EU Survey

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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This survey is an Accelerating Clinical Trials in the EU (ACT EU) initiative under priority action 2 on the Clinical Trials Regulation (CTR) implementation. It has been developed by the European Commission, the European Medicines Agency (EMA), the Heads of Medicines Agencies (HMA), and the Clinical Trials Coordination Group (CTCG).

On 31 January 2023, the Clinical Trials Information System (CTIS), the information system supporting the implementation of the CTR, will become the single-entry point for sponsors and regulators of clinical trials for the submission and assessment of initial clinical trial applications. The CTR applies since 31 January 2022, and CTIS is available from that date, starting a transition period when clinical trial applications can be submitted under the Clinical Trials Directive (CTD) or under the CTR, via CTIS. During this 1st year transition period stakeholders have been able to gain some initial experience on the new CTR rules, on the way they are implemented and on the use of CTIS.

This EU survey was launched on 18 July until 9 September 2022 to collect feedback from sponsors and stakeholders in order to:

- understand the overarching hurdles that hamper a smooth implementation of the CTR
- capture how clear the requirements of the CTR are to the stakeholders.

The sponsors were contacted via two mailing lists, the Stakeholders Organisations Contact points and participants (EMA/213027/2019) and the Clinical Trial Application Sponsor union contact points (EMA/639737/2022).

62 sponsors and other stakeholders provided their views on the new regulatory environment provided by the CTR and their experience with CTIS.

The survey was designed to identify the issues encountered but positive feedback was also received regarding CTIS and the new rules in place.

The reported experience does not necessarily reflect the current status of CTIS user experience and the CTR implementation. Many of the issues reported have been addressed in the meantime via resolution of the encountered defects and new functionalities in CTIS, alignment of national legislation, additional guidance material for sponsors, as well as targeted modification of the rules of the CTR by a delegated act[1].

[1] Commission Delegated Regulation (EU) 2022/2239 of 6 September 2022 amending Regulation (EU) No 536/2014 of the European Parliament and of the Council as regards labelling requirements for unauthorised investigational and unauthorised auxiliary medicinal products for human use (C/2022/6240), OJ L 294, 15.11.2022, p. 5.

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1. Sponsors profile

Survey respondents were asked to identify themselves regarding the type of sponsor they represent (commercial sponsor – large industry, SME, non-commercial sponsors) and their country of origin.

The results are summarised in tables 1 and 2.

Table 1: sponsor type

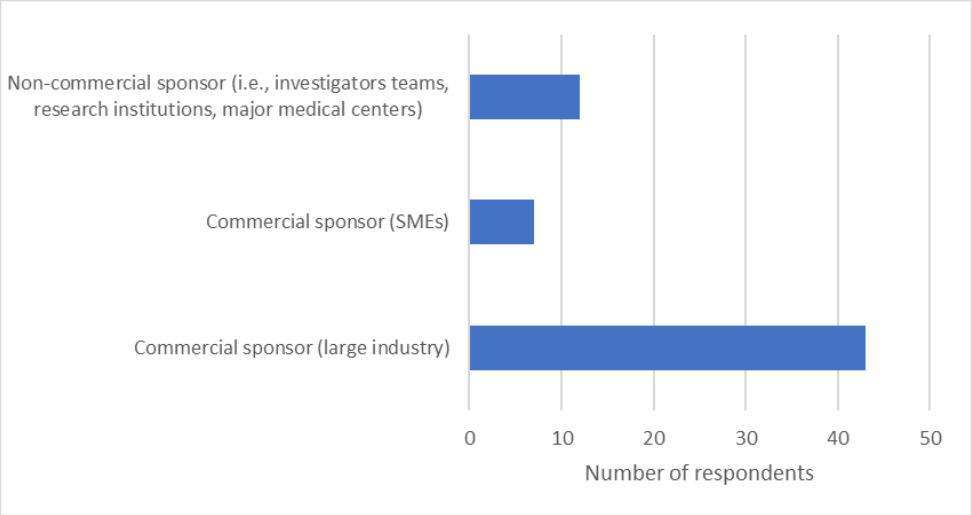
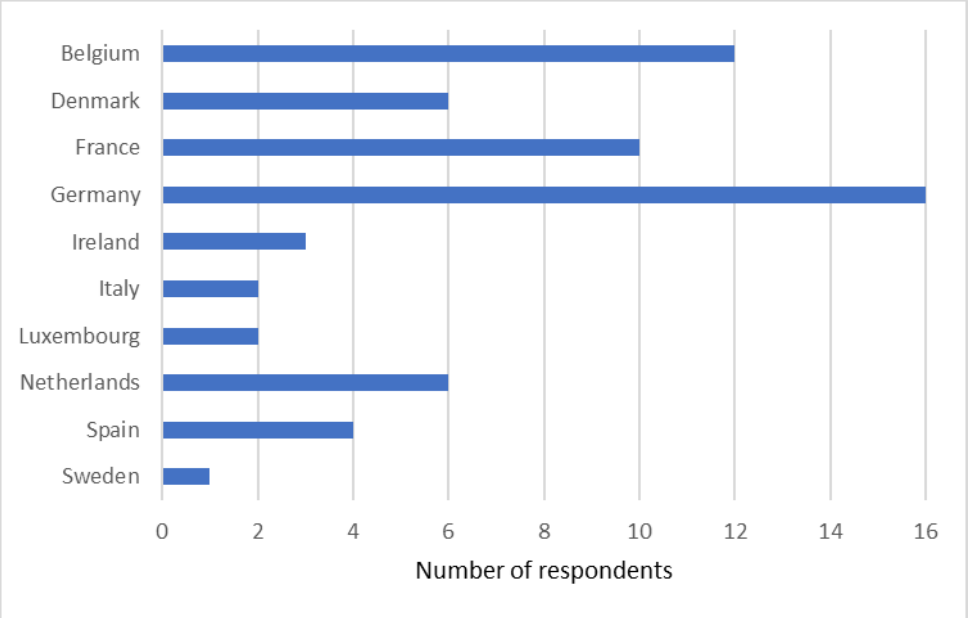


Table 2: country of origin of the sponsor



While the large companies were the most represented group responding to the survey, views were also collected from the other groups, such as SMEs and non-commercial sponsors.

2. Analysis of the answers received

A summary of the comments received is provided below together with the analysis of the answers received.

2.1. Question 1 - What are the blocking issues that are currently driving you to submit the clinical trials applications under the Clinical Trials Directive 2001/20/EC (CTD) instead of the Clinical Trials Regulation (EU) No 536/2014 (CTR)?

a. Issues related to the use of CTIS – lack of knowledge of new system functionalities, experience with technical limitations or problems with the new system.

b. Issues related to the CTR itself – lack of clarity in relation to the legal requirements and/or the interpretations of the new obligations for sponsors.

c. Issues related to a lack of harmonisation within the EU – incoherent approaches between Member States and/or additional (national) requirements.

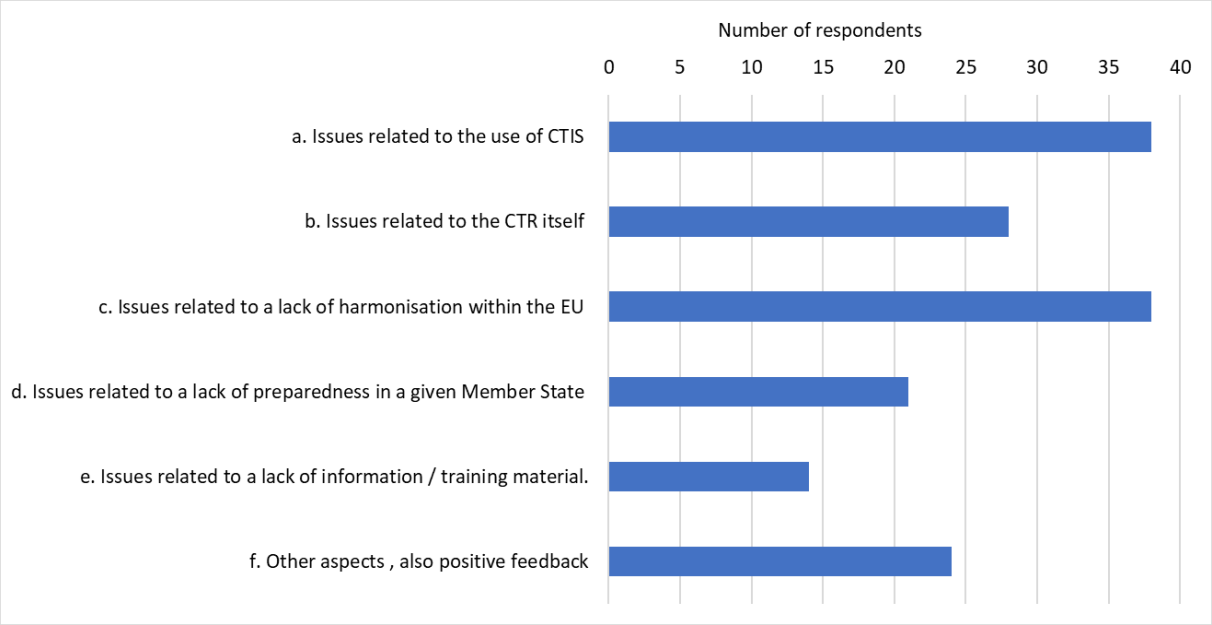
d. Issues related to a lack of preparedness in a given Member State – political uncertainty, lack of expertise, administrative issues.

e. Issues related to a lack of information / training material.

f. Other aspects you wish to raise, also positive feedback, please specify.

The answers received are summarised in table 3 and show that the blocking issues that prevent sponsors applying for authorisation of clinical trials applications under the CTR are related to the use of CTIS, to the CTR itself, and also to the lack of harmonised approach among Member States (MS), including additional national requirements, and the lack of preparedness of some of them. Sponsors welcome the available training material and the guidance documents already available but some sponsors request additional guidance materials.

Table 3: answers to question 1 on the blocking issues that are currently driving submission of clinical trials applications under the CTD instead of the CTR



Summary of the comments provided

a. Issues related to the use of CTIS

Sponsors reported contrasting experiences with CTIS. Positive feedback was received concerning the "one-stop shop" offered by CTIS, and the responsiveness of the helpdesk, while others pointed to difficulties in using CTIS and system stability issues.

Numerous technical problems are reported, such as notification to entities that are not participating in the trial, issues when answering to the request for information (RFI), no access to uploaded documents, deferral request disappearing after submission, incorrect timetable calculation, inability to update application.

Sponsors asked for assurance that CTIS will always preserve the confidentiality of commercial confidential information and asked for more clear guidance about transparency requirements.

Additional functionalities were requested, such as adaptation to handle platform trials and complex trial design, easier process for transition trials, functionality to make easier the application of Article 11 on partial initial application submission of part I and part II. More specific functionalities to enable manual entries for individual site registration

in OMS (now implemented), to indicate missing information when completing the application dossier, to enable the export of the list of submitted documents and an e-mail notification system are requested.

b. Issues related to the CTR itself

The reported issues in the application of the CTR are related to transparency obligations, unclear requirements for patient facing materials, rigidity of the sequential submission of Part I and Part II application, and rigidity of the substantial modification application process.

Managing responses to multiple RFIs within the 12 calendar days, as imposed by the CTR, is perceived as challenging, as well as the IMP validation certification requirements and the labelling requirements in Annex VI.

c. Issues related to a lack of harmonisation within the EU – incoherent approaches between Member States and/or additional (national) requirements.

The lack of harmonisation within the EU is often reported, especially for fees and for patient facing materials and more generally for part II application content (request for a single place to find all the different national requirements).

The lack of clarity of the some national requirements is also mentioned, as well as numerous additional national requirements including informal requests from the Ethics Committees (ECs), requests for IMP import permit, requests for separate payment of fees for National Competent Authorities (NCAs) and ECs, executed site agreements, and documents on the deputy principle investigator.

Sponsors also called for more a harmonised document naming convention (Document naming convention published on the CTCG website [2]) and expressed lack of understanding on reasons for the duration of the deferral period being challenged.

d. Issues related to a lack of preparedness in a given Member State – political uncertainty, lack of expertise, administrative issues.

According to some sponsors, the CTR is not fully integrated in the national legislation of some Member States, and the readiness to deal with the CTR is questioned by some of them, notably regarding the access to CTIS and the lack of some national guidelines. Sponsors claimed that requests from ECs can be unclear and regret the absence of a

[2] https://www.hma.eu/fileadmin/dateien/HMA_joint/00-_About_HMA/03-Working_Groups/CTCG/2022_09_CTCG_Instruction_naming_documents_CTIS_EU_v1.4.pdf

clarification process, as well as the lack of communication between the ECs and the NCAs.

Sponsors also request a central place where to find all the national requirements (national legislation, languages requirements, ECs requirements) applied in the context of the CTR.

e. Issues related to a lack of information / training material.

Sponsors have few requests concerning training, as many training materials and training opportunities are being offered to sponsors, but point to the possibility of further completing certain guidance documents.

Additional guidance documents are requested for a better understanding of the provisions on transparency, for the articulation with the Medical Device Regulation (MDR) and the In Vitro Diagnostic Regulation (IVDR), and for the national requirements for the part II application.

f. Other aspects you wish to raise, also positive feedback, please specify

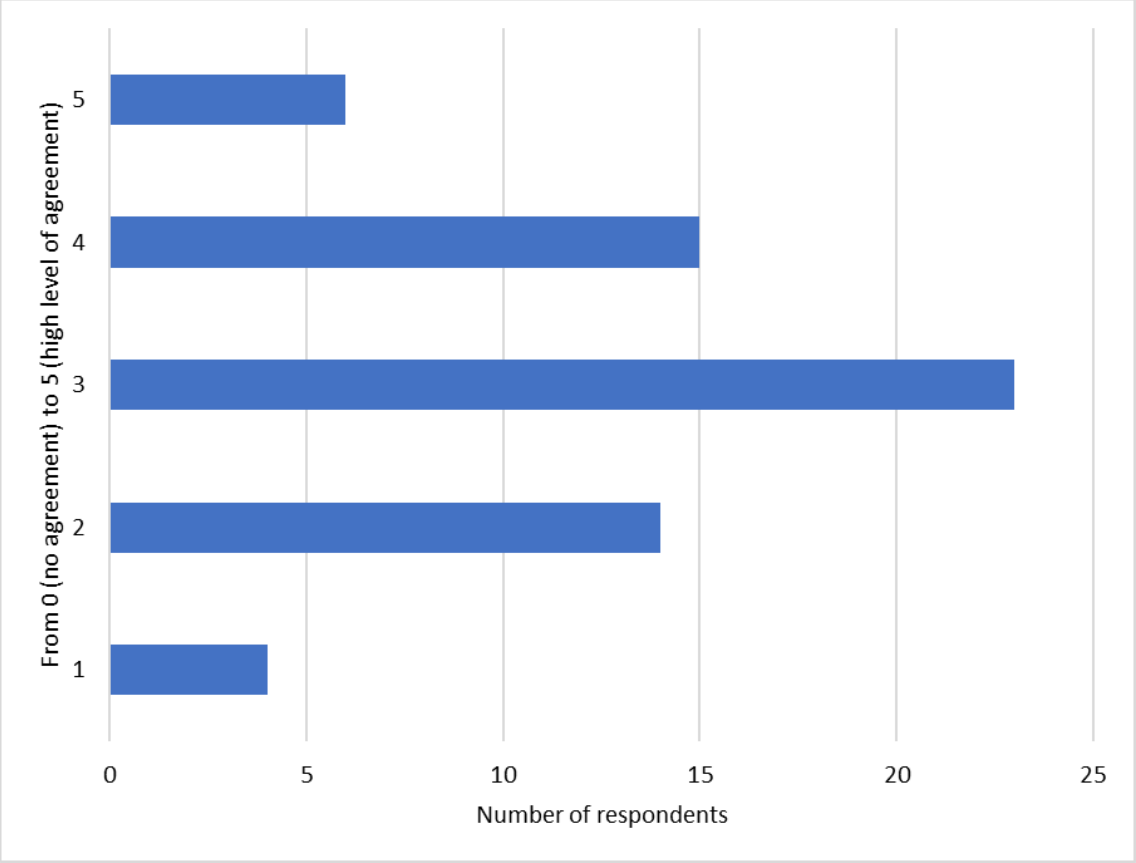
Sponsors appreciate having one tool for all operations related to clinical trial applications.

The lack of preparedness of Contract Research Organisations (CROs) has been reported, as well as the lack of document templates.

2.2. Question 2 - The CTR harmonises the rules for the conduct of clinical trials in the European Union. Based on your experience, to what extent do you agree with this statement from 1 (no agreement) to 5 (high level of agreement) and why?

The answers received are summarised in table 4 and show that the majority of the respondents agree with the statement that the CTR harmonises the rules to conduct clinical trials in the EU, but at different degrees. Comments are provided to explain why the harmonisation is sometimes perceived as incomplete.

Table 4: answers to question 2 on the CTR harmonisation of the rules for the conduct of clinical trials in the European Union



Summary of comments provided

Globally sponsors welcome the harmonisation of the requirements in Part I of the application and regret the lack of harmonisation for the Part II application.

Comments are mainly related to requirements and processes that would go beyond, or not be in line with, the CTR:

- timelines not respected
- RFI not required by the CTR:

- during the validation and Part I Assessment, patient facing materials, CVs and GCP certification for deputy investigators, recruitment process videos by email or Eudralink;

- requests to submit Quality-of-Life validated questionnaires, Case Report Forms requested through an RFI as part of Part I application dossier;
- requests for documents not required under the CTR; and
- country-specific information to be included in the cover letter for the Part I application

- questions sent by email instead of sending RFI in CTIS
- requests to limit response to RFI in the free-text fields in CTIS instead of uploading documents
- request within timeframes shorter than the 12 calendar days
- raising several validation RFI successively instead of compiling them all in one request
- modifying the CTIS timetable during the review because of workload issues

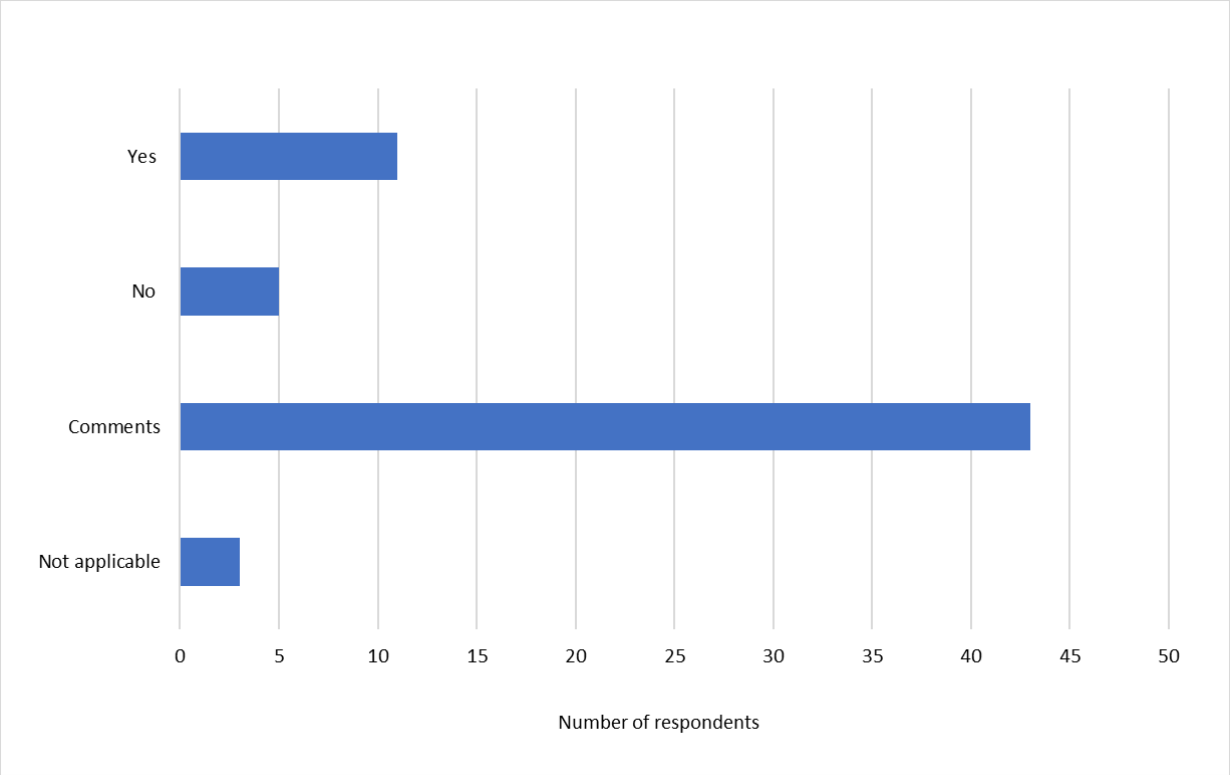
Sponsors also note divergent approaches for completing assessment reports, for naming conventions. They report difficulties in dealing with the 12 days deadline for RFIs answers and call for more transparency on document requirements and for the publication of templates.

2.3. Question 3 - Does the CTR facilitate the set-up of large multi-country trials? If not, what are the obstacles that you have encountered already or that prevent you from setting up multi-country clinical trials under the CTR?

Please explain in max 500 words highlighting the issues that you face systematically. Where possible, without reporting confidential information, you may consider outlining concrete examples.

The answers received are summarised in table 5 and show contrasting views regarding the ability of the CTR to facilitate the set up of large multi-country trials. The comments provided allow for the identification of the encountered obstacles. The obstacles that are often mentioned are the rigidity of the process, which can come from the CTR rules themselves, from CTIS lack of functionalities and/or from different and additional requirements from Member States.

Table 5: answers to question 3 on the CTR ability to set up large multi-country trials and the obstacle to such set up



Summary of comments provided

The respondents have identified the following obstacles in the set-up of large multi-country trials under the CTR:

- difficulties due to the limitation to the harmonisation of requirements,
- specific and additional requirements from Member States;
- rigidity in the sequential submission of substantial modifications and country addition;
- difficulties submitting and coordinating substantial modifications to different MS;
- requirements for registration of clinical trial sites within the Organisation Management Service (OMS) and the lack of flexibility within the OMS;
- lack of protection of company confidential information across the CTIS application and lack of control;
- difficulties managing the limited RFI timelines, especially when RFIs on part II are provided in the local language requiring translation;

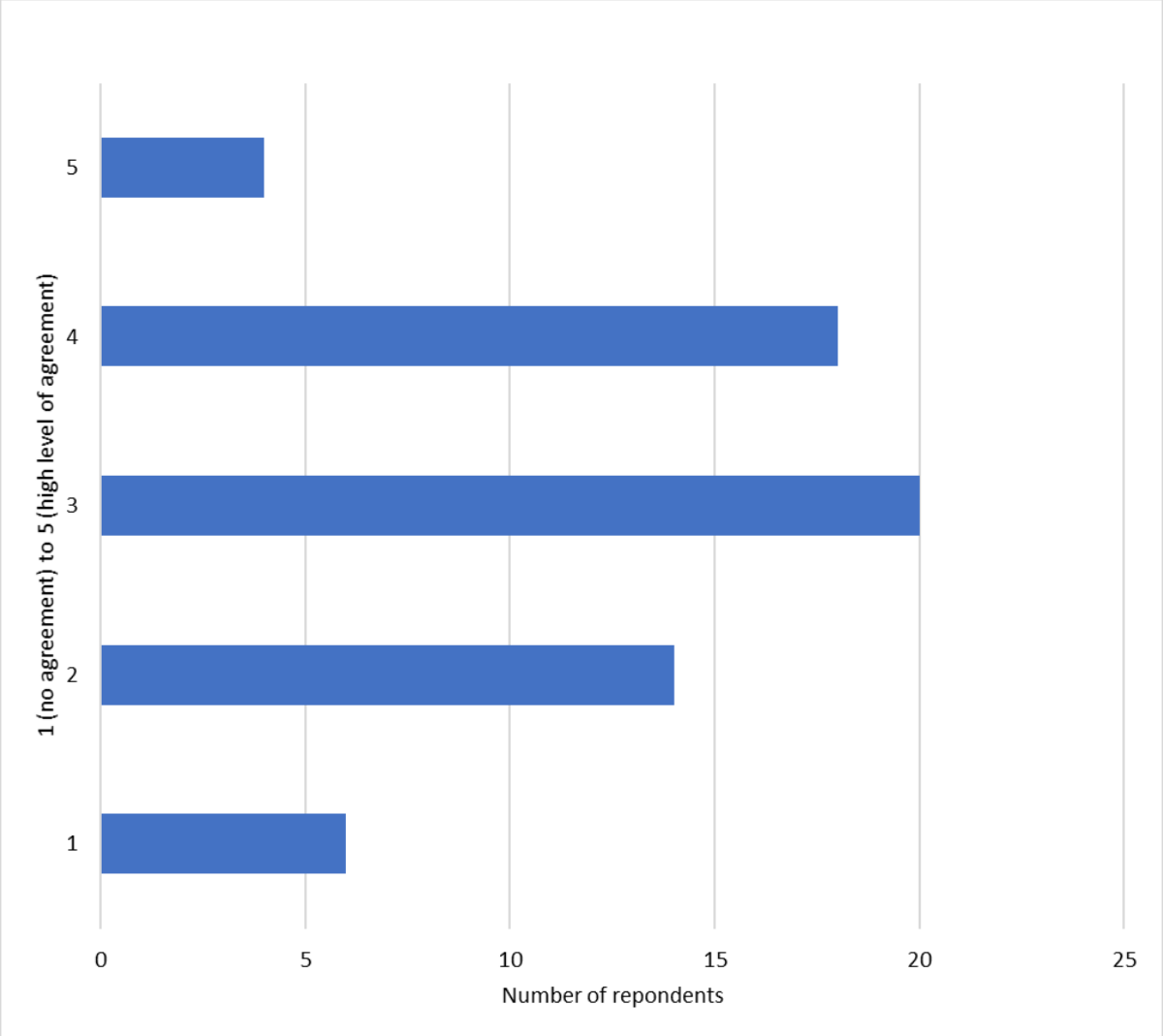
- receiving Part II RFIs before the Part I RFIs (sponsors must reply to Part II RFIs without knowing if Part I RFIs will require updates to Part II documents), for informed consent document in particular;
  limitations to application of Article 11 on partial submission of part I and part II (need to improve the functionalities in CTIS);
- technical issues with CTIS;
- different naming conventions in the MS for part I and part II documents; and
- fragmented approach to review of IVD performance studies hampers the initiation of large, multi-country trials;

Some sponsors also propose that the RMS go beyond the CTR requirements and play an active role in managing Part II queries.

2.4. Question 4 - The CTR aims to ensure the EU offers 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. Based on your experience, to what extent do you agree with this statement from 1 (no agreement) to 5 (high level of agreement) and why?

The answers received are summarised in table 6 and show that two third of the sponsors consider that CTR is making the EU a rather attractive and favourable environment by giving responses between 3 and 5, while the other sponsor respondents disagree more or less strongly with that statement. The comments provided help to understand the reasons for this disagreement, and among these comments, the general view is that the favourable environment for trials in EU has not increased as much as expected because Member States continue to request approximately the same information as before. Difficulties in using CTIS, lack of flexibility of the legislation and lack of harmonised requirements are again mentioned as serious obstacles jeopardizing EU attractiveness for clinical trial research.

Table 6: answers to question 4 on the CTR ability 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



Summary of comments provided

The reasons why some sponsors consider that the CTR does not make the EU so attractive and favourable for carrying out clinical research are often linked to issues already mentioned in the comments related to the previous questions, in particular:

- the difficult transition from CTD to CTR;
- the short RFI timelines;

- technical issues with CTIS;
- lack of harmonised requirements, which require a solid knowledge of the different national rules;
- lack of flexibility of the CTR and / or its interpretation as laid down in Guidance and Q&A documents, especially for adding further Member States concerned (MSCs) and submitting substantial modifications.

New issues are also identified in relation to the new transparency rules. Some sponsors are concerned about the protection of their proprietary data and report the burden of dealing with the extensive redaction requirements. They call for additional guidance and a pragmatic approach for the application of these rules.

Sponsors also mention elements outside the CTR legal framework that can impact clinical trials in the EU: digital flexibility, healthcare systems set up, data privacy, legal framework for contracting etc.

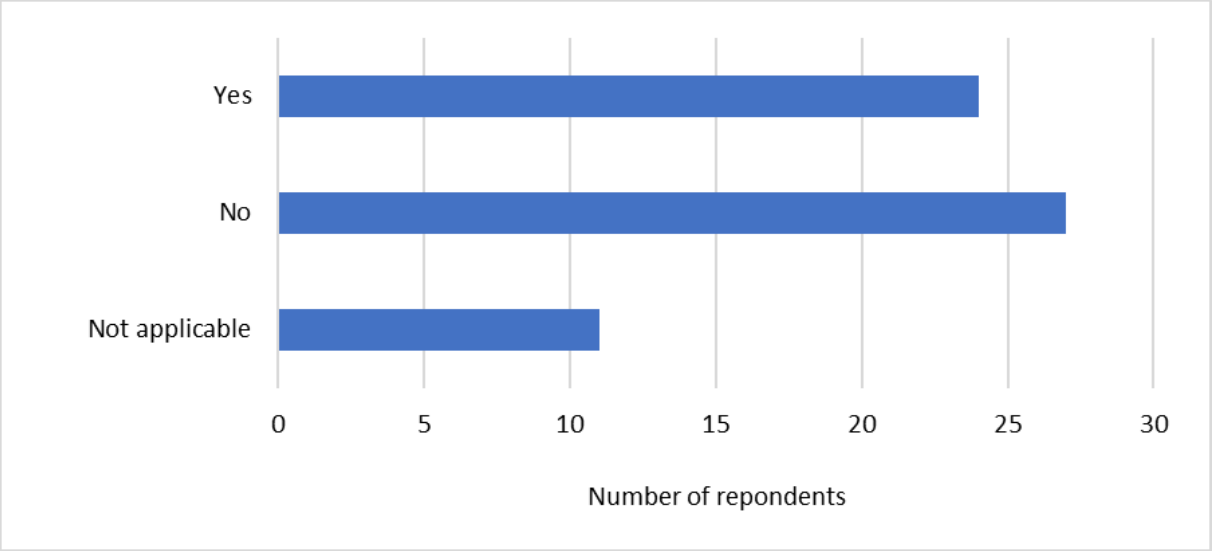
Positive comments are also provided:

- recognising that the new CTR rules are well designed to ensure public transparency and safety for clinical trial participants;
- appreciating the possibility to submit both parts I and II of the application on the same IT portal and the tacit approval mechanism;
- estimating that the transparency is significantly improved with the new rules compared with the Directive.

2.5. Question 5 – From your perspective, do you notice any inconsistencies between the CTR and other EU initiatives (e.g., GDPR, HTA, European Health Data Space) that affect the implementation of the CTR?

The answers received are summarised in table 7 and show that for many respondents there is no inconsistency between the CTR and other EU initiatives. Some respondents did not provide direct answer to this question but provided comments, some of which point to possible inconsistencies and unclear articulation of the rules of the CTR with other legislations, notably the General Data Protection Regulation (GDPR) and the IVDR.

Table 7: answers to question 5 on possible inconsistencies between the CTR and other EU initiatives such as the GDPR, the HTA or the European Health Data Space



Summary of the comments received

The following comments are provided in relation to possible inconsistencies:

- conflicting rules between Data Standards of OMS and Substance, product, organisation and referential (SPOR) master data regarding Private Medical Practice/Clinics and the CTR
- lack of alignment between the CTR and the clinical trial data sharing requirements under the European Health Data Space (EHDS) draft legislation;
- CTR rules on transparency would exceed the rules on personal data laid down in the GDPR (the names and contact details of individual persons acting in the role of the EU Legal Representative);
- Differing Member State views on how to inform patients about GDPR , leading to different procedures for Informed Consent;
- inconsistencies between the 'Guidance on deferrals' (understood as the Appendix on disclosure rules, to the "Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014") for publication and CTIS;
- inconsistencies or lack of clarity between the CTR, the IVDR, the MDR;
- inconsistencies between ICH GCP and CTR;
- lack of clarity regarding the articulation of the CTR (and its guidance) and EMA Policies 0043 and 0070;
- uncertainties regarding

- the assessment of redactions and deferrals; and
- the management of third country data for trials under Paediatric Investigation Plans once EudraCT is decommissioned.

There are also requests for:

- a remediation process put in place to allow post-disclosure corrections in CTIS; and
- information on the articulation of the MDR and the CTR and more particularly for information on how to manage submission of trials with an IVD that require submission both under the IVDR and the CTR

3. Identification and classification and prioritisation of the issues raised in the comments

Sponsors comments have been analysed to identify the remaining blocking issues in the implementation of the CTR. A hundred and eighty-one (181) issues (including repeated issues) were retrieved among the comments.

3.1. Identification of the issues

3.1.1. Solved issues

Some comments point to issues that were already raised and for which a solution was provided, for example, issues on functionalities fixed in CTIS, guidance addressing uncertainties related to the new rules, or a new legislation adopted by Member States.

3.1.2. Persisting issues

Persisting issues can be new or existing issues for which no solution has been identified yet, or known issues that were possibly subject to previous discussions with no agreement on the proposed solution.

3.1.3. Rejected issues

Some comments may be unclear and the issue may be difficult to identify. When not understandable or identifiable, the issue has been considered as rejected.

When the problems are stemming from the new rules of the CTR, no solution has been proposed. For example, the delays fixed in the legislation, or the different national rules concerning Part II of the dossier. However, the issues on the interpretation of the legislation are retained (for example, on the process to submit substantial modifications).

3.2. Classification and allocation of issues

The issues raised by the sponsors were classified according to the their nature and assigned to the different groups or entities (EMA, Member States, European Commission, CTCG, CTAG and CTEG) according to their mandate and responsibilities.

3.2.1. CTIS issues

Issues related to the use of CTIS: defects and lack of functionalities in CTIS, helpdesk.

Entity / group responsible: EMA, in consultation with Member States Product Owners (POs) for priority setting

3.2.2. CTR issues

Issues related to the CTR itself: lack of clarity in relation to the legal requirements and/or the interpretations of the new obligations for sponsors, inconsistencies with other EU initiatives and conflicting rules

Entity / group responsible: CTAG for guidance documents and CTEG for technical expertise and ethic committee issues

3.2.3. Lack of harmonisation and coordination

Lack of harmonisation within the EU, incoherent approaches between Member States and/or additional national requirements

Entity / group responsible: CTCG, Commission to monitor implementation and compliance

3.2.4. Member State preparedness

Issues related to a lack of preparedness in a given Member State – lack of compliance, political uncertainty, lack of expertise, capacity issues and administrative issues

Entity / group responsible: Member States, Commission to monitor implementation

3.3. Prioritisation of issues for providing solutions to the problems

The prioritisation of issues is decided by each of the entities and groups concerned, taking into account the following points:

- the benefit of solving the problem raised vis-à-vis the efficient application of the CTR
- time gained for users (applicant and assessors)
- for horizontal issues, the feasibility of providing a solution acceptable to all the available stakeholders

A first analysis of the comments provided by the sponsors lead to the following possible priorities:

- Fixing all major defects in CTIS ensuring a functional system with minimised burden by 31 January 2023
- Development of clear guidance on the transparency rules minimising the administrative burden related to redaction of documents.
- Making part II and national requirements accessible in a single place
- Explore the development of less rigid processes in line with the CTR such as the need for subsequent submission of SM
- Development of CTIS submission guidance for complex clinical trials
- Enhanced Member State coordination of clinical trials assessment

4. Providing solutions to the issues raised

The Commission will work with EMA and the Member States to provide solutions to the issues raised in the survey. It should be noted that a number of issues are already being addressed through several Network initiatives which are detailed below.

4.1. CTIS

EMA has prioritised improving the CTIS user experience for core CTIS processes by the time the use of the system becomes mandatory. This will be achieved by implementing improvements in the most impactful processes, taking into account the views of the POs and sponsors, notably through this EU survey.

Solutions have already been provided through a number of CTIS updates. A major CTIS release on 7 December provided major improvements, and other releases are planned until the end of January 2023 to correct blocking issues.

Training material is available to help sponsors submit information on their clinical trials data, including their applications for authorisation of a clinical trial. The material is updated regularly to reflect information needs. EMA also runs regular training webinars with sponsors to explain the system, listen to and address concerns.

New functionalities will be developed in 2023 and 2024, along with further user experience improvements, taking into account the views expressed by all users, sponsors, national authorities and ethics committees.

4.2. Full implementation and enforcement of the CTR

The transition from the CTD to the CTR required some modifications of national laws, as well as adaptation of the resources, methods, and modalities to deal with Clinical Trial Applications (CTAs).

Member States have aligned most of their legislation to the new rules of the CTR. The CTAG meeting of 29 April 2022 showed the progress made and the plans to finalise this alignment. The session aimed to understand the status of the implementation of the regulation in the Member States, given that compliance with the new rules includes the adaptation to the new Regulation and the use of CTIS, and the adaptation of the national legislation.

Member States were asked to communicate any remaining issues, the timing needed to solve them, and the temporary solutions to address them. No Member State communicated any inability to deal with a clinical trial application under CTIS. Some Member States communicated the imminent adoption of national legislation to align with the new CTR rules.

The CTAG will continue to monitor the alignment of the national legislations on the CTR and to check compliance with the new rules.

4.3. Enhanced Member State coordination

CTCG coordinates Member States actions under the CTR, notably with the following tools: weekly roundtable of assessors including a monthly Ethics Committee forum, best practices development,. Besides the roundtable of assessors weekly meetings, CTCG launched a forum Teams channel where assessors can track all discussions and agreements related to validation and assessment.

CTCG already provided some solutions to problems raised. For example, CTCG published a Best Practice Guide for Sponsors of document naming in CTIS with recommendations on how to name the documents uploaded by sponsors in CTIS.

CTCG will continue to explore new ways to develop best practices guidances and enhance Member States coordination in the evaluation of clinical trial applications, aiming at an efficient application of the CTR.

4.4. Guidance

Transition trials

The CTR has specific transition provisions under Art. 98 on clinical trials that started under the CTD and that can be continued under the CTR. The regulation does not specify how sponsors shall continue the trials that are still ongoing once the transition period of the regulation comes to an end on 31 January 2025.

The Commission has addressed this matter in a Q&A document on the implementation of the CTR, based on the expertise provided by CTEG. It contains the confirmation on how sponsors can apply for an ongoing trial that has been authorised under the CTD by the national competent authority and approved by the ethics committee in the given Member States.

Transparency rules

EMA conducted a stakeholder consultation on a draft guidance document on how to approach the protection of personal data and commercially confidential information (CCI) in documents uploaded and published in CTIS. This guidance will be published in the beginning of 2023 as part of the ACT EU initiative. Given the urgent need for advise on the application of new transparency requirements, the CTCG will publish at an earlier date a Q&A document disseminating the main principles agreed on protection of CCI and personal data.

CTEG and CTAG will continue to provide guidance on the application of the new rules and review existing guidance with the view of minimising burden and providing the maximum flexibility offered by the CTR.

Member States will provide web pages gathering their specific national requirements and the Commission will provide a repository of these web pages and include this as an Annex to the Q&A document on the implmentation of the CTR.

The solutions to the issues raised in this EU survey will continue to be monitored and reported. Further similar surveys on the implementation of the CTR will be conducted with stakeholders.