Date: 6 October 2023
REF. KN/68.024

To: Relevant contact points in the European Commission, CTCG, HMA, EMA, eurec
Cc: Relevant contact points in patient organisations (EPF, EURORDIS, European Cancer League, SIOPE)

Object: **Inter-Association Recommendation Paper for transitioning Clinical Trials from the Clinical Trials Directive 2001/20/EC (CTD) to the Clinical Trials Regulation 536/2014 (CTR)**

Dear Recipients,

Clinical trial sponsors in the European Union welcome the openness, flexibility, and speed of the European Regulatory Network to ease the procedure for ongoing clinical trials which need to be transitioned from the CTD to the CTR by 30 January 2025. We have been very satisfied with the open and solution-oriented discussions at the recent EMA workshops[1] and ACT-EU stakeholder meeting[2]. Our shared goal is to preserve the EU's attractiveness for the conduct of clinical trials and to ensure that European patients can continue to benefit from new treatment options.

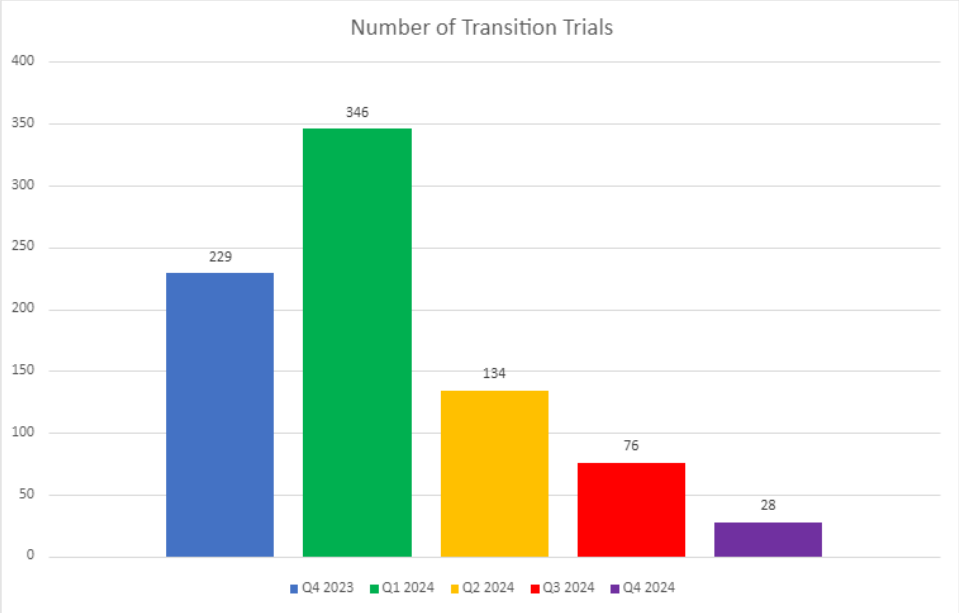
The recently published Guidance for the Transition of clinical trials [3] resolves one of the major challenges previously introduced in question 11.9 in the European Commission Q&A document (version 6.4, February 2023) by removing the deadline of 30 January 2025 for authorization of a Substantial Modification following initial transition. Together with the new expedited approval procedure and the acceptance of consolidation not only for the protocol but also for the IB and IMPD described in the CTCG Best Practice Guide on transition[4], this flexibility will facilitate the completion of transition applications.

To support the success of the legal transition requirement, sponsors are committed to plan and submit their transitioning applications as swiftly and as early as possible to avoid any disruptions or premature endings of ongoing clinical trials with potential associated negative consequences for patients in Europe and on EU competitiveness for the conduct of clinical trials. However, sponsors may not be able to execute transitions according to their planning due to some unresolved obstacles that may contribute to delaying or even preventing the transition of clinical trials. Sponsors want to avoid having to prematurely end trials in Europe to balance the risks and burden of the transition.

The remaining issues that are seen as risks for the successful and timely transition of clinical trials are described in the below table. We are providing recommendations for further efficiencies and more flexible transition approaches to facilitate the transition of a still very high number of clinical trials and thus reduce the burden of this administrative submission for both sponsors and Member States (see *Annex 1: Table of transition concerns and proposed solutions*).

[1] Clinical Trials Information System Webinar: Second Year of Transition, 4-5 July 2023
[2] ACT EU multi-stakeholder platform kick-off workshop, 22-23 June 2023
[3] Guidance for the Transition of clinical trials from the Clinical Trials Directive to the Clinical Trials Regulation, 19 July 2023
[4] CTCG 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, Version 2, 12 September 2023

According to a study conducted with sponsors (22 respondents in total), **813** trials remain to be transitioned and **39** trials which are at risk of failing transition (see attached Excel spreadsheet for details):



A summary of the most critical remaining concerns and potential solutions to address them is provided here:

- We are facing delays or even rejections of amendments in Member States under CTD that are currently necessary to be completed prior to the transition application.
    - Consolidation is expected to be acceptable for all documents, even when substantial differences between documents exist. There should be no assessment performed of the degree of substantiality of differences of these documents between Member States under the CTD.
    - Implicit approval of CTD substantial amendments should be considered. At least, the conditions should be alleviated or standard timelines for Substantial Amendment applications should be agreed upon. For instance, IB submissions could be conducted across trials with a single product-specific procedure under the Directive.
    - If this cannot be achieved, CTCG should provide a formalized escalation mechanism to address outstanding Substantial Amendments in those Member States where it remains a lengthy process.
    - Further, NCAs should proactively communicate with and encourage national Ethics Committees to swiftly approve pending clinical trial amendments. Alignment of all NCAs/Ethics Committees is key to avoid unnecessary delays.
    - Other alternatives include:
        - the transition of trials to be performed in parallel to an ongoing Substantial Amendment;
        - the option of transition application to incorporate a planned Substantial Amendment.
- We have difficulty identifying transition windows for complex trials with very active amendment cycles due to frequent protocol or IB updates, mostly related to patient safety.

- In these exceptional circumstances, transition conditions should be more flexible. Sponsors can identify early these exceptional trials and work with the future RMS to discuss the transition timing for those trials; these should be prioritized. Inspectors should be briefed that in these cases sponsors might have to potentially hold back submissions of modifications for the transition period and this should not create critical observations.
- Where unplanned Substantial Amendments arise, it should be possible to perform an USM under the Directive while the transition application assessment is ongoing and implement the necessary modifications under the CTR once the transition is complete.
- For the exceptional cases where despite all efforts, transition cannot be completed under normal procedures and timelines, an agreement should be found amongst regulators to approve the transition in a couple of days to prevent the trial from falling out of a legal basis.

- We are facing delays for the approval of transition applications in the agreed timeline of 22 days. Some Member States are raising RFIs during the validation period which by default are adding 15 days to the timelines.
  - No additional documentation requests from Member States under transition applications (including under Part II) should be acceptable.
  - Alternatively, there should be guidance for what Member States are allowed to require on top of minimum transition documentation to avoid validation issues. Documents should not be required to be uploaded in the application if they are no longer in use for the conduct of the trial (no retrospective application). Blank documents would be uploaded in the system instead. Templates will only be updated as and when documents need to be amended post-transition. Regarding the IMPD more specifically, it should be acceptable to only include the core IMPD-Q as the minimum required document in the transition dossier and not additional sub-documents.
  - All Member States should commit to adhere to the maximum timeline of 22 days for approving transitional applications in CTIS.

We would like to continue the open dialogue to identify and agree further practical solutions that can facilitate the timely submission and approval of transitional trials.

Respectfully,

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Annex 1: Table of transition concerns and proposed solutions

Issue	Comment/Recommendation
Major concerns	
Consolidation of all documents **Key message:** There should not be cases where harmonization of documents is necessary, even when substantial differences between documents exist. • Consolidation is currently the only option because Member States refuse to change their approach to their approval of a trial, understandably so since the trial is already ongoing. For MSCs, agreeing to a harmonized version of some documents due to potential substantial differences would mean giving in to earlier raised concerns which have been addressed in the country-specific version of these documents. In addition, requiring for Substantial Amendments under the Directive for the sole purpose of building a harmonized dossier due to substantial differences between documents, which would be challenged by Member States not willing to change the design of an ongoing study, creates unnecessary risks of delaying the transition application while proceeding with an application under the CTD which would be unsuccessful anyways. Therefore, there should not be any cases where harmonization of documents, even when differences are substantial, should be necessary. Consolidation should be the common practice for all types of documents, without performance of an evaluation of substantiality of differences. • Regarding the protocol, there are trials for which the primary objectives are different across MSCs, which makes consolidation complicated with divergence over such an important characteristic of the trial – those trials cannot meet the criteria for consolidation according to CTCG guidance. They also cannot be harmonised, because Members States would refuse to change the study design during the study. Splitting the trial into a separate CTIS authorisation for specific Member States with a different primary objective is a risk for data integrity, complex and burdensome for sites and patients, with new consent needed, etc. and is thus unacceptable. Consolidation should be allowed even in cases where the primary objectives differ, with country-specific appendices capturing Member States' differences which can be attached to the protocol.	• Allow for consolidation of all documents, even when substantial differences between documents exist. There should be no substantiality assessment performed. • Creation of provisions for 'core information' for the IMPD-Q.
Long Substantial Amendment assessment period **Key message:** The unpredictability and misalignment of timelines for Substantial Amendments under the CTD may create delays in changes which remain to be approved before transitioning to CTR and prevent sponsors from submitting a transition application. Alignment of Ethics	• Consider implicit approval of amendments under the CTD. • Alleviate conditions in Member States or agree on standard timelines for Substantial Amendment applications.

Issue	Comment/Recommendation
Committees with NCA's pragmatic approach is essential for trials to meet the transition deadline. • Some amendments under the CTD prior to transition are currently inevitable (e.g., PI passed away, urgent operations) with a risk that these will not be approved in time prior to transition cut off, or approved by some but not all Member States, therefore requiring resubmission and increasing the risk of missing the transition deadline. • NCAs/Ethics Committees may be delaying approval of the clinical protocol that is required prior to transition due to a parallel IVDR submission for the country, even though this is submitted under a different Regulation and different procedure. *Reference: 'Only clinical trials without any ongoing assessment of documents in any of the EU/EEA countries are eligible for the transition: clinical trials for which a request for a Substantial Amendment is under assessment are not eligible to the transition until the procedure is completed.'*[5]	• CTCG to provide a formalized escalation mechanism to help with lengthy Substantial Amendments. • It should be possible to conduct IB submissions across trials with a single product-specific procedure under the Directive. • Ensure alignment of all NCAs/Ethics Committees with the rules to avoid unnecessary delays. • Allow for transition of trials in parallel to an ongoing Substantial Amendment or allow for the transition application to incorporate a planned Substantial Amendment. • The Substantial Modification following transition can subsequently include the outcome of the IVDR assessment.
Silent period cannot be found for transition **Key message:** Support is needed to deal with trials where a 'silent' period is not possible. • For trials with a significant number of EU countries participating (~15+), with complex trial designs such as platform studies and trials with a large number of IMPs, it may be impossible to find a silent period window even just between IB updates. In some countries, these updates take a very long time due to long approval timelines in some Member States under the Directive framework. • This may also have a ripple effect across several trials which are using the same IMPD. • If an unexpected safety event means a Substantial Amendment needs to be submitted while the transition application is still ongoing, there is a risk that this would prevent the ability to find a silent period for transition later.	• Sponsors can identify early and work with the future RMS to discuss the transition timing for complex trials where a silent period is impossible to plan. • It should be possible to conduct IB submissions across trials with a single product-specific procedure under the Directive. • Brief inspectors that sponsors might slightly delay the submission of modifications to perform the transition application. • Regarding unplanned Substantial Amendments due to patient safety concerns, allow for a USM to be conducted under the CTD even if a transition application is ongoing and to implement the necessary modifications under

[5] Guidance for the Transition of clinical trials from the Clinical Trials Directive to the Clinical Trials Regulation, 19 July 2023, Question #4 *What are the conditions to transition a trial to the Regulation?*

Issue	Comment/Recommendation
	CTR once the transition is complete. • For the exceptional cases where despite all efforts, transition cannot be completed under normal procedures and timelines, an agreement should be found amongst regulators to approve the transition in a couple of days to prevent the trial from falling out of a legal basis. These trials should be exempt from obligations under the CTD. • Clarify that a trial is deemed transitioned at the time a decision is made by the first Member State.
Issues with Member States asking for additional documentation in the transition application **Key message:** Sponsors should have reassurance that Member States will comply with the CTCG guidance and updated Commission Guidance. • Documentation predictability is an important consideration – there should not be any case where Member States can require additional documentation on top of the required minimal list of documents for transition for either Part I or Part II[6] – this will lead to delays. • It should also be clear that Member States cannot ask for retroactive documents or documents with no further legal basis under the EU CTR Annex I. Currently, Q.8 of the Commission Guidance[7] states that site suitability statements do not need to be retrospectively created. This statement should not only apply to site suitability forms. • Q.8 also states that *'The upload of new template documents in the trial already completed, e.g., if recruitment of trial participants has ended, is not required.'* There are two possible interpretations of this text – if recruitment is complete before transition, either there is no need to use the CTR templates and CTD templates can remain	• Requests for additional documentation are not acceptable. • As a second resort, there should be guidance for what Member States are allowed to require on top of the minimally required documentation to avoid validation issues. • Documents may not be uploaded in the application if they are no longer in use for the conduct of the trial (no retrospective application). Blank documents would be uploaded to the system instead. • Templates will only be updated as and when documents need to be amended post-transition. • It should be acceptable to only include the core IMPD-Q as the minimum required document in the transition dossier and not additional sub-documents which

[6] Guidance for the Transition of clinical trials from the Clinical Trials Directive to the Clinical Trials Regulation, 19 July 2023, Questions #5 & 6 *How shall a sponsor proceed in case of mono-national/multi-national clinical trials?*

[7] Guidance for the Transition of clinical trials from the Clinical Trials Directive to the Clinical Trials Regulation, 19 July 2023, Question #8 *When is a sponsor expected to update trial documents and labels?*

Issue	Comment/Recommendation
within the application; or the entire document e.g., recruitment arrangements, does not need to be uploaded at all in the application under CTR because this would be retrospective use of documentation (since recruitment already ended). This should be clarified. • It must also be clarified that Member States cannot issue conditional transition approvals linked to the obligation of submitting a Substantial Modification with additional CTR-specific documents within a defined period. Despite the updated guidance, sponsors are still experiencing requests for documents outside of the agreed CTCG and Commission position; in other cases, some Member States have issued a conditional approval requesting CTR-specific documents to be submitted as a Substantial Modification within three months of approval (e.g., Germany). We will continue to monitor the situation.	have only been requested and assessed under the Directive by a few MSCs, such as CoA, TSE certificates, Virus reports.
Medium concerns	
Timeline predictability **Key message:** Alignment of Ethics Committees with NCAs' pragmatic approach is essential. • Timeline predictability is needed within the expedited procedure. One single Member State could prevent the expedited procedure to move forward as expected. • Member States should make sure that both Ethics Committees and NCAs are progressing the application through CTIS in line with the expedited procedure in a timely fashion and do not raise additional questions. It is suggested that NCAs could take the responsibility to "click through" the CTIS system themselves since no assessment is needed. Experience to date has shown that certain Member States continue to exhaust maximum timelines for assessment under transition applications. While we have observed that some Member States are applying fast turnaround timelines to come to a Part II acceptance and a final decision (e.g., Denmark and Spain within 5 working days); some Member States (e.g., Poland) are applying the tacit approval route and provide a final decision up to 45 days after the validation acceptance. This discrepancy causes unnecessary delays in the submission of follow-up Substantial Modifications as the CTIS system remains blocked until all Member States have accepted the transition. The 22-day timeframe cannot be achieved if validation RFIs are raised by default. We have calculated an average time of 61 days necessary to complete a transition application since the CTCG adopted their	• Wherever possible, ensure that MSCs will manually progress the application through CTIS tasks to completion respecting shorter timeline and not exhaust the maximum permitted timeline. • Clarify that a trial is deemed transitioned at the time a decision is made by the first Member State.

Issue	Comment/Recommendation
guidance[8], mainly due to validation questions received. We will continue to monitor the situation. *Reference:* *'The maximum timeline for the expedited transition procedure … is estimated to be maximum 22 days'*[9]	
Issues with cross referencing to third-party information (IMPD-Q) **Key message:** Guidance is needed on how to manage transition for trials cross-referencing to third-party data under the CTD. Available guidance is not flexible enough on how to transition a trial where the study references data supplied by a third party; it is unclear whether the separate IMPD-Q-only trial concept is permitted for transition trials. ➔ Concerns when a password protected IMPD was submitted by the sponsor under the Directive (the sponsor is not the MAH). ➔ Concerns when a full IMPD was submitted by the MAH in parallel to the sponsor's application under the Directive. ➔ Concerns when a cross-reference letter to an IMPD (approved under the Directive) (LoA) was submitted by the sponsor under the Directive (the sponsor is not the MAH).	• It is understood that the separate IMPD-Q-only trial concept is permitted for transition trials. This should be rapidly clarified in guidance to avoid additional delays. • A more innovative approach would be to manage the IMPD-Q across trials for a common product instead of having to do one IMPD-Q-only submission for each trial which use a similar product.
More Flexibility for Substantial Modifications **Key message:** A flexible approach to Substantial Modifications following initial transition applications approval should be allowed. • In previous versions of the European Commission CTR Q&A, questions on the completion of the dossier with missing documents and on the alignment of existing documents with the EU-CTR requirements were separate. They have then been combined[10]. Since then, it has been unclear whether this question is about bringing the content of documents in line with CTR requirements (including EUCT number in all documents and complying with Part II templates) or completing the dossier with missing documentation to fulfil the Annex I list of documents, or both. • The option of a flexible approach to trial modifications following the life of the trial, with Substantial Modifications at the document-	Update the content of documents to meet CTR requirements only when a Substantial Modification is required for this specific document. It should not be mandatory to update the content of other documents in other CTIS sections. The content of other documents already part of the dossier since transition would be brought in line with CTR requirements when they require a Substantial Modification.

[8] CTCG Best Practice Guide for sponsors of multinational clinical trials with different protocol versions approved in different Member States under the Directive 2001/10/EC that will transition to the Regulation (EU) No. 536/2014, version 2, 12 September 2023

[9] Guidance for the Transition of clinical trials from the Clinical Trials Directive to the Clinical Trials Regulation, 19 July 2023, Introduction

[10] Guidance for the Transition of clinical trials from the Clinical Trials Directive to the Clinical Trials Regulation, 19 July 2023, Question #8 *When is a sponsor expected to update trial documents and labels?*

Issue	Comment/Recommendation
level instead of the Part I/II level, would offer a seamless transition from the Directive to the Regulation framework. • Generally, there should be no re-creation of existing documents or a re-assessment of existing content.	