

Second survey on the implementation of the Clinical Trials Regulation (EU) No 536/2014

Fields marked with * are mandatory.



Background

A first EU survey was developed by the European Commission in collaboration with EMA, HMA, and the Clinical Trials Coordination Group (CTCG) in 2022. It collected views from sponsors and stakeholders on the Clinical Trials Regulation (EU) No 536/2014 (CTR) and the use of the Clinical Trials Information System (CTIS). This EU survey was launched on 18 July until 9 September 2022. The analysis of the answers received, the identified problems and the solutions provided so far are summarised in a [report](#).

Since 31 January 2023, CTIS is mandatory for the submission of initial clinical trial applications. Since the first survey was launched, CTIS functionalities have been improved, further guidance documents have been provided, and CTIS user experience has improved. This second EU survey is aimed at collecting further views of sponsors and stakeholders on this updated regulatory and IT environment, identifying the remaining blocking issues, in order to address them and monitor their resolution.

The deadline for responses is **4 October 2023**.

This survey is made up of **10** questions and completion is expected to take approximately **20** minutes. The objectives of this survey are as follows:

- To understand the remaining hurdles that hamper:
 - a smooth implementation of the CTR;
 - a smooth transition of the clinical trials from EudraCT to CTIS;
 - CTIS user friendliness.
- To measure the progress achieved since the last survey.

The findings of this survey will be analysed and addressed under the ACT EU initiative, and the identified issues will be tackled by the different entities responsible (EMA, European Commission, Member States, Clinical Trial Coordination Group, Clinical Trials Advisory Group and Clinical Trials Expert Group).

Sponsors are invited to respond to the following questions to help facilitate a fertile environment for research and innovation for the benefit of patients, fostered together with the EU Institutions and national regulators.

Organization details

*** Please identify the type of sponsor you represent**

- Commercial sponsor (large industry)
- Commercial sponsor (small and medium-sized enterprises - SMEs)
- Non-commercial sponsor (i.e., investigators teams, research institutions, major medical centers)
- Other

If other, please specify

Industry Organization (ACRO -- Association of Clinical Research Organizations)

*** Please identify the country where you are located**

US - United States of America

Survey

*** 1. Did you participate in the previous EU survey on the CTR implementation?**

- Yes
- No



2. Since the first EU survey on CTR implementation, several initiatives aimed at facilitating the CTR implementation have been realised: CTIS releases to improve user experience, [EMA training and support on CTIS](#), ACT EU [Q&A](#) on the protection of Commercially Confidential Information (CCI) and Personal Data (PD) while using CTIS, [Guidance document](#) (and [Annex](#)) on how to approach the protection of PD and CCI while using CTIS, the [Quick guide for sponsors](#), updated [CTR Q&A](#), [Recommendation paper](#) on decentralised elements in clinical trials, [Commission Delegated Regulation \(EU\) 2022/2239](#) as regards labelling requirements for unauthorised investigational and unauthorised auxiliary medicinal products for human use.

How would you rate the progress achieved in the last year?

(Please provide a score from 1 to 5, where 1 star is "no progress" and 5 stars is "significant progress")

Progress achieved on the implementation of the CTR by Member States (competent authorities and ethics committees)



Progress achieved on the guidance material provided	
Progress achieved on the CTIS user experience	

Please comment if needed

2000 character(s) maximum

1—Lack of harmonization of requirements (e.g., Requests for annual progress reports; patient documents, naming convention)

2—New guidance is helpful, but inconsistent messaging across different guidelines (e.g., transition guidance notes that additional MSC can be added via SM but do not the need to align documents after transition for studies that will end without any SM being submitted)

3--Inconsistent information on which Part II templates need to be submitted to align the dossier with the EU CTR for a trial that has transitioned to the EU CTR (e.g., site suitability template confirmed as not needed – expect this to apply to the declaration of interest too)

4--CTIS is more stable and responsive. Still some errors to be corrected (e.g., tacit rejections issued with acceptable part I and II conclusions)

5-- Not all MSs are acting as RMS as needed – making the consolidation of the considerations and failing to push back considerations out of scope of CTR -- MSC acting as RMS are not fulfilling their role of RMS by coordinating the assessment of Part I across other MSC resulting in the same RFIs being received multiple times or inconsistency in opinion of assessment

6--Internal disharmonization – MS are not aligned with Part I and Part II, coming into situations where 7-- Protocol and ICFs are not aligned which triggers the need to submit SM , delaying the site activation

8--National requirements – High number of requests of national nature not foreseen in Annex I of the Regulation

9--Transition rules – not all MSs are following new CTEG guidance. We had requests to change CTD approved ICFs in expedited transition process.

10--For IN application number of bugs have decreased

11--Increased number of issues/bugs identified for SM / Add MSC/ Notifications /Adhoc Assessments

PLEASE NOTE--

Continuing answer to this question below in space for Question # 3(b) below] Please see below

3. What are the blocking issues currently preventing you to submit clinical trials applications under the CTR since 31 January 2023 and/or preventing you to make use of the Clinical trial information system (CTIS)?

Please select the option that most represents the issue you encountered and further explain it in the open text box, including concrete example, where possible (without confidential information)

	Yes	No	Not applicable
* a. Issues related to the use of CTIS	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>
* b. Issues related to the CTR itself? (E.g. lack of clarity in relation to the legal requirements and/or the interpretations of the new obligations for sponsors).	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>

* c. Issues related to a lack of harmonisation within the EU? (E.g. incoherent approaches between Member States and/or additional (national) requirements).	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>
* d. Issues related to a lack of information / training material?	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>
* e. Any other aspects you wish to raise, including positive feedback.	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>

*** a. Issues related to the use of CTIS?**

2000 character(s) maximum

Answers to A and B included here below--

A—Mainly Performance issues

B—Lack of clarity re timing for submission of third part inspection reports and type of reports (i.e. GCP and GMP inspections or GCP only)

*** b. Issues related to the CTR itself? (E.g. lack of clarity in relation to the legal requirements and/or the interpretations of the new obligations for sponsors).**

2000 character(s) maximum

PLEASE NOTE--

Using this space to continue our Answer to Question 2 (above)--

12--Critical/Blocking issues with huge trials – Trial completely blocked – Performance issue – This is a very serious issue and we need clarification from EMA that this should be fixed on a structure level and not as a clinical trial data fix.

13--EMA helpdesk is not being able to respond to all tickets

14--EMA helpdesk is not being able to identify and prioritize critical tickets

15--The CTIS specifications do not align fully with EMA supporting documents. For example, Page 133-136 of the Q&A states a protocol amendment can be submitted as a NSM, however this is not possible in CTIS.

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

Please mention the Member State(s) in question and the part of the application that raises the issue - the EU Clinical Trial number for a concrete example can also be provided.

2000 character(s) maximum

C--Greater coordination of Part I and Part II assessments is required, to prevent Part I RFI being received which impact documents previously finalised within a Part II assessment. MS approaches to the fulfilment of conditions is disharmonised and inconsistent (eg. some MSC will request a SM is submitted and approved to fulfil the same condition that other MSCs do not).

*** 4. What would be the priority to improve CTIS user experience?**

Please rank the following items (from the most urgent to the least urgent):

Use drag&drop or the up/down buttons to change the order or [accept the initial order](#).

- ⋮ Helpdesk
- ⋮ Stability of the system
- ⋮ Backlog bug fixing (to replace the most time-consuming workarounds)
- ⋮ New functionalities

5. How would you evaluate the requests for information (RFIs)?

a. Part I

	RFIs are proportionate and manageable in the given timeframe	RFIs are disproportionate and not manageable in the given timeframe
* Proportionality	<input checked="" type="radio"/>	<input type="radio"/>

b. Part I

	RFIs are clear and manageable in the given timeframe	RFIs are unclear and not manageable in the given timeframe
* Clarity of the questions raised	<input checked="" type="radio"/>	<input type="radio"/>

Please provide any comments and where possible, make reference to a particular clinical trial application using its EU number

2000 character(s) maximum

Although RFIs are generally reasonable, we still receive inappropriate RFIs
 e.g.: request to update file naming referencing old naming convention guidance and considering that this is only a guidance for sponsors.
 Request to submit documents not required per EUCTR
 Request to update fields in CTIS that are not editable (request to update MP strength in case of an unauthorized MP)
 In addition CTIS misses a functionality to unlock part II following the request to update part I documents impacting ICFs.
 Some RFIs aren't clear and time is needed to clarify expectation with the MSC therefore responding within the deadline is challenging.

RFIs are received when not significant (e.g. 40 Part I RFIs in one case), not all are considered 'critical' and multiple rounds of RFIs (up to 3 rounds) have been received – This is against the Q&A “only one request for information will be feasible during the assessment period. Therefore, the RFI should focus only on critical issues that need to be addressed by the sponsor”

c. Part II

	RFIs are proportionate and manageable in the given timeframe	RFIs are disproportionate and not manageable in the given timeframe
	<input type="radio"/>	<input type="radio"/>

* Proportionality	<input type="radio"/>	<input checked="" type="radio"/>
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d. Part II

	RFIs are clear and manageable in the given timeframe	RFIs are unclear and not manageable in the given timeframe
* Clarity of the questions raised	<input checked="" type="radio"/>	<input type="radio"/>

Please provide any comments and where possible, make reference to a particular clinical trial application using its EU number

2000 character(s) maximum

Seeing some improvement. However, for the same country depending on the EC involved we can have completely different situations.

Although RFIs are generally reasonable, we still receive inappropriate RFIs

We see requests to submit documents not required per EUCTR

CTIS lacks a functionality to unlock part II following the request to update part I documents impacting ICFs. This impacts start up timelines significantly by adding up to 95 days, making the clinical trial environment in the EU favorable. No consistency between MSC on how they are handling this situation e.g. some request a SM after approval, some will open a 'dummy' Part II, some allow emails to be submitted with the application outside of CTIS and via email – could result in future audit findings

Some RFIs aren't clear and time is needed to clarify expectation with the MSC therefore responding within the deadline is challenging

* e. Alignment of Part I and Part II.

Part I and Part II are processed separately. What is your experience with this?

- Good approach or advantages of a separate approach of Part I and Part II
- Closer alignment might be needed or disadvantages of this approach; please specify the reasons.

* Please specify the reason(s)

2000 character(s) maximum

MS alignment is CRITICAL to avoid further SMs after decision to harmonise ICFs in Protocols. CTIS lacks a functionality to unlock part II following the request to update part I documents impacting ICFs e.g. when a Part I request impact Part II requiring an additional submission. As mentioned in relation to Q3, greater coordination of Part I and Part II assessments is required, to prevent Part I RFI being received which impact documents previously finalised within a Part II assessment.

* 6. Did you experience or do you envisage difficulties when transitioning trials from EudraCT to CTIS?

- Yes

- No
- Not applicable

* If you answered Yes, what are the difficulties?

1000 character(s) maximum

Even with the current simplifications, we need all MSs following CTG guidance
There's no clear definition of the transition approval date. Transition decisions are issued per country.
Some MSc do not issue part II conclusion and wait for tacit approval of 106 days.
RFIs received which are requesting to provide documents that were not part of the CTD submission and are not in line with the CTR.
Not enough clarity on which Part II templates need to be submitted to align the dossier with the EU CTR for a trial that has transitioned to the EU CTR e.g. site suitability template confirmed as not needed - this should apply to declaration of interest too
No harmonized approach to fee payments. Range from none to full iCTA fee.

*** 7. If you applied or envisage to apply for a Clinical Trial involving an Investigated Medicinal Product (IMP) belonging to a third party with proprietary data (the sponsor of the clinical trial is not the product owner of the IMP and should not have access to the quality IMPD), are you satisfied with the solution provided in the updated CTR Q&A document (2.15)?**

- Yes
- No
- Not applicable

* If you answered No, what element of the process should be improved and how?

1000 character(s) maximum

IMPD-Q only application cannot be cross referenced in other trials or re-used in subsequent substantial modification applications (continued burdensome rework. No guidance on what will happen legally after 2 years, when IMPD-Q only application no longer legally valid. (Acceptable decision shall expire on the IMPDQ only application). No guidance on how to manage IMPD-Q SMs.
The solution implemented is a temporary solution and not at all optimal or realistic.
A different approach should be discussed with Sponsors.

*** 8. If you applied or envisage to apply for a combined trial including a clinical trial application under the CTR and a clinical investigation under the Medical Device Regulation, are there any inconsistencies between the two processes of authorisation or obstacles you have identified for such combined trial?**

(Select not applicable if you have no experience or plan for such combined trials)

- Yes
- No
- Not applicable

*** 9. If you applied or envisage to apply for a combined trial including a clinical trial application under the CTR and a performance study under the In Vitro Diagnostic Regulation, are there any inconsistencies between the two processes of authorisation or obstacles you have identified for such combined trial? (Select not applicable if you have no experience or plan for such combined trials)**

- Yes
- No
- Not applicable

* If you answered Yes, what are these inconsistencies or obstacles?

1000 character(s) maximum

Delays to starting clinical trials due to lengthy process with notified body assessment of parallel performance evaluation protocols, especially for oncology studies.

* **10. Based on your experience, what are the practical aspects to improve at CTIS level or at CTR implementation level?**

(You can name up to four aspects and provide examples of concrete cases, you can also suggest improvements).

2000 character(s) maximum

TOP PRIORITY—Enforced and applied harmonization of document and information requirements across countries especially for part II content.

CTIS stability and reliable functioning is required. Issues with CTIS functionality occur on a daily basis, where buttons are not active and steps not possible. Help Desk interactions currently constitute a significant portion of an EU Regulatory team's work, creating significant burden. Reliability of CTIS functionality is greatly anticipated.

Improve MSs harmonization -- clear communication of MSc-specific requirements in line with CTR

Improve CTIS Performance, Helpdesk and other critical issues

Thank you.

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