EU Survey 2023

Targeted consultation on the implementation of the Clinical Trials Regulation (EU) No 536/2014

Factual summary report

Disclaimer: This document should be regarded solely as a summary of the contributions made by the targeted stakeholders to the EU survey on the implementation of the Clinical Trials Regulation (EU) No 536/2014.

It cannot in any circumstances be regarded as the official position of the Commission or its services. Responses to the consultation activities cannot be considered as a representative sample of the views of the EU population.

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1. Executive summary

The 'Accelerating Clinical Trials in the EU' (ACT EU) initiative was launched in January 2022 by the Commission, the European Medicines Agency (EMA) and Heads of Medicines Agencies (HMA). ACT EU has a multi-annual programme that is structured in priority actions. Priority Action 2 is about the implementation of the EU Clinical Trials Regulation 536/2014 (CTR). As part of this Priority Action, a survey was issued in 2022. The scope of the survey was to collect initial feedback from sponsors on the challenges they faced with the implementation of the CTR, and whether the CTR requirements are clear enough.

Between Q4 2022 and Q4 2023, the regulatory network took action to address the concerns and doubts reported in the survey.

A second survey (hereafter 'survey n.2') was conducted in September 2023. The aim was to collect again sponsors' feedback on their experience with the implementation of the CTR and on the use of Clinical Trials Information System (CTIS). In addition, the survey n.2 was meant to assess whether the training and guidance material issued in the previous months were useful and whether the user-experience with CTIS has improved. Of note, the survey n.2 took into account the transitional period as described in Article 98 of the CTR.

In the survey n.2, sponsors highlighted a few challenges that persist such as CTIS functionality and user experience, harmonisation and national requirements across the EU, training material and guidance, timelines described in the CTR, and transparency rules. The feedback received on clinical trials combined with medical devices / in vitro diagnostic medical devices highlight the need for clearer guidance, harmonised regulatory processes, and improved communication to address main challenges. Sponsors provided positive feedback too and acknowledged efforts made to address the challenges pointed out in the first survey (survey n.1). It was also noted that useful guidance material has been issued, CTIS functionalities are gradually improving, and there is a good perspective for further harmonisation in the EU.

Since 2022, the Commission, EMA and the Member States have been engaging with sponsors to address the challenges they face. The regulatory network is committed to foster clinical research in Europe and several activities continue to be pursued.

The experience sponsors reported in this survey does not necessarily reflect the most recent status of CTIS user experience and the CTR implementation. Many of the issues reported have been addressed in the meantime (e.g. guidance supporting transition from the Directive to the Regulation on the clinical trials, review of the CTIS transparency rules etc.).

2. Legal framework

The Clinical Trials Regulation (EU) 536/2014 (CTR) applies since 31 January 2022 CTIS, the information system supporting the implementation of the CTR, has become the single-entry point for sponsors and regulators of clinical trials for the submission and assessment of clinical trial applications. The Commission Implementing Regulation (EU) 2022/20 lays down rules for the application of the CTR and setting up the rules and procedures for the cooperation of the Member States in safety assessment of clinical trials. The Commission Delegated Regulation (EU) 2022/2239 of 6 September 2022 amending Regulation (EU) No 536/2014 with regards to labelling requirements for unauthorised investigational and unauthorised auxiliary medicinal products for human use was adopted by the Commission on 6 September 2022. All delegated and implementing acts and other applicable legislation listed on the Commission dedicated website.

The CTR repealed the Clinical Trials Directive (EC) 2001/20/EC and national implementing legislation in the EU Member States, which regulated clinical trials in the EU until 30 January 2022.

The CTR aims to make the EU an attractive and favourable environment for carrying out clinical research on a large scale, with high standards of public transparency and safety for clinical trial participants. The CTR harmonises the processes for assessment and supervision of clinical trials throughout the EU. Yet, the evaluation, authorisation and supervision of clinical trials remain responsibilities of the EU Member States and European Economic Area (EEA) countries.
As per Article 98 of the CTR, the co-legislators agreed on a 3-year of transitional period, starting from the application of the CTR (i.e., transitional period ending on 30 January 2025):

1. During the 1st year transitional period (31 January 2022 – 30 January 2023), clinical trial applications could be submitted either under the CTD in EudraCT[1] or under the CTR via CTIS[2].
2. From 31 January 2023, all initial clinical trial applications must be submitted under the CTR rules.
3. By 31 January 2025, any ongoing trials approved under the CTD will fall under the CTR and information about them will need to be transferred to CTIS.

This transitional phase has been designed for regulators and stakeholders to gain experience on the new CTR rules, on the way they are implemented, and on the use of CTIS.

[1] EudraCT (European Union Drug Regulating Authorities Clinical Trials Database) is the database for all interventional clinical trials on medicinal products submitted to the National Competent Authorities (NCAs) of the European Union (EU)/European Economic Area (EEA) from 1 May 2004 until 30 January 2023 under Directive 2001/20/EC
[2] CTIS (Clinical Trials Information System) is an information system for the submission and assessment of the clinical trials. Articles 80 and 81 of the Regulation 536/2014 assigned the EMA the task of creating an EU Portal and Database. CTIS was launched on 31 January 2022.

From 31 January 2025 onwards, only one set of rules apply, and national implementing legislation in the EU Member States and EEA countries will need to be compliant with the CTR and its Acts (for more information, please see EudraLex volume 10).

If the clinical trials have not transitioned to the CTR by the end of the transitional period contemplated in Article 98 of the CTR, these trials are to be considered as non-compliant with the CTR and sponsors may be subject to corrective measures by Member States pursuant to Article 77 of the CTR.

3. Introduction

In 2022, for the period July-September, commercial and non-commercial users were invited to reply to the first survey on their experience with the implementation of the CTR. The EU survey tool was used to collect the replies, and these have been analysed, and a report was issued in 2023. A report summarizing the findings can be found at this link on the implementation Clinical Trials Regulation 536/2014.

Survey n.2 was launched on 6 September until 4 October 2023 to collect feedback from sponsors in order to:

- evaluate whether the issues identified in the first survey conducted in 2022 have been properly addressed in the meantime,
- capture whether there is clarity on the legal requirements and whether the guidance material provided suffices or further guidance is needed,
- identify possible new challenges.

Sponsors were contacted via two mailing lists: the Stakeholders Organisations Contact points and participants and the Clinical Trial Application Sponsor union contact points.

A total of 186 replies were received for the survey n.2, compared to 62 replies received for the previous CTR survey n.1. Among 186 respondents, 43 had also participated to the previous survey n.1 (~70% of the total respondents to the survey n.1).

The CTR survey n.2 was primarily designed to assess the progress achieved on the implementation of the CTR and the use of the CTIS. Also, the aim was to check whether measures put in place between 2022 and 2023 meet the needs of the sponsors. The results of the survey n.2 will be further elaborated by the regulatory network to identify root causes and adequate solutions.

4. Sponsors profile

Survey n.2 respondents were asked to identify themselves regarding the type of sponsor they represent: (i) commercial sponsor (large industry or SME), (ii) non-commercial sponsors, or (iii) other research structures. Also, they were asked about the country where they are located.

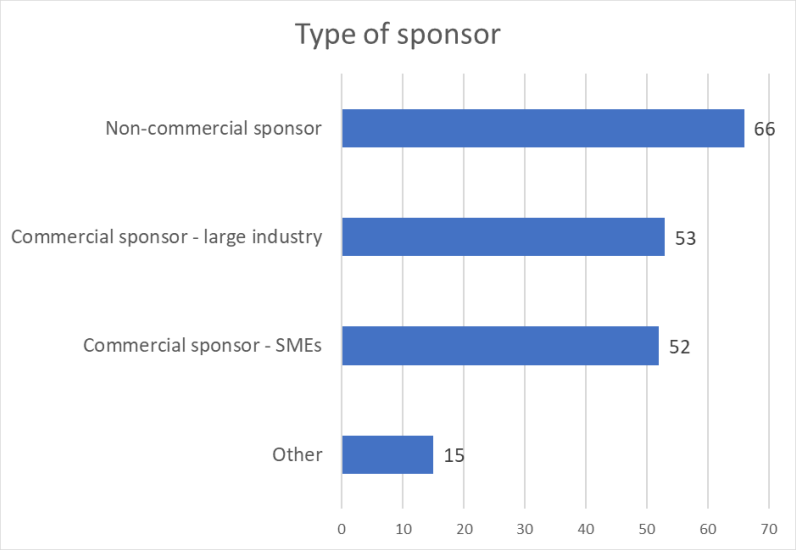

Figure 1. *The distribution of the respondents to the CTR survey n.2. categorised according to sponsor type.*

In 2022, the majority of those that replied to the survey n.1 were large commercial sponsors (18 out of 62) and other sponsors including, commercial sponsors - SME (9 out of 62), non-commercial sponsors (10 out of 62) and other (6 out of 62). In 2023, the number of replies from non-commercial sponsors increased and non-commercial sponsors was the type of sponsors that replied the most (66 out of 186) (figure 1). Chapter 14 in this report outlines the main issues reported by non-commercial sponsors.

In EU/EEA, the majority of those that replied are based in Germany (25 replies), followed by the Netherlands (24), Denmark (17), France (17) Belgium (15) and Italy (12). Respondents from Belgium, 10 out of the 15, notified as non-commercial sponsors. Most of the responses were from 17 EU Member States (119 out of 186 responses).

In addition, some responses were received from non-EU countries, including: the United Kingdom (27), Switzerland (1), Serbia (1), India (2), and China (1). Globally, the majority of those that replied are based in the USA (27).

Figure 2. *Respondents to the CTR survey n.2 categorised based on where the sponsor is located.*

5. Analysis of the answers of survey n.1 vs survey n.2

Chapter 5 provides a summary of the feedback and comments received in the survey 2023. More specifically, this chapter outlines the replies provided by those that contributed to both CTR surveys n.1 and n.2. In the survey n.1, a total of 57 comments (out of 62 replies) were provided on the application of the CTR in the Member States. Several challenges were highlighted at that time, and they have been addressed in the meantime.

5.1 Question 1 – Did you participate in the previous survey on the Clinical Trials Regulation implementation?

At the beginning of the survey, the respondents were asked to indicate whether they had already participated in the survey n.1 in 2022. In total, 43 out of the 186 respondents (23%), indicated that they had participated in the previous survey (figure 3). A total of 62 replies were collected with the survey n.1. This means that ~70% of those that replied to the survey n.1 contributed also to survey n.2.

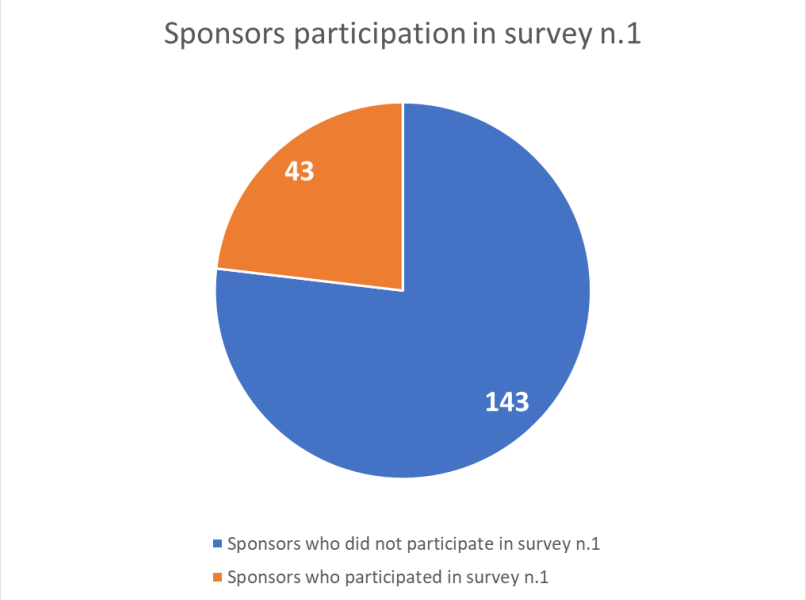

Figure 3. *In total, 23 % of the respondents (43 out of 186) to survey n.2 also participated in the previous Clinical Trials Regulation implementation survey n.1.*

5.2 Question 2 - How would you rate the progress achieved in the last year?

The aim of the CTR survey n.2 was to explore whether there had been progress with the implementation of the CTR taking into account main three aspects:

- the implementation of the CTR by the Member States (national competent authorities (NCAs) and ethics committees),
- the guidance material provided,
- the CTIS functioning and user experience.

Respondents were asked to provide a score to the questions from 1 to 5, where **1 star** was for "**no progress**" and **5 stars** for "**significant progress**". In addition, it was possible to further expand the replies providing additional comments.

5.2.1 Question 2a - Progress achieved on Clinical Trials Regulation implementation

Overall, respondents noticed a slight improvement regarding the CTR implementation (graph on the left-hand side below, figure 4). Nevertheless, respondents that participated in both surveys considered that little progress was done (graph on the right-hand side below, figure 4).

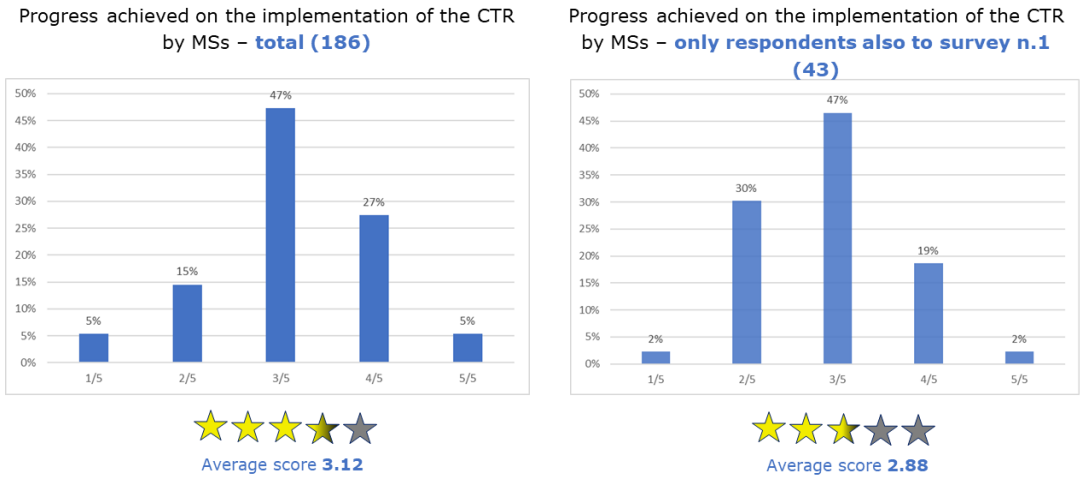

Figure 4. *Progress achieved on the implementation of the CTR. Overall the average score is 3.12 out of 5 considering all the respondents and slightly less if we consider only the respondents also to the survey n.1.*

Respondents were asked to provide comments on progress achieved on the implementation of the CTR. The answers emphasized room for improvement on several aspects:

- NCAs and ethics committees need to comply at the national level with the requirements of the CTR.
- Ethics committees are not necessarily using CTIS system for communicating with sponsors.
- There is a perception that NCAs and ethics committees are overloaded.
- The process for clinical trial approvals with conditions needs to be improved.
- The timelines described in the CTR are considered very stringent.
- Member States require country-specific documents not foreseen in the CTR.
- The coordination role of the reporting Member States (RMS) must be improved.
- There is a lack of harmonisation on transition clinical trials.

5.2.2 Question 2b - Progress achieved on the guidance material provided

Respondents considered that there was an improvement regarding the guidance material available online. The progress achieved got an average score 3.35 out of 5 (on the left side, figure 5). On the other hand, respondents of the survey n.1 acknowledged the progress achieved, but with a slight lower score in comparison with overall evaluation 3.25 to 3.35 (on the right side, figure.5).

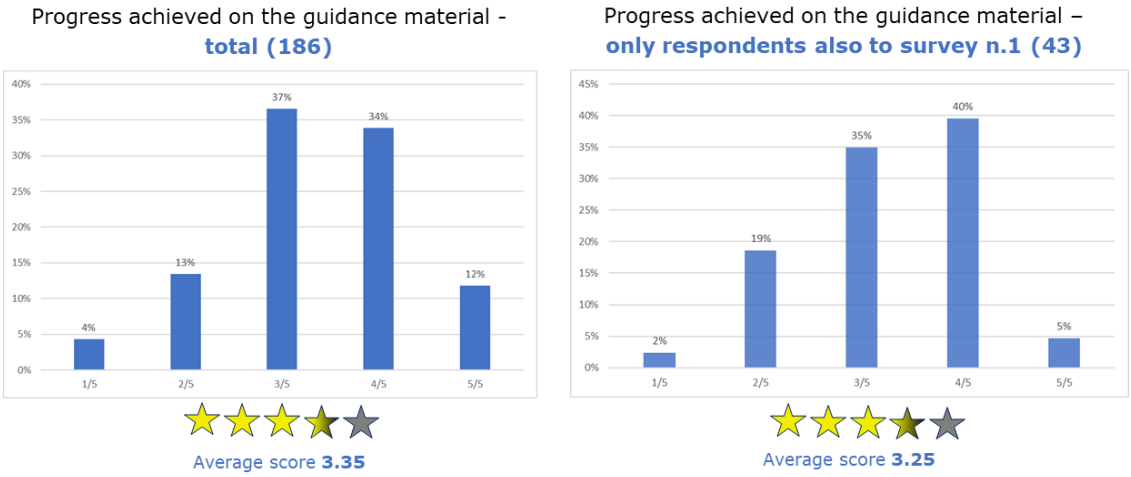

Figure 5. *Progress achieved with regards to the available guidance material.*

However, sponsors provided feedback in the free text where they pointed out a series of challenges that still persist such as difficulties in navigating and understanding available material, contradictory information among different legislative documents (e.g. guidance), extensive documents are provided, difficult to identify updated information in guidance documents.

5.2.3 Question 2c - Progress achieved on the Clinical Trials Information System user experience

The CTIS user experience has got an average score of 2.86 out of 5 (on the left side, figure 6). In general, respondents considered that there was no satisfactory improvement regarding the CTIS user experience.

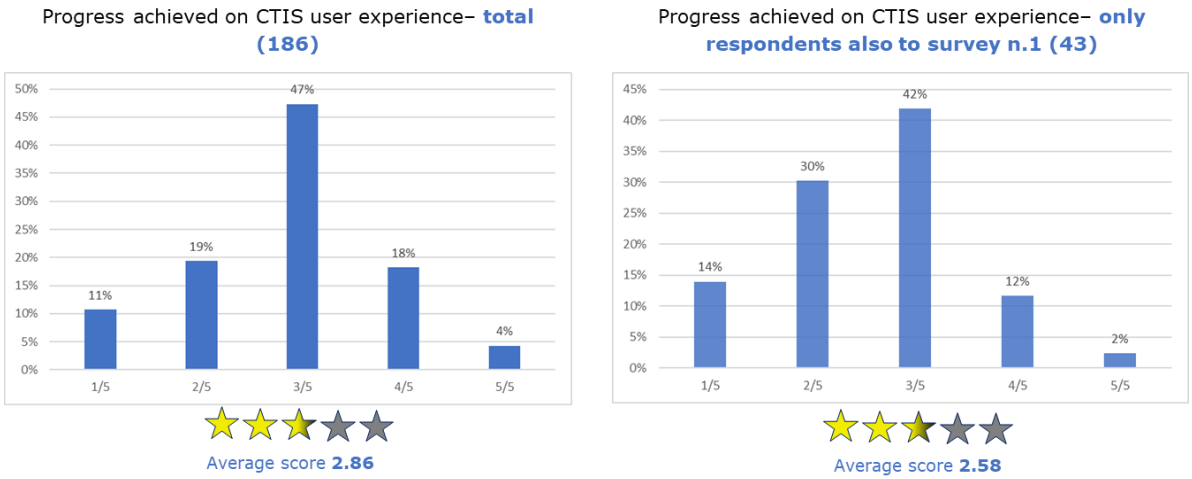

Figure 6. *Progress achieved on the Clinical Trial Information System (CTIS) user experience.*

When providing more details, sponsors reported the following shortcomings that remain:

- CTIS design.
- CTIS system still has many technical bugs and therefore sponsors and regulators have to apply work-arounds.
- The system does not generate alerts.
- The responsiveness of the CTIS helpdesk is slow.
- The system is not user-friendly and is outdated.

6. Identification of blocking issues experienced since 31 January 2023

Chapter 6 outlines the issues that sponsors reported in the survey and that they encountered since the mandatory use of the CTR/CTIS for new initial clinical trials applications (e.g. since 31 January 2023). More specifically, this part of the survey wanted to identify issues that sponsors faced with:

- the use of CTIS,
- the implementation of the CTR itself,
- the harmonisation (or lack thereof) among the Member States, and
- whether there is still need of information / training material.

Sponsors considered the use of the CTIS system (94 out of 186), lack of harmonisation with the EU (86 out of 186) and the application of the CTR (67 out of 186) as the most critical challenges

when submitting the application for authorisation of clinical trials (figure 7).

In the survey n.2, sponsors welcomed the available training material and the guidance documents. On the other hand, some sponsors also emphasised the need of additional guidance materials.

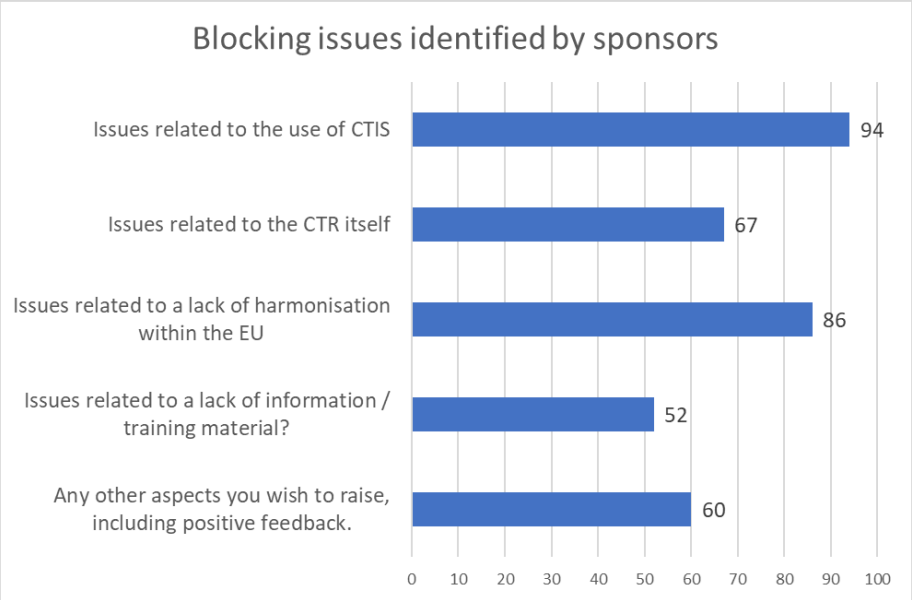

Figure 7. *Blocking issues preventing the submission of clinical trials applications and/or preventing the usage of Clinical Trials Information System.*

6.1 Question 3a - Issues related to the use of Clinical Trial Information System

To inform of the issues related to the use of CTIS, sponsors could select from multiple options. In total, 94 comments were provided representing 51% of participating respondents. The issues related to the CTIS system were listed as follows: CTIS design (48), number of bugs and works-around identified in the system (41), user-friendliness (20), responsiveness of the CTIS helpdesk (18), and alerts not generated by the system (16) (figure 8).

The design of CTIS was ranked at the first position as the most challenging part of the system. This aspect was already noted in the survey n.1 and also the issues related with CTIS were highlighted by the sponsors in paragraph, where they were asked to note a progress achieved on CTIS performance - *Question 2c - Progress achieved on the Clinical Trials Information System user experience.*

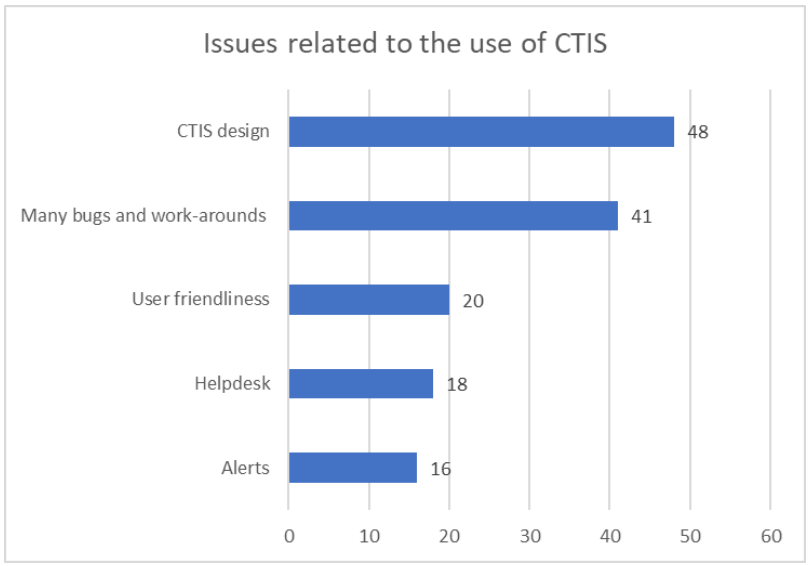

Figure 8. *Issues related to the use of Clinical Trials Information System.*

In the survey n.1 conducted in 2022, 57 comments were received on CTIS. The main concerns identified on CTIS system were related to similar matters as in the survey n.2:

- CTIS design on new functionalities,
- CTIS helpdesk,
- technical problems,
- user-friendliness of the system,
- alerts not generated by the system.

On the matters related to CTIS design, the respondents reported a number of issues:

- managing request for information (RFIs), engaging with the RMS,
- submission of Part I only application followed by a substantial modification,
- managing non-substantial modifications (NSM) and administrative changes,
- submission of investigational medicinal product dossier on quality (IMPD-Q),
- extended EudraVigilance medicinal product dictionary (XEVMPD) database responsible for the collection of the suspected unexpected serious adverse reactions (SUSARS) to medicines.

6.2 Question 3b - Issues related to the Clinical Trials Regulation itself

This question aimed to identify aspects that contribute to the lack of clarity and/or the interpretation of the CTR.

In total, 67 comments (36%) were received (figure 7). Almost half of the comments highlighted issues with the CTR itself (33) and more specifically with stringent timelines of CTR, applicable timelines for substantial modification applications (SM) and non-substantial modifications (NSM), and unclarity related to the General Data Protection Regulation (GDPR) (figure 9).

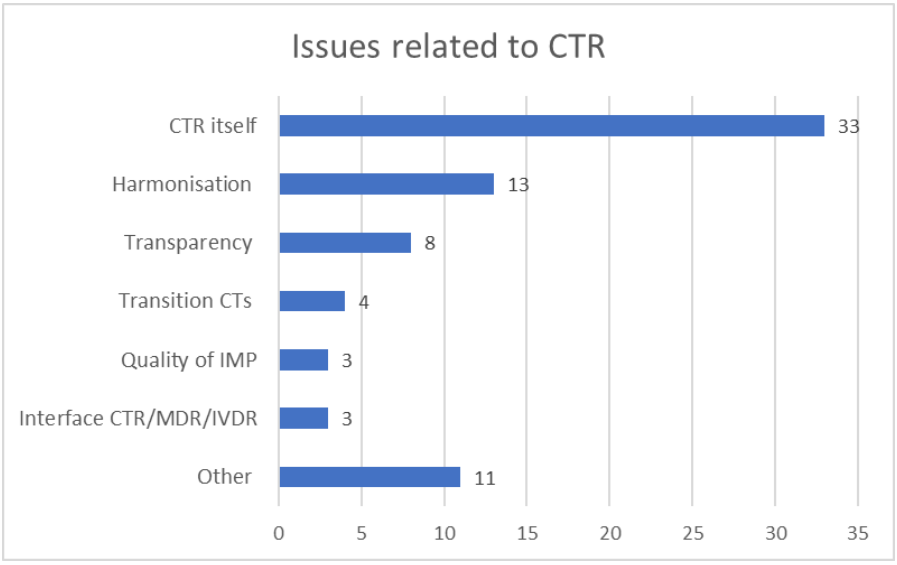

Figure 9. *Issues related to the Clinical Trials Regulation.*

Sponsors reported challenges due to lack of harmonisation across the Members States. For instance, national authorities request documents that are not requested by the CTR. The sponsors are requested to use local requirements and templates[3]. Also, sponsors pointed out inconsistencies between the requirements as described in the CTR, guidance documents, and CTIS system.

6.3 Question 3c - Issues related to lack of harmonisation within the EU

The survey intended to identify issues related to the lack of harmonisation within the EU looking at possible incoherent approaches among the Member States and/or additional (national) requirements. In total, 46% of the respondents provided 85 comments and reported

[3] The sponsors are requested to use templates that are applicable in the local context disregarding the fact that there are templates available on EudraLex volume 10 for Part II documents, which were developed and endorsed by the national contact points (CTAG).

issues with harmonisation (figure 10).

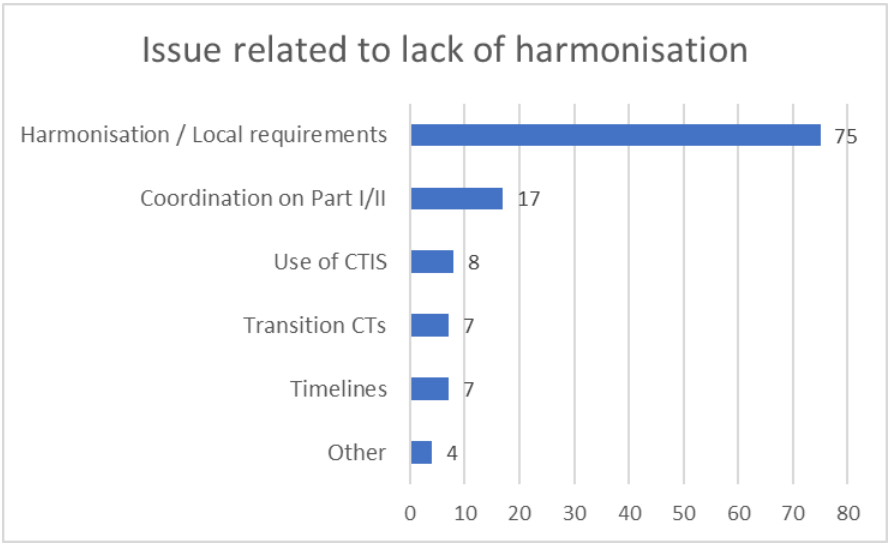

Figure 10. *Issues related to lack of harmonisation.*

The main issues identified were on:

- Heterogeneous interpretation of CTR timelines: implementation of timelines in CTIS and different calculations by sponsors.
- Delays caused by local/national requests e.g national competent authorities and ethics committees (patient-facing materials, Good Clinical Practice (GCP) certifications and translations).
- Little acceptability of EU templates.
- Requests for separate fees, in particular introduction of additional fees by ethics committees at national level.
- Transparency rules linked to the publication of the information on the public portal.
- Lack of clarity on the interface between the CTR and the MDR/IVDR regulations.
- Lack of knowledge of the use of CTIS.

6.4 Question 3d – Issues related to the lack of information / training material

Sponsors provided feedback on the availability and clarity of guidance documents and training material. They noted challenges with retrieving information and/or understanding the texts, thus interfering with the submission of clinical trials applications. In total, 52 comments were received from almost 30% of the respondents (figure 11).

Sponsors pointed out the lack of information on the new topics suggested (22):

- national requirements,
- transition of clinical trials from the Directive to the Regulation,
- auxiliary products,
- combined clinical trials with medical devices/in vitro diagnostic devices,
- annual safety report and development safety update report ASR

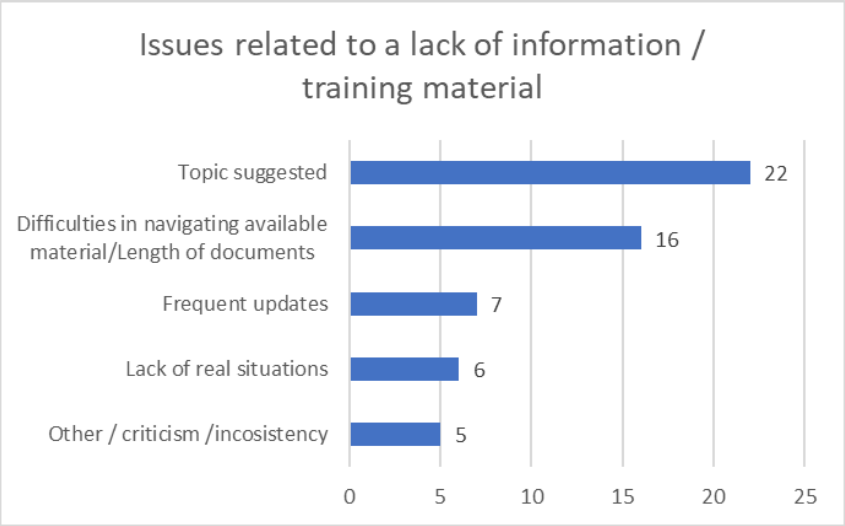

Figure 11. *Issues related to lack of information / training material.*

In addition, sponsors responded that it is difficult to navigate through available documents, as documents are in big volume and lengthy (16). Also, sponsors noted that official regulatory documents are frequently updated, and it is difficult to keep track and implement the requirements provided in the latest version (7). In the training materials provided use cases are lacking real situation examples (6).

In comparison, in the survey report n.1, 14 comments were received on the lack of information including: low intervention clinical trials, inconsistencies on between guidance document (e.g. guidance on deferrals for publication) and CTIS requirements, request for separate fees and

procedures, complete Q&A appendix 2 and 3, submission of complex clinical trial applications in CTIS (e.g. submission of master protocols), contradictory information given to specific topics through different communication channels: Commission Q&A, EMAs webinars and Member State concerned (MSC) in CTIS.

6.5 Question 3e. Other aspects

In the last section of the survey, sponsors reported positive remarks as well as challenges not necessarily covered in the previous sections such as: transparency rules linked to the information publicly available on CTIS, stability and functionalities issues of CTIS, number of bugs related to the use of CTIS, additional national requirements. Sponsors reported challenges when submitting applications for complex clinical trials and platform clinical trials with a master protocol and needed additional guidance.

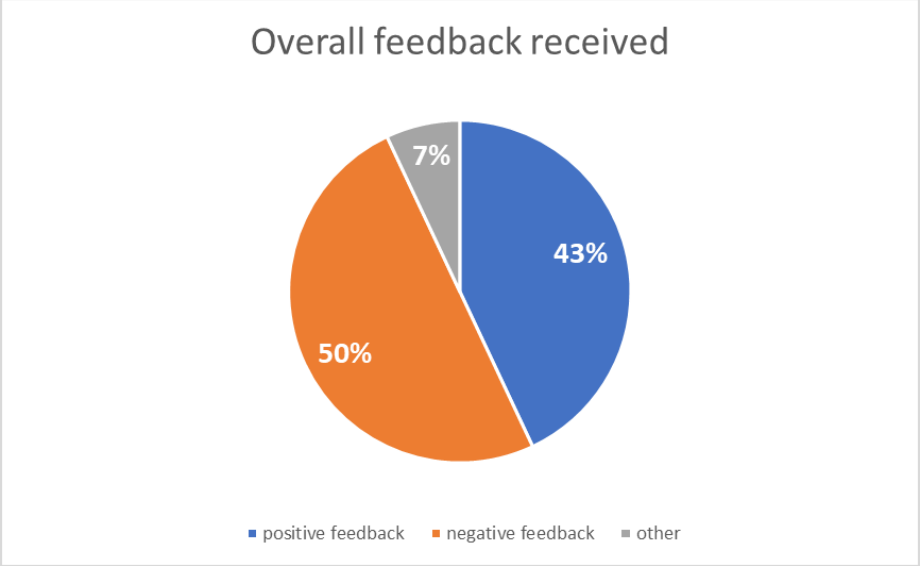

Figure 12. *Issues related to other aspects (positive feedback, negative feedback, other).*

Despite the remaining challenges with the implementation of the CTR and with the use of CTIS, it was acknowledged that efforts have been made and the environment for clinical trials has improved. It was noted that there is accessible useful guidance material, the functionalities of CTIS are gradually improving, and that there is a good perspective for further harmonisation in the EU.

7. Question 4 - What would be the priority to improve CTIS user experience?

This section assessed the functioning of CTIS and what can be done to improve the user experience of the system (figure 13). Respondents were asked to rank from the most urgent to the least urgent 4 problematic areas.

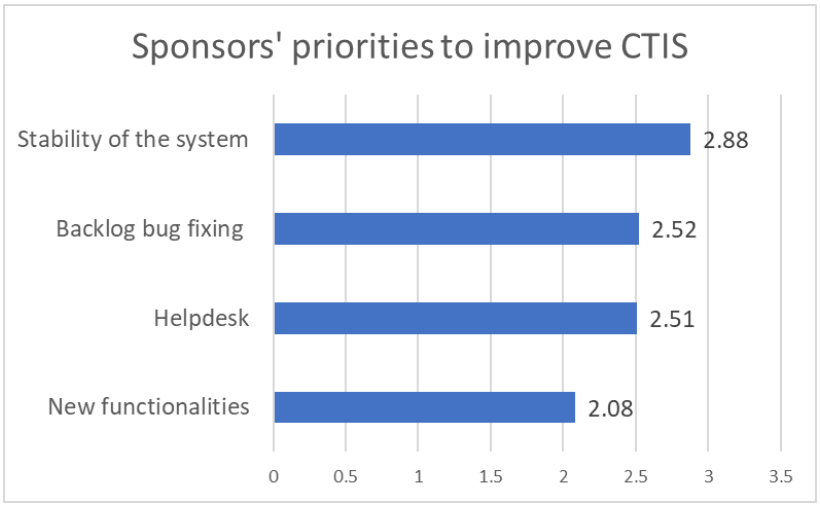

Figure 13. *Elements to be improved of the Clinical Trials Information System.*

The key problematic areas were ranked as follows: the most urgent is on improving stability of the system (2.88) and followed by backlog bug fixing (2.52) and enhancement of CTIS helpdesk functionality (2.51). Development of new functionalities (2.08) was considered as the least urgent compared to the other three issues mentioned above.

8. Question 5 - Requests for information (RFIs)

According to the requirements of the CTR, the clinical trial application is divided into two parts: Part I and Part II. Part I contains scientific and medicinal product documentation. Part II contains the national and patient-level related documentation focusing on aspects as informed consent, compensation arrangements, recruitment of subjects and protection of personal data.
The reporting Member State (RMS) and the Member States concerned (MSCs) can raise requests for information (RFI)s during the Part I assessment and during the Part II assessment, respectively.
This section of the survey n.2 investigated the proportionality and the clarity of the RFIs that sponsors receive, looking at both Part I and Part II of the dossier.

8.1. Question 5a - How would you evaluate the requests for information (RFIs Part I)?

About the proportionality of the RFIs on Part I of clinical trials application, the respondents agreed more to the statement that RFIs are proportionate and manageable in the given timeframe (111 to 75 out of 186) (figure 14). Similarly, respondents agreed on the fact that RFIs are clearer and in principle more manageable in the given timeframe under the CTR requirements (108 to 78 out of 186). Multiple rounds of RFIs can causes burden to sponsors.

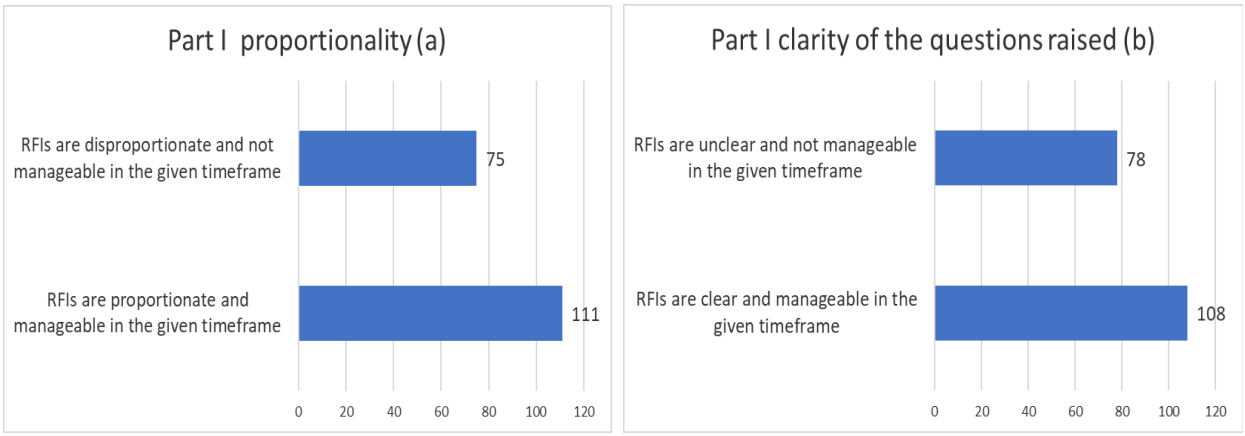

Figure 14. *Assessment of the requests for information (RFI) on Part I through proportionality (a) and clarity aspects (b).*

In addition, the respondents highlighted a few aspects related to RFIs on Part I application, notably:

- **Timeframe for responding to request of information (RFI)**. Many respondents found that given timeframe for responding to RFI is challenging, especially when significant updates to documents are required.
- **Reporting Member State (RMS) coordination**. RMS should better coordinate and consolidate the comments received from different Member States concerned to avoid duplication of requests received. Also, a long list of requests that contains contradictory information should be avoided.
- **Direct communication on request of information (RFI)**. RFIs are not always clear and there is no direct communication channel with the RMS to clarify the request.
- **Redundance and relevance of** considerations in the **request of information (RFI)**. Often the questions received are redundant or irrelevant, and the multiple sequential rounds of RFIs are challenging to manage.
- **Alert notifications**. CTIS system does not generate neither for sponsors nor for the

Member States e-mail alerts when RFIs are submitted leading to potential delays in response from both parties.

8.2. Question 5b - How would you evaluate the requests for information (RFIs Part II)?

Respondents were rather negative about the considerations raised in the request for information for Part II. The majority considers that considerations are disproportionate and not manageable in the given timeframe (107 to 79 out of 186) (figure 15).

Nevertheless, the sponsors were more supportive to the statement that RFIs are clear and manageable in the given timeframe (108 to 78 out of 186)

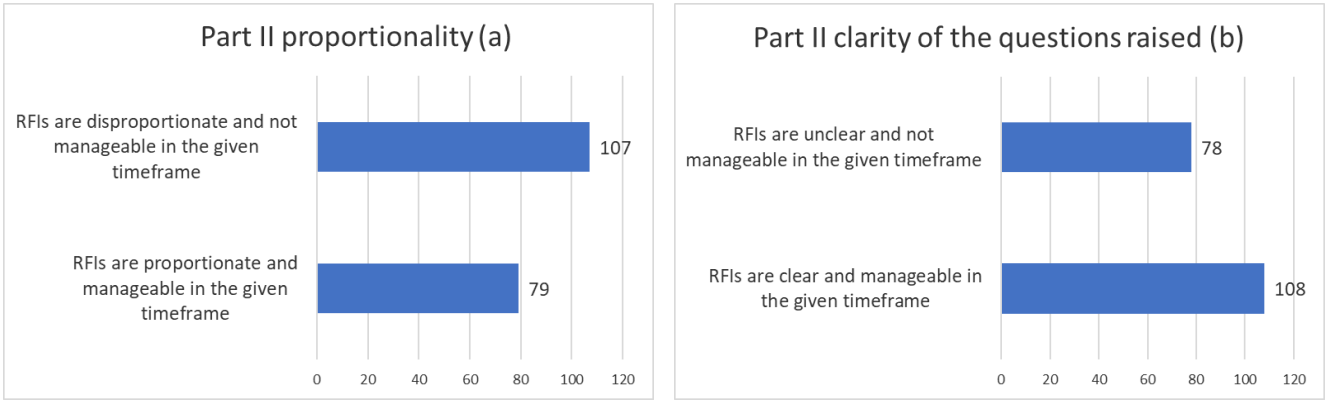

Figure 15. *Evaluation on the requests for information (RFI) Part II through the proportionality (a) and clarity aspects (b).*

In addition, the respondents identified a number of challenges related to RFIs for Part II:

- **Timelines for responding to request for information.** The timeframe available to respond to RFIs is too short, especially considering translation requirements, document updates, and cross-functional alignment.
- **Clarity of questions.** Respondents were rather positive with regards to the clarity of the questions. Though, as per Part I of RFIs, respondents mentioned repetitions in RFIs.
- **National languages.** Issues on languages were identified, as some RFIs are received in a local language, causing delays due to the need to translate and respond.
- **Coordination between Part I and Part II.** Lack of coordination between parts I and II of the application leading to increased workload.
- **Proportionality.** Most of the respondents find the number of considerations neither

proportionate nor manageable in regard to Part II.

- **Communication**. Respondents expressed difficulties with seeking clarifications with regards to the RFIs.

8.3. Question 5c. - Alignment of Part I and Part II

The respondents pointed out that closer alignment of both parts I and II might be needed (figure 16).

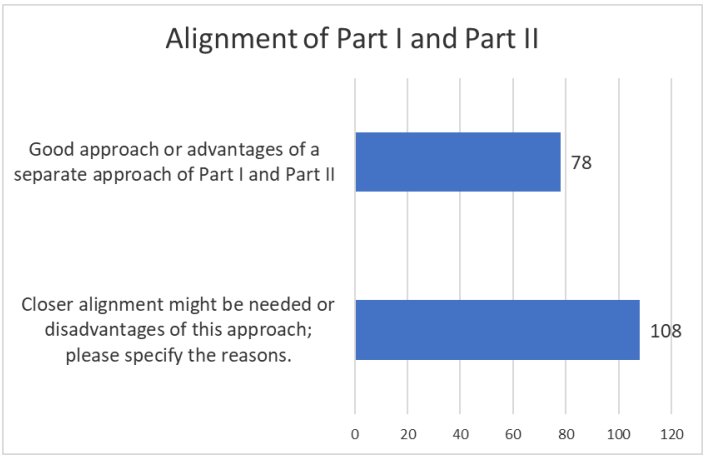

Figure 16. *Alignment of Part I and Part II*

The fact that the clinical trial application is designed and assessed in two parts, Part I and Part II, is generally appreciated. It was noted that the separation of the assessment for parts I and II allows a better distribution of tasks and responsibilities between national competent authorities and ethics committees.

Though, coordination and alignment on parts I and II on the RFIs can be improved to avoid potential delays and multiple submissions. The two assessment procedures for parts I and II can negatively impact the efficiency of the process, especially when there is the request to update documents that impact both parts. The process can be time-consuming and may not achieve the intended goal of speeding up the approval process.

9. Question 6 - Transitioning trials from EudraCT to CTIS

From 31 January 2025, only the rules laid down in the CTR and its delegated acts apply. Therefore, sponsors and regulators must adapt to the new regulatory regime. The clinical trials that are expected to be ongoing after 31 January 2025 will need to be in line with the CTR

requirements and sponsors must transition as soon as possible these trials from EudraCT to CTIS.

In July 2023, the Commission published a stand-alone guidance document to support the transitioning process from the Directive to the Regulation. In addition, the Clinical Trials Coordination Group (CTCG) published a guidance document and a cover letter template to facilitate the transition process.

Sponsors were asked to say whether they could foresee difficulties with the transition (figure 17). In total, 75% of the sponsors envisaged issues when transitioning to the requirements of the CTR.

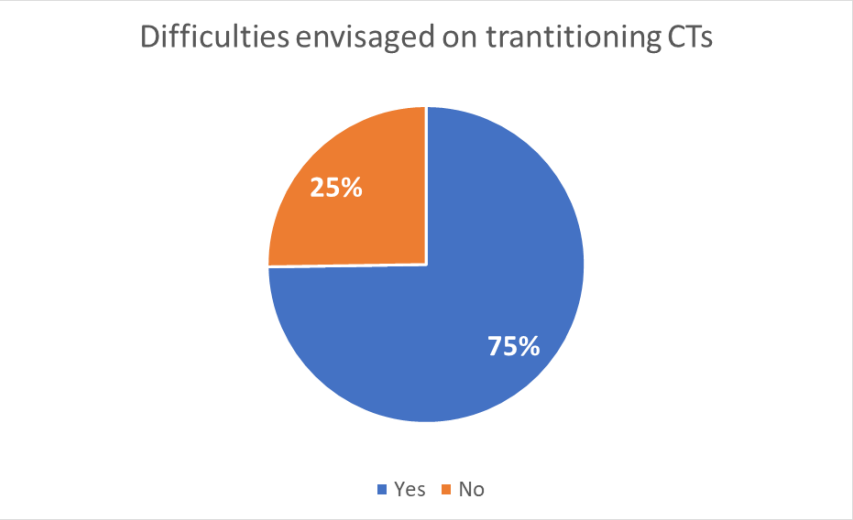

Figure 17. *Difficulties envisaged by sponsors when transitioning trials from EudraCT to Clinical Trials Information System.*

Respondents outlined the following concerns:

- Lack of harmonisation and insufficient guidance material in the Member States.
- Difficulty to find a period without any ongoing assessment for the clinical trials that need to transition from one system into another, especially for those with ongoing substantial modification assessment (SM) and where multiple Member States are involved.
- Delays in approval of substantial modification applications (SM) under the Directive for clinical trials. This affects the planning of the entire processes.

- Documents requested by the Member States but not requested by the CTR and guidance.
- Little capacity of the Member States to handle the surge of transitioning applications, potentially leading to further delays and issues in the process.

Overall, sponsors stressed the need for clearer guidance, better harmonisation among Member States, and more efficient processes to address these challenges and improve the transition experience.

10. Question 7 - Clinical trial involving an investigated medicinal product (IMP) belonging to a third party with proprietary data

Most of the respondents (62%) that participated in the survey n.2 did not envisage issues on clinical trials that involve an investigational medicinal product (IMP) belonging to the third-party with proprietary data (figure 18).

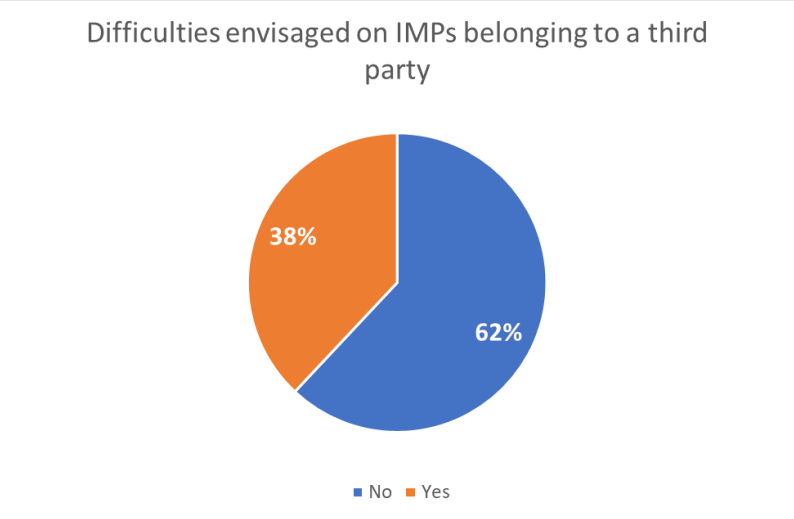

Figure 18. *Clinical trial involving an Investigational Medicinal Product belonging to a third party with proprietary data.*

The remaining 38% of sponsors that provided responses shared concerns on several aspects:

- Complexity and inefficiency of the processes, in particular when the application involves investigational medicinal product dossier on quality (IMPD-Q) only application.
- Difficulty to align parallel submission applications and managing SM in the CTIS system.
- Lack of clear guidance on the transitioning process and conflicting advice is provided

in official documentation.

- Process is time-consuming that leads to increased workload and administrative burden for sponsors and the third parties. Preference for a simpler cross-reference option or a separate role for a product owner within the trial.
- Technical problems with CTIS system performance.
- Lack of familiarity with the official guidance documentation provided among the Member States.

11. Question 8 - Combined clinical trial including a medical device

Combined clinical trials are commonly conducted and are important to ensure that innovative medicinal products and treatments can be available for the patients. Combined clinical trials contain regulatory requirements for the respective individual authorisation process for clinical trials, performance studies in case of in vitro diagnostic (IVD), and clinical investigation in case of medical devices (MD).

Overall, respondents were rather negative on the matters related to combined clinical trials.

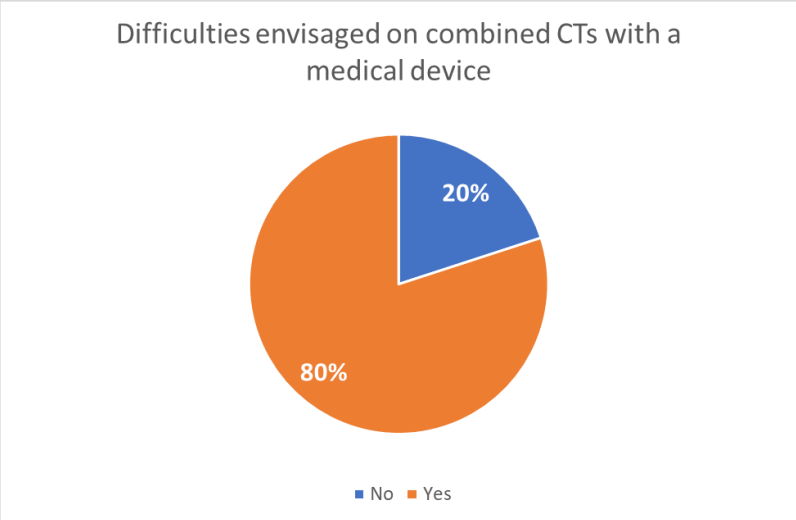

Figure 19. *Issues related to combined clinical trials including a medical device.*

In total, 80% (26 out of 30) of the respondents indicated that they experience difficulties in performing combined clinical trials that involve a clinical application under the CTR and a clinical investigation under the Medical Device Regulation (MDR) (figure 19).

A summary of reported issues related to clinical trials combined with medical devices is listed as follows:

- Lack of clarity and guidance on classifying devices and submission requirements.
- Different interpretations of the regulatory frameworks in the EU Member States on combined clinical trials requirements, thus creating fragmentation and inconsistency.
- Duplication of work and high administrative burden to provide documentation to multiple ethics committees.
- National timelines are lengthy and unpredictable when it comes to clinical trial applications combined with medical devices.
- Weak communication and collaboration among national authorities leading to contradictory requests or lack of clarity.

12. Question 9 - Combined clinical trial application under the Clinical Trials Regulation and a performance study under the In Vitro Diagnostic Regulation

Overall, sponsors provided negative feedback on the identified issues on combined clinical trial application under the CTR together with a performance study under the Regulation on *in vitro* diagnostic device (IVDR). In total, 79% (33 out of 42) of the sponsors that replied to these questions envisage certain issues (figure 20).

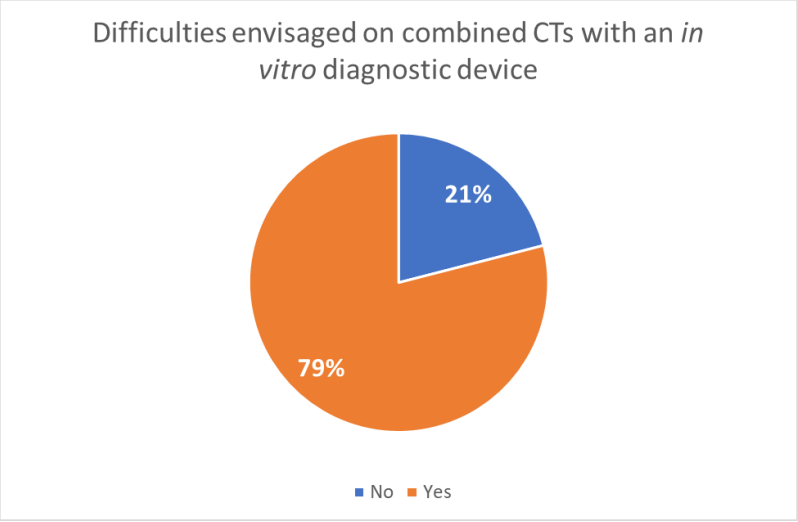

Figure 20. *Issues related to combined clinical trials including an in vitro diagnostic device.*

A summary of reported issues related to clinical trials combined with IVD is listed as follows:

- Lack of coordination and harmonisation between CTR and IVDR regulations.
- National timelines are lengthy and unpredictable when it comes to clinical trial applications combined with IVD.
- Lack of clear guidance on the submission package, applicability of IVDR, and responsibilities of medicines and IVD manufacturers.
- Different interpretations of the requirements based on the stakeholder involved (CROs, Member States, ethics committees, medical doctors and medicines sponsors) leading towards the inconsistency through all the process.
- Difficulties with obtaining feedback from multiple regulators and lack of harmonized feedback.
- Lack of guidance for both sponsors and the Member States.

13. Question 10 - Based on your experience, what are the practical aspects to improve at Clinical Trial Information System level or at Clinical Trials Regulation implementation level?

In this final section of the survey n.2 the respondents were invited to share views based on their experience and provide suggestions on possible improvements related to CTIS or /and implementation of the CTR. Reflections were assessed and grouped into thematic sections illustrated in figure 21 and listed as follow: (i) CTIS design and user experience; (ii) harmonisation / legal requirements; (iii) training material and guidance; (iv) timelines; (v) matters on Part I and Part II of clinical trials application; (vi) CTIS helpdesk; (vii) request for information (RFI); (viii) non substantial modification (NSM) / substantial modification (SM); (ix) transparency rules; (x) IMPD / Auxiliary medicinal products dossier (AxMPD); (xi) MDR / IVDR; (xii) other.

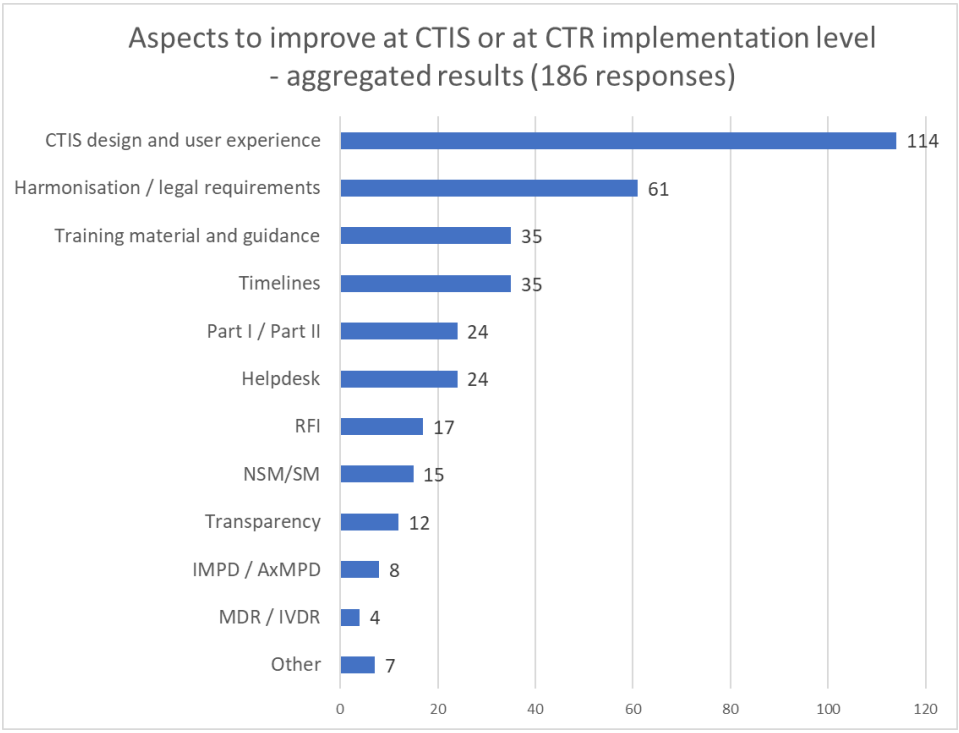

Figure 21. *Issues related to practical aspects to be improved at Clinical Trials Information System level or at Clinical Trials Regulation implementation level.*

Respondents indicated that, based on their experience, the most important practical aspects that need to be improved are related to CTIS system, with particular attention to the **CTIS design and user experience**. Among the comments received on CTIS (114 in total), one aspect was raised several times (28 comments): **the need to have a notification** sent to the sponsor (and regulators) whenever there is an action to be performed in an application (e.g. RFIs uploaded in the system). Other aspects are related to timetable functionalities, bug fixing and system stability and user-friendliness in general.

Then, sponsors consider critical a list of factors that would contribute to foster **harmonisation with the implementation of the CTR and legal certainty,** and therefore simplifying the application procedure:

- Harmonised interpretation and application at Member State level of the CTR.
- Acceptability to use standardised templates.
- Possibility to use English language for most of the documentation.
- Alignment of required submission documents for all Member States.
- Request for more flexibility within the limits of the EU law when it comes to specific

issues such as transition of clinical trials.

Regarding **training material and guidance**, respondents provided both positive and negative reflections. Some respondents found the available training material helpful, while others felt overwhelmed by the amount of information provided and requested more concise and user-friendly guidance, and to have more harmonised national requirements.

Timelines and deadlines were also specified as aspects to be improved. Timelines for responding to requests for information (RFIs) and processing modification applications are perceived as too short and sponsors request more flexibility. At the same time, in sponsors' view, the timelines for the assessment of a clinical trial application are deemed too long.

Many comments (25) are related to **Part I and Part II** of the clinical trial application (e.g. timeline for the assessment, the lack of coordination and need for more alignment).

CTIS Helpdesk was also a recurrent topic. Some respondents appreciated the support provided by the EMA staff to support with the use of CTIS system, while the others found it unsatisfactory.

Respondents identified the process with the **requests for information** (RFIs) as another priority that must be improved (e.g. high number of requests, detailed requirements, differences compared to other jurisdictions, short timelines for the responses, the need of consolidation of the list of considerations by the RMS).

The sponsors also mentioned the need for a smooth implementation of the **Article 81(9) on non-substantial modification (NSM**), and a streamlined process to add Member States.

Respondents also considered critical the **transparency rules** in place with the CTR implementation. The rules are perceived as complex, and sponsors required more clarity and simplification within the limit set by the law.

Some sponsors commented on the need for clarification and harmonisation on **combination studies involving MDs or IVDs**.

Lastly, other comments about:

- Facilitating non-commercial clinical trials.
- The importance of patient centricity.

- Leverage possible flexibilities within the limit of the CTR.
- Need to allocate more resources for processing the clinical trial application.

Overall, various views were put forward with regards to CTIS functioning and the implementation of the CTR. While it was acknowledged that CTIS has improved, praising the efforts of the CTIS helpdesk and welcoming the training material issued in 2022-2023, respondents stressed the need to address key areas that hamper the smooth implementation of the CTR: CTIS functionalities, Member States requirements, divergencies with the duration of the assessment, coordination role of the RMS, transparency rules of the public portal, and training opportunities.

14. Question 10 - Analysis of the responses of non-commercial sponsors

Most of the academic / non-commercial sponsors conduct mono-national clinical trials. The regulatory network intends to support academic / non-commercial sponsors with setting up large multi-national clinical trials.
This objective is mentioned in recital 81 of the CTR which reads as follows:

As regards Directive 2001/20/EC, experience also shows that a large proportion of clinical trials are conducted by non-commercial sponsors. Non-commercial sponsors frequently rely on funding which comes partly or entirely from public funds or charities. In order to maximise the valuable contribution of such non-commercial sponsors and to further stimulate their research but without compromising the quality of clinical trials, measures should be taken by Member States to encourage clinical trials conducted by those sponsors.

Therefore, to set up impactful actions to support non-commercial sponsors, the analysis of the responses to question n.10 has been broken down to sponsor type, in order to better identify the needs of this subgroup.
A total of 66 out of the 186 respondents to the survey n.2 are non-commercial sponsors. According to the replies of non-commercial sponsors, the most important aspect that needs to be improved is CTIS, followed by training material / guidance, and CTIS helpdesk.

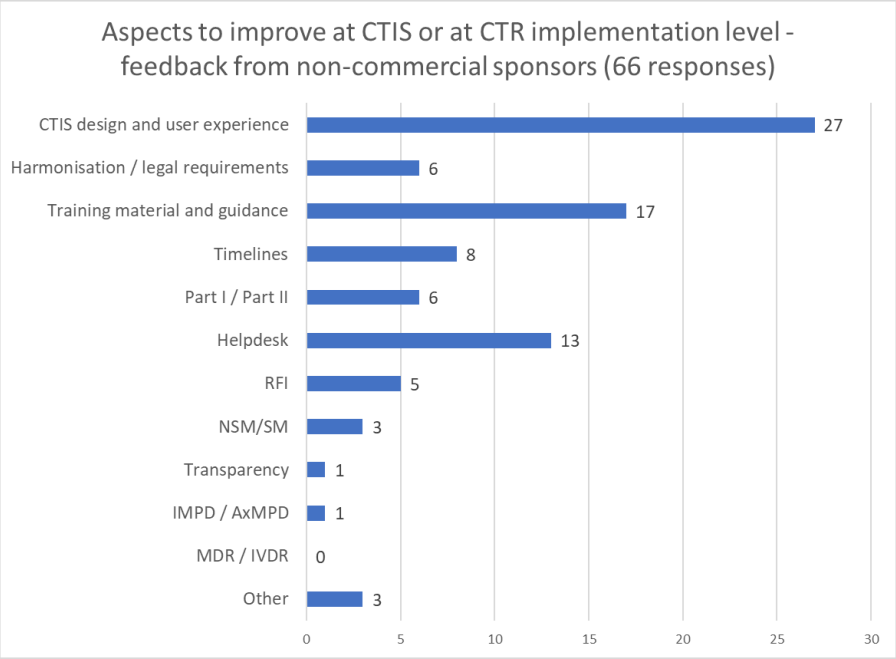

***Figure 22**. Responses to question n.10 received by non-commercial sponsors.*

This analysis can give valuable input and guidance on the need for targeted actions to support non-commercial sponsors to conduct research and comply with the CTR.

15. Identification and classification of the issues raised by sponsors

With the same approach applied to the survey n.1, this chapter explains how the issues were classified and it outlines whether solutions have been provided in the meantime. The issues raised by the sponsors were related to the CTR, CTIS or issues related to lack of harmonisation and coordination across the Member States

15.1. Identification of the issues

With the survey conducted in September 2023, the regulatory network collected a total of 186 responses from sponsors. The comments have been analysed to identify the blocking issues in the implementation of the CTR.

- **Rejected issues:** some replies may be unclear, and the issues may be difficult to

identify. When not understandable or identifiable, the issue has been considered as rejected. Also, the comment is rejected if the (perceived) issue is not going to be addressed any time soon. For instance, timelines outlined in the CTR have been implemented in CTIS. It should be noted that the Regulation 1182/1971 (EEC, Euratom) applies to all due dates of the CTR (e.g. a due date for a Member State cannot fall on a weekend or a national holiday).

- **Solved issues:** at times, sponsors pointed out issues that have been in the meantime or that would soon be addressed.
- **Persisting issues:** persisting issues can be new or existing issues for which no solution has been identified yet between the two surveys.

15.2. Challenges that have been addressed or where action is ongoing

The Commission works with EMA and Member States to discuss possible solutions to the issues identified in survey n.1 and n.2. It should be noted that several issues have been addressed or will be addressed in the near future following the publication of the report of the survey n.2.

15.2.1. Solutions to address issues related to the implementation and enforcement of the CTR

In sponsors views provided in the survey n.2, there is a room for improvement on some issues on the CTR implementation. In the list below there are outlined issues and actions that are implemented and ongoing that are related to the implementation of the CTR.

Issue reported by sponsors	Actions implemented / ongoing
Lack of clarity of legal requirements / request for flexibilities within the limit of the EU law	Regular review of the Q&A document on CTR to clarify elements when sponsors raise questions. • Revision of Q&A with regards to submission of substantial modification applications for aspects covered in Part II; use of conditions; application for additional Member State concerned. • Introduction of Annex III with the list of

	national websites where sponsors can find the information they need in their language. The websites are expected to be complete and kept up-to-date by the responsible national authorities. • Quick guide for sponsors: limited version of the Q&A document with key information.
Auxiliary Medicinal Products in Clinical Trials	Revision of the Recommendations document on the use of Auxiliary Medicinal Products in clinical trials.
Challenges with clinical trial applications that require compliance with the CTR as well as with the Medical Device Regulation and / or In Vitro Diagnostic Regulation.	COMBINE project was launched in 2023 to look at the issues linked to the operational interface between CTR/MDR/IVDR. The COMBINE analysis report has been published on 15 May 2024.
Transitional trials	• Q&A document specifically to support sponsors with a smooth transition from the Directive to the Regulation. • There is a decision-making flow chart to support sponsors decide whether they need to transit their trial. • Increased clarity and transparency on the documents Member States require in addition to the minimum package. • Clarification with regards to the legal implications in case trials authorised under the Directive continue to be conducted under the old regulatory regime on and after 31 January 2025. • CTCG published a *Best Practice Guide* for sponsors of multinational clinical trials with different protocol versions approved in different

	Member States under the Directive 2001/20/EC that will transition to the Regulation (EU) No. 536/2014. Please check the guidance document regularly. • CTCG prepared cover letter template • CTCG prepared Best Practice Guide to sponsors updating the application dossier Part I after CTR transition. • Annex I, Cover letter template First SM after transition. • Annex II, first SM application Part I and/or Part II after CTR transition. • Annex III First SM Part II after transition.
Lack of harmonisation across Europe and different request for documentation and information	In 2024 the Commission has established a 'special group' of ethics committees named MedEthicsEU, which scope is to find convergence on Part II aspects and increase transparency on the national regulatory requirements.

15.2.2. Solutions to address issues related to CTIS

The survey n.2 gave the possibility to sponsors and CTIS users to report their experience with the system. Overall, feedback provided is mixed with many comments highlighting the progress made in the last year and many comments still requesting improvements and/or reporting persisting issues with the use of CTIS. To support CTIS many initiatives are already in place such as:

- **Regular communications**
  - Clinical trials KPI reports are published as part of the ACT EU programme (link)
  - Bi-weekly Newsflash to all users - link
  - Clinical Trials Highlights Newsletter – link
  - CTIS Release Communications - link
- **Regular Events related to CTIS**

- CTIS Walk-in Clinics - link
- Bitesize talks - link
- CTIS Forum
- CTIS Info Day – 25 March 2024 - link

- **Trainings & related materials related to CTIS**
  - Sponsor end user training – 10-13 June
  - CTIS Training environment – survey link to request access
  - Query Management Working Group Q&A on CTR and CTIS – link
  - Step-by-step guide on registering organisations locally in CTIS - link
  - Q&A on protection of personal data & CCI in CTIS – link
  - CTIS website section on transitioning trials – link

Among the issues identified by the sponsors some have already been addressed and implemented while other are ongoing:

Issue reported by sponsors	Actions implemented / ongoing
Increase the user friendliness of the system	Activities ongoing for the modernisation of the system
Facilitate the upload / download of the list of documents	Actions ongoing in the CTIS Simplification[4] task force
Implement missing specific functionalities (e.g. change of the sponsor)	Activities ongoing for the modernisation of the system
Improve the design of the system platform	Activities ongoing for the modernisation of the system
Improvements in the system performance causing delays in the submissions	Continuous Delivery Pipeline (Maintenance) - this involve continues performance improvements being under implementation. E.g. some measures to facilitate the creation of SM for trials involving many MSs
Facilitate the submission of SM or additional Member State applications while other CTAs are under evaluation	Actions ongoing on submission rules

[4] CTIS simplification task force – the aim to improve the user experience, increase operational stability, deliver more efficient training and change management. TF started working in Q1 2024. Membership consists of Commissions, HMA, CTIS PO Member States, CTIS PO EMA, sponsors SMEs (commercial and non-commercial), EMA.

Increase the flexibility for the submission of NSM	Actions ongoing on submission rules
Simplification of the Organisation Management Service (OMS) registration process in OMS	To circumvent the limitations to register certain sites in OMS, EMA introduced the possibility to register sites locally in certain areas of the system
Alternative solutions for the IMPD-Q only submission	Topic to be considered for simplification
Application of transparency rules	Revised CTIS transparency rules and new portal to be launched in production on 18th June

15.2.3. Lack of harmonisation and coordination across the Member States

In the survey report n.2 sponsors provided number of issues related lack of harmonisation and coordination across the Member States. Though a number of solutions have been achieved and some other actions will be undertaken. For instance, issues were reported by the sponsors related to incoherent approaches between the Member States and/or additional national requirements for the sponsors such as different interpretation of the legal requirements (e.g. timelines), lack of usage of standartalised templates, request to translate documentation in national languages, lack of interface between CTR and MDR/IVDR and transitional clinical trials.

Some coordination activities are taking place through the CTCG[5]. Some other aspects directly linked to the implementation of the CTR are handled by the CTAG[6]. For more information on the governance structure of the Clinical Trials landscape in the EU, please refer to the Priority Action 1 of the Accelerating Clinical Trials in the EU on *Governance Rationalisation*.

15.3. Classification of the persisting issues

In the report n.2 number of the issues are identified as persistent and will be assigned to the

[5] CTCG – Clinical Trials Coordination Group, is a group under the Heads of Medicines Agencies (HMA) which is responsible for collaboration among the national competent authorities especially on matters of national competence.
[6] CTAG - Clinical Trials Coordination and Advisory Group, is set by the Clinical Trials Regulation (EU) No 536/2014 in order to support the exchange of information between the Member States and the Commission on the experience acquired with regard to its implementation and assist the Commission on the effective and efficient implementation of the Regulation, including also its implementing acts.

different groups or entities according to their mandate and responsibilities (Commission, EMA, CTAG, CTCG, MedEthicsEU, CTIS Simplification Task Force).

15.3.1. Persisting issues on Clinical Trials Regulation implementation

Some persistent issues reported by the sponsors related to the CTR itself (e.g. timelines, SM and NSM), lack of harmonisation across the Member States e.g. request of additional documentation that is not part of the CTR requirements, transparency rules, transitioning clinical trials, multiple requests of RFIs etc.

15.3.2. Persisting issues Clinical Trials Information System

Majority of the sponsor's feedback received relates to the need for introduction of improvements in the system to address persisting issues:

- Increase the user friendliness of the system.
- Facilitate the upload / download of the list of documents.
- Implement missing specific functionalities (e.g. Change of the sponsor).
- Generate notices and alerts via email.
- Improve the design of the system platform.
- Improvements in the system performance causing delays in the submissions.
- Facilitate the submission of substantial modifications (SM) or additional member states. while others Clinical Trial Applications (CTA) are under evaluation.
- Increase the flexibility for the submission of non-substantial modification (NSM).
- Simplification of the OMS registration process in OMS.
- XEVMPD database and synchronization issues.
- Alternative solutions for the IMPD-Q only submission.
- Application of transparency rules.

In addition, some of the most reported issues by sponsors related to the use of CTIS are:

- Numerous bugs and workarounds still present to date.
- Issues with the timetable functionality.
- Issues with RFIs on Part I and Part II.

Moreover, sponsors requested to improve the timelines for the helpdesk support.

EMA, in consultation with Member States and sponsors will further work on improving user experience with the system and simplification and harmonisation, CTIS Simplification Task Force.

15.3.3. Persisting issues with the lack of harmonisation and coordination

Lack of harmonisation within the EU, incoherent approaches between the Member States and/or additional national requirements for the sponsors such as low acceptance to use standardised templates for Part II documents.

Way forward

Overall, the survey n.2 revealed many challenges have been addressed between Q4 2023 and Q2 2024.

The 5 most critical remaining challenges are:

- Management of RFIs, including the role of the RMS and notifications,
- CTIS use continue to be burdensome,
- Requests from Member States for additional documents not requested by the EU law,
- A smoother communication channel between Member States and between Member States and sponsors is needed,
- IMPD-Q applications.

The regulatory network will continue to improve the clinical trial environment for the benefit of patients and clinical research advancements. To achieve these public health objectives, close collaboration with all the stakeholders is crucial.

Sponsors will continue to be consulted on their experience with the implementation of the CTR.