TO COMBINED STUDIES. LINKS ARE PROVIDED FOR EASE OF USE.

Document	Medicinal product/ In vitro diagnostic/ Medical device	In progress /Published	Topic(s) included	Link
Regulatory advice on combined studies	Medicinal product, Medical device, In vitro diagnostic		Within Accelerating Clinical Trials in the EU (ACT EU) initiative PA7 on scientific advice a pilot process is being established for providing regulatory advice on combined studies involving national experts within CTR, MDR and IVDR respectively.	https://accelerating-clinical-trials.europa.eu/our-work/scientific-advice_en
CLINICAL TRIALS REGULATION (EU) NO 536/2014 QUESTIONS & ANSWERS	Medicinal product	Published	Overall CTR guidance. Specific Question 1.12: A study might involve a medical device – what does this mean in terms of EU Regulation of clinical trials?	regulation5362014_qa_en.pdf (europa.eu)
Q&A on the interface between Regulation (EU) 536/2014 on clinical trials for medicinal products for human use (CTR)	Medicinal product, In vitro diagnostic	Published		mdcg_2022-10_en.pdf (europa.eu)

and Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR)				
Q&A on performance studies	In vitro diagnostic	In progress		Will be published here: https://health.ec.europa.eu/medical-devices-sector/new-regulations/guidance-mdcg-endorsed-documents-and-other-guidance_en#sec12
MDCG 2021-6 Revision 1: Regulation (EU) 2017/745 – Questions & Answers regarding clinical investigation	Medical device	Published	Guidance on clinical investigation under MDR including "Annex III: Does my combination product study require an MDR clinical investigation submission?"	https://health.ec.europa.eu/document/download/f124f630-389e-4c45-90dc-24ec0a707838_en?filename=mdcg_2021-6_en.pdf
MDCG 2021-8: Clinical investigation application / notification documents	Medical device	Published	In absence of EUDAMED, MDCG has these suggested application forms for Member States for clinical investigations (MDR)	https://health.ec.europa.eu/document/download/13265ec7-1776-41af-afb6-e0a64bc407b5_en?filename=mdcg_2021-8_en.pdf
MDCG 2022-19: Performance study application/ notification documents	In vitro diagnostic	Published	In absence of EUDAMED, MDCG has these suggested application forms for Member	https://health.ec.europa.eu/document/download/4e1f946d-a71a-42c7-bd98-

			States for performance studies (IVDR)	0e9977752669_en?filename=mdcg_2022-19_en.pdf
MDCG xxxx-xx: Guidance on content of the Investigator's Brochure for clinical investigations of medical devices (MDR only)	Medical device	In progress		Will be published here: https://health.ec.europa.eu/medical-devices-sector/new-regulations/guidance-mdcg-endorsed-documents-and-other-guidance_en#sec12
MDCG xxxx-xx: Guidance on content of the Clinical Investigation Plan for clinical investigations of medical devices (MDR only)	Medical device	In progress		Planned to be published here January 2024: https://health.ec.europa.eu/medical-devices-sector/new-regulations/guidance-mdcg-endorsed-documents-and-other-guidance_en#sec12
MDCG 2023-1: Guidance on the health institution exemption under Article 5(5) of Regulation (EU) 2017/745 and Regulation (EU) 2017/746	Medical device and In vitro diagnostic	Published	Explains requirements for MD and IVDs that are not CE market, but manufactured and used in routine clinical practice, within a health institution, according to the exemption in MDR/IVDR article 5(5)	https://health.ec.europa.eu/document/download/05b15d55-1bcf-4e17-99c4-15c706325847_en?filename=mdcg_2023-1_en.pdf
EMA/37991/2019: Questions & Answers for applicants, marketing authorisation holders	Medicinal product, Medical device,	Published	Integral products and medicinal products that include a medical device. Not	Questions & Answers for applicants, marketing authorisation holders of medicinal products and

of medicinal products and notified bodies with respect to the implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations ((EU) 2017/745 and (EU) 2017/746)	In vitro diagnostic		specific for trials but generally for applicants.	notified bodies with respect to the implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations ((EU) 2017/745 and (EU) 2017/746) (europa.eu)
EMA/CHMP/QWP/BWP/259165/2019: Guideline on quality documentation for medicinal products when used with a medical device	Medicinal product, medical device	Published	Product-specific quality aspects of a medical device, or device part, that may have an impact on the quality, safety and/or efficacy of a medicinal product.	QWP-BWP Guideline on medicinal products used with a medical device (europa.eu)
EMA/CHMP/BWP/534898/2008 Rev. 2 - Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials – 27 January 2022.	Medicinal product, medical device	Published	Quality requirements for biological medicinal product but includes some information about medical device in section P.7. Container closure system.	https://health.ec.europa.eu/document/download/bd71e2e7-4df1-491a-8775-c6483a97f749_en?filename=mp_eudralex_guideline-quality_en_0.pdf
EMA/CHMP/BWP/545525/2017 Rev. 2 - Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal	Medicinal product, medical device	Published	Quality requirements for chemical/pharmaceutical medicinal product but includes some information about medical device in section 2.2.1.P.7 Container closure system.	https://health.ec.europa.eu/document/download/257ad13a-c480-4c34-82df-1760ad1d5f68_en?filename=mp_eudralex_guideline-chemical_en_1.pdf

products in clinical trials – 27 January 2022.				
EMA/298712/2022: Complex clinical trials – Questions and answers	Medicinal product	Published	Question 5: Which principles apply, and which regulatory pathways should be considered when using biomarkers and biomarker assays in complex clinical trials and consequently applying for marketing authorisations?	medicinal_qa_complex_clinical-trials_en.pdf (europa.eu)
MDCG xxxx-xx: Guidance on Safety reporting in performance studies of *in vitro* diagnostic medical devices Regulation (EU) 2017/746	In vitro diagnostic	Draft	i.e. how to report Serious Adverse Device Effects (SADE's) during a performance study	Will be published here: https://health.ec.europa.eu/medical-devices-sector/new-regulations/guidance-mdcg-endorsed-documents-and-other-guidance_en#sec12
MDCG 2020-10/1: Guidance on safety reporting in clinical investigations	Medical device	Published	I.e. how to report Serious Adverse Device Effects (SADE's) during a clinical investigation	https://health.ec.europa.eu/system/files/2022-11/md_mdcg_2020-10-1_guidance_safety_reporting_en.pdf
MDCG 2020-16: Guidance on Classification Rules for in vitro Diagnostic Medical Devices under Regulation (EU) 2017/746	In vitro diagnostic	Published	For example, included clarification of the companion diagnostics definition.	https://health.ec.europa.eu/system/files/2023-02/md_mdcg_2020_guidance_classification_ivd-md_en.pdf

MDCG 2021-24: Guidance on classification of medical devices	Medical device	Published		https://health.ec.europa.eu/system/files/2021-10/mdcg_2021-24_en_0.pdf
MDCG xxxx-xx: Guidance on borderline issues for in vitro diagnostic medical devices	In vitro diagnostic	Draft	Guidelines about IVD qualification which is being adapted to the IVDR.	Update of current document from 2012: https://www.medical-device-regulation.eu/wp-content/uploads/2019/05/2_14_1_rev2_ol_en.pdf
Manual on Borderline and Classification in the Community Regulatory Framework for Medical Devices	Medical device, In vitro diagnostic	Published	It records the agreements reached by Member States for borderline cases. Regularly updated.	https://health.ec.europa.eu/medical-devices-sector/new-regulations/guidance-mdcg-endorsed-documents-and-other-guidance_en
Guideline on predictive biomarker-based assay development in the context of drug development and lifecycle	Medicinal product, In vitro diagnostic	Coming guidance	In follow-up to the Concept Paper EMA/CHMP/800914/2016; please refer to the consolidated 3-year workplan of the Methodology Working Party	Concept paper on predictive biomarker-based assay development in the context of drug development and lifecycle (europa.eu)
Frequently asked questions on medicinal products development and assessment involving companion diagnostic (CDx)	Medicinal product, In vitro diagnostic	Published		frequently-asked-questions-medicinal-products-development-and-assessment-involving-companion-diagnostic-cdx_en.pdf (europa.eu)

ISO 14155:2020 **Clinical investigation of medical devices for human subjects** **Good clinical practice**	Medical device	Published	GCP for clinical investigations of medical devices	Standard Can be bought at national standardization organization or from ISO ISO 14155:2020 - Clinical investigation of medical devices for human subjects — Good clinical practice
ISO 20916:2019 - In vitro diagnostic medical devices **Clinical performance studies using specimens from human subjects** **Good study practice.**	In vitro diagnostic	Published	GCP for performance studies	Standard Can be bought at national standardization organization or from ISO ISO 20916:2019 - In vitro diagnostic medical devices — Clinical performance studies using specimens from human subjects — Good study practice
Guideline for good clinical practice E6(R2)	Medicinal product	Published	R3 under revision	ICH E6 (R2) Good clinical practice - Scientific guideline | European Medicines Agency (europa.eu)

Annex D: Issue list

Annex D: Issue list

Annex E: Contribution from MedTech Europe

This data is provided for information. Inclusion of this information should not be seen as an endorsement of the accuracy or the validity of the data by the COMBINE project group.

Annex E: MedTech Europe

Annex F: Contribution from EFPIA

This data is provided for information. Inclusion of this information should not be seen as an endorsement of the accuracy or the validity of the data by the COMBINE project group.

Annex F: EFPIA