COLLABORATE STAKEHOLDER MEETING 11 Sep 2024

SESSION 2 : Issue list and proposals for solutions

Claire Bahans, Limoges University Hospital, FR (EC)

Elke Stahl, Federal Institute for Drugs and Medical Devices (BfArM), DE (NCA)

Ann Marie Janson Lang, Swedish Medical Products Agency, SE (NCA)

Jane Bryant, National Office for Research Ethics Committees, IE (EC)

DISCLAIMER:

The views presented here do not reflect the official position of the European Commission.

Collaborate – issue compilation

- ✓ A list of issues relating to **clinical trial submissions**, **reviews** and **decisions** was collected based on broad input from **National Competent Authorities** (NCAs) and **Ethics Committees** (ECs) across EU/EEA Member States in **2023.** Issues raised by Sponsors through the Commission's first survey were also added to those collected.

- ✓ A survey on compiled issues asking for additional ones was then developed by a working group including 9 Member States (AT, DE, EE, ES, FR, IE, NL, SI, SE) with representatives from both NCAs and ECs

- ✓ Responses to the survey were received from NCAs and ECs of 15 Member States. They were structured and prioritised into the following categories :

Issue priority category	Number of issues
Critical	18
Major	14
Minor	15

Collaborate – solutions for critical issues

- ✓ The discussion on proposed solutions started with the **critical issues**
- ✓ A working group including 9 Member States (AT, BE, DE, ES, FR, IE, NL, NO, IT, SE) with representatives from both NCAs and ECs arranged seven scheduled virtual meetings Feb – Apr 2024 to discuss proposed solutions on the 18 critical issues
- ✓ The solutions were categorised into different groups depending on their nature
- ✓ **The final list of solutions was commented, prioritised and endorsed** by working group members and endorsed by a CTR Collaborate Plenary meeting end of April 2024
- ✓ Work continues in meetings addressing identified major and minor issues (May-September 2024)

#	Issue description	Impact(s) of Issue	Category	Grading	Keywords
1	Timelines of Part I and Part II do not align	Difficulties in updating one Dossier in response to RFI for other Dossier if timelines do not align, can necessitate SM after authorisation.If changes part I has impact on part II these cannot be handled in part II anymore because max timeline part II has past. This lead to conditional approvals and SMs later. High administrative burden and costs.	NCA Issue	Critical	Assessment, Divergence, Conclusion/AR
2	Quality of Dossiers	Incorrect documentation requiring extensive validation and assessment RFI	Ethics Issue, NCA Issue	Critical	Documentation, Validation, Procedure Type
5	CTIS Issues and generation/communication of work-arounds	CTIS issues arising from bugs in system (in some cases, for some trials only), causing problems in performing tasks/procedures for Sponsors and RMS/MSC. Additional communication by email becomes necessary to implement workarounds. Tasks are not generated or cannot be completed. CTIS BI does not function as promised yet, only template outputs possible. Document metadata in 'All Documents' section	CTIS Issue	Critical	Assessment, Validation, Conclusion/AR

Proposed solutions to critical problems

- Most critical CTIS issues – slides 5 -12
- Related topics – slides 13 -14
- Other critical issues – slides 15 -38 (in order of priority)
- Solutions to major and minor problems – slide 39

Most critical CTIS issues
CTIS ROADMAP

Priority 1

- ✓ **Confirm implementation of all CTIS functionalities planned in the CTIS 2024 Roadmap* presented at the CTCG plenary April 15 2024 (e.g. non-SM, notifications, download)**

*CTIS 2024 ROADMAP, also presented at CTIS Forum July 18 2024 under agenda item 8 CTIS Delivery update *see pdf 8. CTIS Delivery update circulated July 24 2024*

Most critical CTIS issues

Priority 2

Management of substantial modifications

- Documents submitted in an SM application not identified as new documents:

Submission date of pre-existing documents is changed to SM date, the correct information on submission date is lost in the dossier

✓ **Enable view and bulk download Part I and/or Part II restricted to only new or modified SM documents**

- For SM part II only applications, the validator part II submitter role is prevented from creating RFI in the validation assessment

✓ **Correct CTIS bug to allow validation by part II validator submitters**

Most critical CTIS issues

Priority 3 Misalignment between Application Part I and Part II assessment deadlines and handling of multiple RFIs

If timeline in CTIS is extended when need for an expert opinion (e.g. ATMP) , **the timeline is only extended for Part I and not for Part II.** Part II is concluded way ahead of Part I

CTR legal text in fact emphasizes that the **assessment time for Part I and Part II should not be coordinated**

*Regulation 1182/1971 (EEC, Euratom) applies when Part I subphase due dates occur on weekends or national holidays of RMS, why Part I is typically longer than Part II - even if both assessment phases are 45 days

For most trials (without extending Part I timeline), the only partial solution to align Part I and Part II timelines is to **introduce an artificial Part II RFI in order to conclude Part II as late as possible**.
But raising several RFIs does not solve the issue of misalignment - **Part I assessment time still longer***

Alignment between Part I and Part II timelines would be preferred

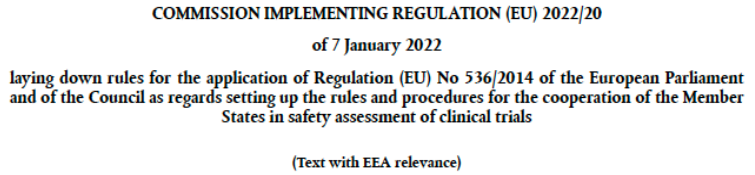
- ✓ **Preferred if legally defined timeline for Part II aligned with Part I, since raising several RFIs does not solve the issue of misalignment between Part I and Part II timelines**
- ✓ **Facilitate CTIS communication within Part I (between RMS and MSCs)** as well as **between Part I and Part II assessors**
- ✓ **Ensure that CTIS tasks are sent also for subsequent assessment RFIs** (not only for the first one) if multiple RFIs are submitted to the sponsor
- ✓ A **similar task generation tool** should be introduced for several, subsequent **validation RFIs**

Most critical CTIS issues

Priority 4

Safety monitoring, assessment and notifications

Clarity and system support needed for safety issues specified in Implementing Regulation (EU) 2022/20



COMMISSION IMPLEMENTING REGULATION (EU) 2022/20

of 7 January 2022

laying down rules for the application of Regulation (EU) No 536/2014 of the European Parliament and of the Council as regards setting up the rules and procedures for the cooperation of the Member States in safety assessment of clinical trials

(Text with EEA relevance)

- ✓ **Ensure that safety cooperation has a clear and reliable workflow(s) in CTIS**, including selection of saMS (also allowing non-MSCs to be selected)
- ✓ **Introduce new functionality for Member State handling of sponsor notifications linking them with**
  - ✓ **i) a user-friendly tick-box** clearly indicating that the notification needs to be ticked before the notification is publicly available
  - ✓ **Ii) a free text field** (not for public) clarifying for Member States that the notification has been looked at and if it is acceptable to proceed without further activities or if an ad-hoc assessment is needed

Most critical CTIS issues
IMPD-Q only submission

Priority 5

The workaround process now in place is burdensome for Member States and Sponsors

- ✓ A final solution must be included in CTIS when **the Sponsor of a trial is not the IMP Product Owner**. **A separate role for a third party (not the sponsor) only involved in the IMPD-Q** of an application is recommended

- ✓ This could also be of use **for non-authorised Auxiliary Medicinal Products when the Sponsor is not the product owner**

Most critical CTIS issues

Priority 6

Diverse daily time-consuming technical issues 1(3)

✓ **Stop automatically redirecting users into each trial when assigning tasks**

After assigning a task, CTIS will redirect the user away from the task tab into the specific trial page. This is a huge time waste especially when assigning multiple tasks, because the user is removed from the task tab into the trial application, and has to manually go back to the task tab

✓ **Implement the new DAR templates** (adopted by CTCG) within the near future

Note that the current versions were provided before CTIS go-live and that the new versions also include input from Ethics Committees via the Collaborate project Track 2b

✓ Develop functionality to **provide overview of all conditions Part I and Part II** (including situations when a Part I substantial change impacts Part II)

To avoid rejection of applications, the CTR QnA published at EudraLex Volume 10 opens for more frequent use of conditions. An overview of these, and if they are fulfilled or not, is urgent. Conditions could also be of use as a partial solution to misalignment Part I and Part II (see priority 3 above) – if used when a Part I change impacts Part II

Most critical CTIS issues

Priority 6

Diverse daily time-consuming technical issues 2(3)

✓ Allow **replacement of Member State wrong documents**

It would be beneficial if Member State administrators could replace wrongly uploaded FAR or decision letter, but nor allowing RMS to first submit a preliminary Final Assessment Report (FAR) in time before the due date, and later (after the due date) replace it with a final version

✓ **Enable the uploaded decision letter for SM restricted to Part I** to be visible for Sponsors

Although possible to upload a decision letter for an SM Part I application, it is not visible for the sponsor

✓ **Adapt CTIS to include partial MSCs (initial submission Part I only) in subsequent SM applications (scope Part I) in line with CTR and QnA published at EudraLex Volume 10 describing agreed future IT development**

Partial initial submission is not working properly: Sponsors have to withdraw initial partial MSC when need for SM Part I in MSCs where trial already started. Need to add status 'Partial MSC' in CTIS and include this partial MSC in subsequent SM Part I application reviews – in the interim period a harmonised workaround procedure should be developed

Most critical CTIS issues

Priority 6

Diverse daily time-consuming technical issues 3(3)

✓ **Implement missing notices**

Notices are missing for applications (e.g. if a MSC was intially partial and then forced to be withdrawn by CTIS and reintroduced as an addMSC)

✓ **Adapt the corrective measure functionality**

Allow procedure to proceed if an opinion from the Sponsor is received before the maximum 7 days (Article 77) and allow corrective measure modification to be applied immediately if needed anytime after starting the hearing with the sponsor and/or other Member States

✓ **Correct Timelines - should be identical in Timetables and Tasks**

Timelines shown in Timetables and Tasks are different

✓ **Consider simplification of Part II assessment tasks**

Part II assessment tasks mirror functionalities for coordination of part I, which is not useful for most Member States

Other critical issues relating to CTIS topics (CTR and Commission Implementing Regulation (EU) 2022/20) 1(2)

Solution agreed in Collaborate Track 2b	Group responsible for implementation
Updated known issues and workarounds for CTIS should be published by EMA (no updates available October 2023 – May 2024)	CTIS Simplification Task Force, share with CTIS (SAFe)Agile MS representatives – implemented in CTIS May release
MedEthicsEU and CTCG recommended to repeat surveys among their members on most burdensome CTIS issues	CTCG and MedEthicsEU
BI-tool for CTIS should be developed ensuring that it is available for all, both NCAs and ECs in all Member States	CTIS BI SAFe/Agile
Parallel Part II submission should be allowed in different MSCs (AddMSC, CTR Article 11)	CTIS Simplification Task Force - planned release end of 2024

Other critical issues relating to CTIS topics (CTR and Commission Implementing Regulation (EU) 2022/20) 2(2)

Solution agreed in Collaborate Track 2b	Group responsible for implementation
Tools to support tracking of MSCs intended to be partial should be developed (see proposed workaround on partial initial submission with placeholder Part II and condition, slide 19) e.g. introduce one standard placeholder site per Member State for MSCs intended to be partial (**CTIS Partial submission *Member State*)** before importing list of trial sites from OMS to CTIS	CTIS Simplification Task Force, share with CTIS (SAFe)Agile MS representatives (procedure under discussion in CTAG)
Clarification on issue identifying limitations for *AddMSC procedure: not allowed to upload new Part I documents, only translations of earlier submitted dossier.* Implement training on CTCG BP for the additional MSC procedure, including 'workaround' if e.g. IMP manufacturing done at a decentral point of care	CTCG
Training on best practices, including lessons learned, should be developed, promoting aligned procedures including those for safety monitoring in line with available CTCG Best Practices on Safety Surveillance in Clinical Trials	CTCG Best Practice and Safety subgroups (involve MedEthicsEU where applicable) and HADEA-financed Joint Action CT-SAFE
Best practices should be implemented to harmonise corrective measures (scope Part I and/or Part II) in several Member States coordinating identified safety issues	CTCG (Safety Subgroup), involve MedEthicsEU where applicable)

Solutions for the rest of the identified critical problems - prioritised by Collaborate Track 2b members, mean of all individual priority settings

Mean values validated and endorsed by Track 2b Members and Collaborate Plenary

Priority scale:

High	**3**
Medium	**2**
Low	**1**

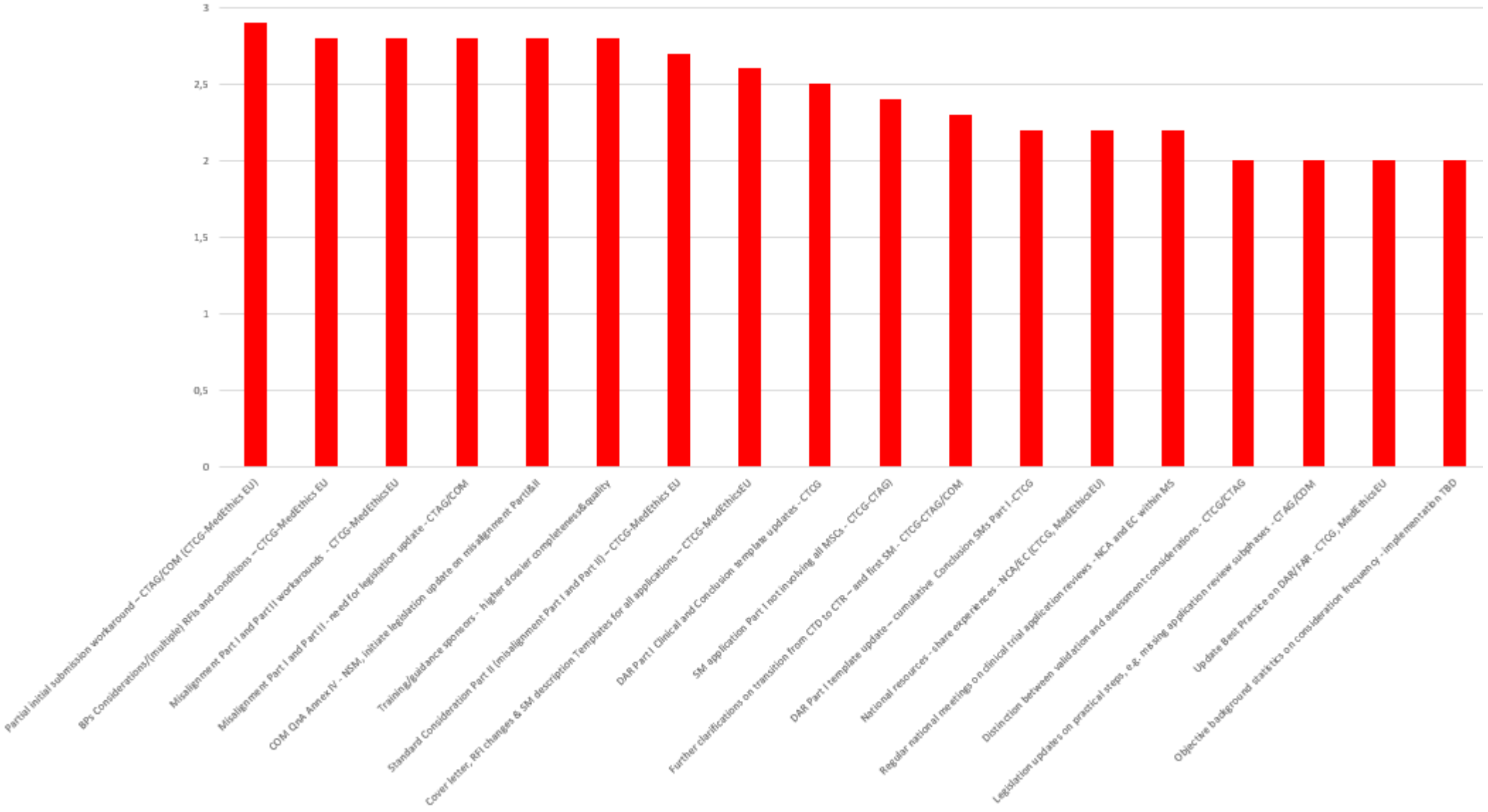
Solutions to critical problems in order of Collaborate priority – responsible body 1(2)

- Partial initial submission workaround (partial MSC involved in subsequent SM Part I review) – CTAG/COM (CTCG-MedEthics EU)
- BPs on Considerations/(multiple) RFIs and Conditions – CTCG-MedEthics EU
- Misalignment Part I and Part II workarounds – CTCG-MedEthicsEU
- Misalignment Part I and Part II – need for legislation update - CTAG/COM
- Amendment to COM QnA Annex IV non-substantial changes - CTAG/COM
- Sponsor training/guidance on higher dossier completeness and quality - Collaborate?
- Standard text Part II consideration addressing Part I/Part II misalignment – CTCG-MedEthics EU
- Cover letter, RFI changes and SM description Templates for all applications – CTCG-MedEthicsEU
- DAR Part I Clinical and Conclusion template updates – CTCG

Solutions to critical problems in order of Collaborate priority – responsible body 2(2)

- SM application Part I not involving all MSCs (e.g. complex trial subprotocol) - CTCG and CTAG
- Further clarifications on transition from CTD to CTR and first SM updating documents in line with CTR - CTCG and CTAG/COM
- DAR Part I template update – cumulative Conclusion for SMs Part I – CTCG
- National resources – share experiences - NCA/EC (CTCG, MedEthicsEU)
- Regular national meetings on clinical trial application reviews - NCA and EC within MS
- Distinction between validation and assessment considerations - CTCG/CTAG
- Legislation updates on practical steps, e.g. missing legally defined application review subphases - CTAG/COM
- Update of Best Practice on DAR/FAR - CTCG, MedEthicsEU
- Objective background statistics on consideration frequency – implementation TBD

Priorities for solutions to critical problems endorsed by Collaborate



Solution - highest priority score 2.9 – for CTAG & COM to implement (involve CTCG, MedEthicsEU)

Partial initial submission workaround - partial MSCs involved in subsequent SM Part I review

Topic introduced at CTCG, MedEthicsEU and CTAG

In brief, **sponsors should be encouraged to include all MSCs** where trials planned to be conducted in the initial application allowing partial MSCs (Part I only) to be involved also in subsequent Part I substantial modification application reviews (in line with COM QnA 3.6 and 3.9). Today, CTIS forces sponsors to withdraw partial MSCs when there is a need for a substantial modification Part I application and then add these MSCs again as Additional MSCs

Since CTIS is not likely to be adapted in the near future (although this issue identified as highest legal priority), a workaround has been proposed with placeholder Part II trial site and documents followed by approval with condition, e.g.:

'In MSCs intended to be partial (<list those Member States Concerned>), the sponsor is not authorised to recruit or include subjects or start the trial before a full Part II dossier in line with CTR Article 7 and Annex I has been authorised in an SM application with the scope Part II by the respective MSC. This SM Part II (or Part I and Part II) application should fully align the Part II dossier with the latest authorised or applicable Part I dossier submission. Note that the First Subject must be included within two years after this decision (Article 8.9) unless justified and approved in a substantial modification application Part II'

This approach was broadly supported by Collaborate members and is scheduled for further discussion at upcoming CTAG meetings, involving both ECs and NCAs in preparations

Solution - second highest priority score 2.8 – for CTCG & MedEthicsEU to implement

Further develop CTCG Best Practices on Considerations/RFIs and Conditions 1(4)

In line with current CTCG Best Practices, Collaborate emphasised that considerations not considered critical (could lead to rejection or condition) should *not* be raised by MSCs. However, if critical information is missing in the dossier, there could be a need to ask for this, even if not identified directly as leading to rejection or condition

MSCs recommended to wait introducing their considerations until the RMS has uploaded the DAR and its considerations to CTIS

Reinforce importance of well formulated, precise considerations including consequence for the application if not sufficiently responded to by sponsor

Preferable that an MSC adds comments to an already existing consideration submitted to CTIS instead of adding a new one

Solution - second highest priority score 2.8 – for CTCG & MedEthicsEU to implement

Further develop CTCG Best Practices on Considerations/RFIs and Conditions 2(4)

MSCs recommended to *merge considerations in their own Member State* (NCA and Ethics Committee). At the same time important to *respect considerations raised by Ethics Committees*. Need for further discussion on the role of an MSC to consolidate on issues to avoid misunderstanding

RMS should also follow the Best Practice on Considerations/RFI and *not include 'nice-to-know' matters*. Considerations that are not critical (could lead to rejection or condition) should in general not be included by the RMS in the RFI to the sponsor. If critical information is missing in the dossier, there could be a need to ask for this even if not identified directly as leading to rejection or condition. Also important for RMS to merge considerations where possible

Solution - second highest priority score 2.8 – for CTCG & MedEthicsEU to implement

Further develop CTCG Best Practices on Considerations/RFIs and Conditions 3(4)

Avoid multiple sequential RFIs (however in application procedures lacking a validation phase, an early assessment RFI could raise issues on completeness of application)

Preferred to use *single main scientific Part I RFI* during the assessment phase of multinational trial applications delivered with the Draft Assessment Report in line with the CTR timeline (Day 26 for initial application, Day 19 for substantial modification applications)

Sequential RFIs should not be raised on NEW aspects of the trial. Generally preferred to allow sponsors to add NON-substantial CHANGES to the application dossier

Solution - second highest priority score 2.8 – for CTCG & MedEthicsEU to implement
Further develop CTCG Best Practices on Considerations/RFIs and Conditions 4(4)

RMS should not raise additional RFIs to give the sponsor more time to respond to considerations raised in a first RFI

However, RMS recommended to allow the sponsor to correct a response, if it appears that there is a misunderstanding/lack of clarity in the response to a consideration and the RMS considers that a quick correction opportunity should be given to avoid rejection/condition

Further assessor training on the Best Practices on Considerations/RFIs and Conditions important

Prepare a **survey** (CTCG, MedEthicsEU) on current practice using multiple sequential RFIs and on issue if every MSC (NCA and EC) looks at sponsor's responses to all considerations or if e.g. ECs only look at their own considerations

Solution - second highest priority score 2.8 – for CTCG & MedEthicsEU to implement

Misalignment Part I and Part II - workarounds

Further discuss possible alternative interim workaround solutions for misalignment Part I and Part II assessment, e.g. could solution to Part II issue be done within Part I (longer assessment phase) and then introduced as Part II (in non-SM)?

The group underlines that raising several RFIs is only a partial solution and does not solve the issue of misalignment between Part I and Part II (see also slide 27 on standard text for Part II consideration to address misalignment)

Solution - second highest priority score 2.8 – discuss implementation with CTAG & COM

Amendment to COM QnA on non-substantial changes and start discussion updating legislation on misalignment Part I and Part II

Address need to update the QnA Annex IV on non-substantial changes (in line with CTR Article 81.9) at CTAG. Also allow cover letter for non-substantial changes

Changes agreed would require planning further adaptation of CTIS on non-substantial changes

Start discussion with the European Commission on need to change the legal text (CTR) so that assessment timelines for Part I and Part II will be aligned in the future

Solution - second highest priority score 2.8 – implementation by Collaborate

Sponsor training/guidance on higher dossier completeness and quality

Promote interaction between the CTR project Collaborate and sponsors

No forum exists with broad participation of ECs and NCAs (not all NCAs and ECs participate in EMA/COM/HMA Multistakeholder Platform)

Implement steps (training/guidance) to increase completeness and quality of trial applications submitted by sponsors. This would reduce need for validation and assessment considerations during the application review and reduce the number of applications lapsing or being withdrawn

Discourage sponsors to upload documents not required in CTR (e.g. trial site appointment cards, CRFs and information about the trial not related to Part II documents listed in CTR)

Clarify that sponsors should not submit scanned image documents but searchable texts

Discourage sponsors to submit images or digital tools/websites/app used for recruitment. This leads to voluminous, high size files

Discourage sponsors to upload documents with signatures in CTIS

Solution - third highest priority score 2.7 – for CTCG and MedEthicsEU to implement

Standard text Part II consideration to address Part I/Part II misalignment

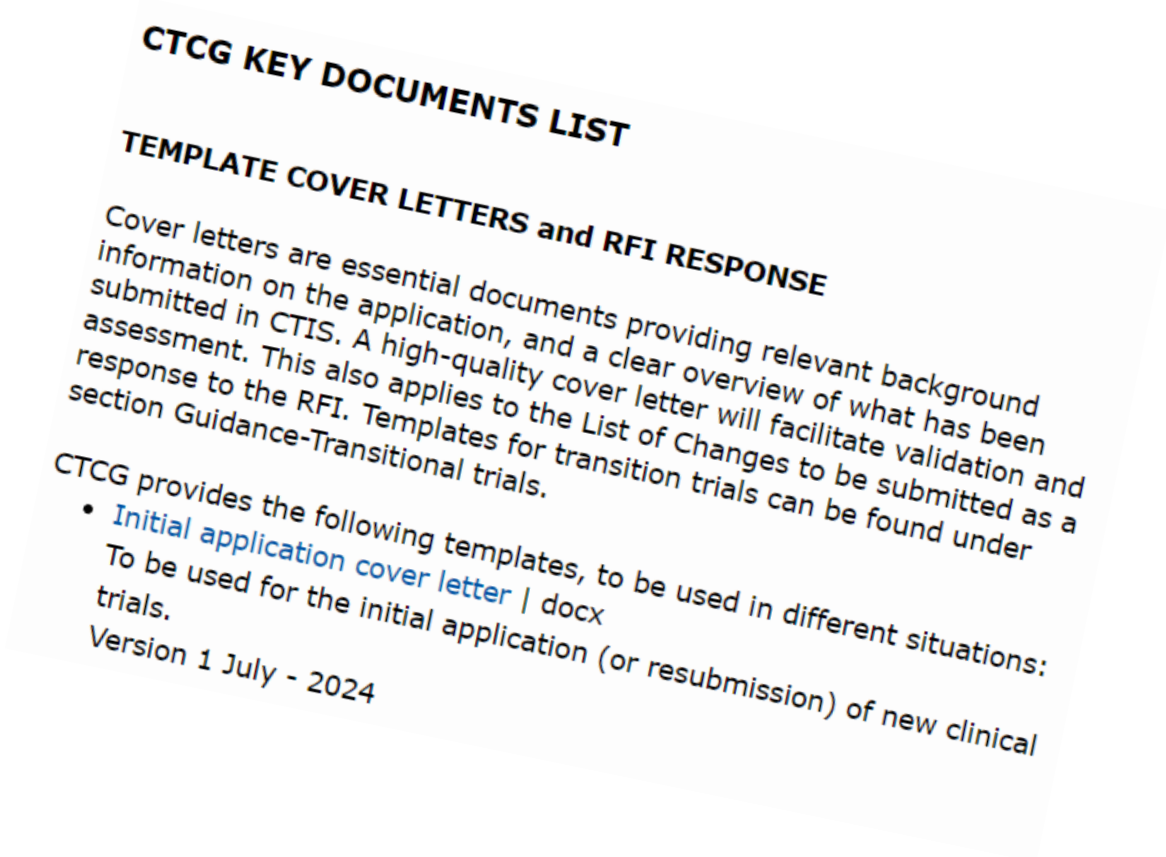
Consider using Part II standard text to partially solve the non-alignment Part I and Part II (now used by some MSs). Proposed 'standard text' for such Part II consideration:

'If the Part I dossier, e.g. the protocol, will be substantially changed during the Part I review and this impacts the Part II dossier, e.g. the informed consent or participant information leaflet, the application decision could include a condition to adapt these documents unless possible to perform an update during the parallel Part II assessment phase'

Solution - fourth highest priority score 2.6 – already implemented by CTCG

Cover letter, RFI changes and SM description Templates for all applications

Sponsors recommended to use templates for all Initial and Substantial Modification Application Cover Letters, for the RFI list of changes and for the SM description of changes – see Heads of Medicines Agencies: Clinical Trials Coordination Group (hma.eu) under Key Documents List



CTCG KEY DOCUMENTS LIST

TEMPLATE COVER LETTERS and RFI RESPONSE

Cover letters are essential documents providing relevant background information on the application, and a clear overview of what has been submitted in CTIS. A high-quality cover letter will facilitate validation and assessment. This also applies to the List of Changes to be submitted as a response to the RFI. Templates for transition trials can be found under section Guidance-Transitional trials.

CTCG provides the following templates, to be used in different situations:

- Initial application cover letter | docx
  To be used for the initial application (or resubmission) of new clinical trials.
  Version 1 July - 2024

Solution - fifth highest priority score 2.5 – already implemented by CTCG

DAR Part I template updates

New Part I DAR templates, feedback from Collaborate taken into consideration when adopted by CTCG in April 2024

Proposed by Track 2b members to add:
CLINICAL TEMPLATE

i) 'continued access of IMP for subjects´' (related to CTR Annex I 17.ag ethical considerations)
ii) description of patient involvement in trial design (see CTR Annex I 17.e)
iii) section on patient-facing documents (note however, this is typically not assessed by the RMS but evaluated by each MSC. MSCs, except BG, DK, FI, NL, NO, PL, require patient-facing documents in national language – see language requirements in Annex II of COM QnA (note for IE and MT English is national language)

CONCLUSION TEMPLATE

i) list of Part I conditions in final vs of DAR for initial and substantial modification applications
ii) tick-box if earlier raised condition Part I considered by RMS to be solved (also include list in FAR sent to sponsors)

Solution - sixth highest priority score 2.4 – for CTCG & CTAG to implement
SM application Part I not involving all MSCs (e.g. complex trial subprotocol)

No possibility in CTIS to submit SM part I only to a selection of MSCs (e.g. could be treatment arm relating to subset of MSCs in a complex clinical trial design or in trial substudy/subprotocol), discuss if acceptable not to involve all MSCs in SM Part I applications if changes only relevant to some MSCs

Clarify consequences of this related to fees for the application

Discuss this topic also with CTAG and European Commission

Solution - seventh highest priority score 2.3 – already implemented by CTCG and COM

Further clarifications on transition from CTD to CTR – and first SM

Promote further harmonised simplification of transition application procedure (CTD-CTR) both regarding Part I and Part II initial and first substantial modification applications (see COM guidance at EudraLex Volume 10 and CTCG guidance at the CTCG/HMA website under Key documents list

For Part I, a minimum dossier agreed to be sufficient for the initial CTIS application

Implement internal CTCG BP on transition (training of assessors):

- MSCs should not ask for documents approved under CTD in addition to the Part I minimum dossier initial CTIS application. Do not ask sponsors to upload e.g. layperson protocol synopsis, patent-facing documents or labelling in languages indicated in the COM QnA Annex II
- At the same time, if sponsors choose to upload incorrect additional documents Part I outside the minimum dossier, e.g. layperson synopsis approved under CTD, MSCs could raise considerations asking the sponsor to correct these documents
- Sponsors should only upload CTD approved documents (Part II) if these are required under CTR
- A clear overview of documents required per MSC for Part II beyond the minimum dossier and for the first SM is provided at the CTCG-HMA website, under Key documents list CTCG-HMA website – including templates for the transition

As proposed by Collaborate, COM transition guidance added information on combined studies, (parallel investigation of medical device and/or in vitro diagnostic performance)

Solution - eighth highest priority score 2.2 – already implemented by CTCG

DAR Part I template update – cumulative Conclusion for SMs Part I

New Draft Assessment Report (DAR) templates adopted by CTCG including Collaborate proposal organising the DAR CONCLUSION TEMPLATE as a cumulative SM Conclusion Part I DAR summarising substantial changes after the initial application (non-clinical, clinical, statistical, regulatory substantial changes)

Discuss further if cumulative conclusion should also be included in FAR sent to sponsor (including earlier approved SM applications)

Solution - eighth highest priority score 2.2 – for NCAs & ECs to implement (CTCG, MedEthicsEU)

National resources – share experiences

Lack of resources for NCA or ECs is a matter of concern for the respective Member State Ministries (Health, Education etc.)

Although issues linked to resources are within the remit of each Member State, Collaborate recommends to share experiences in efforts to strengthen national resources for bodies reviewing clinical trial applications (e.g. in MedEthicsEU). This could allow "learning from each other" on steps taken to ensure sufficient resources for NCA/EC, e.g. when restructuring ECs

The number of ECs per Member State expected to be described when results from the European Commission Union Control Survey carried out earlier this year will be published

Solution - eighth highest priority score 2.2 – for NCAs and ECs to implement

Regular national meetings on clinical trial application reviews

Promote common regular meetings *within* a Member State Concerned between ECs and NCAs *on trial applications*

Solution - ninth highest priority score 2.0 – already implemented by CTCG

Distinction between validation and assessment considerations

Clarify in BP on Considerations/RFI what is a validation consideration and what is an assessment consideration. Collaborate proposal implemented by CTCG.

Validation addresses completeness of dossier, assessment addresses quality and content of dossier. This should also be included in training for assessors

At the same time noted that some CTR/CTIS procedures lack validation phases (e.g. addMSC). Further training needed

Solution - ninth highest priority score 2.0 – for CTAG & European Commission to implement

Legislation updates on practical steps, e.g. missing legally defined application review subphases

Start discussion with European Commission to update legal text of CTR when it comes to practical issues not foreseen by CTR legislators (e.g. introducing validation, assessment and decision phases for all application procedures and clarity on patient-facing documents – Part I or Part II?)

Solution - ninth highest priority score 2.0 – for CTCG & MedEthicsEU to implement

Update Best Practice on DAR/FAR

BP on DAR/FAR recommended to be updated, including assessor training/recommendations how to fill in the document

The agreed assessment day for the Part I DAR circulation should be adhered to

Note that there is no new DAR/FAR Part I during the AddMSC procedure, but other application procedures all require both a DAR and a FAR Part I

Recommended to add an executive summary to Best Practice DAR/FAR texts

Solution - ninth highest priority score 2.0 – implementation TBD

Objective background statistics on consideration frequency

Analyse which parts of the dossier lead to the highest number of considerations raised by MSCs, e.g. Part II subject information leaflet and informed consent form

Based on the results, sponsors could be encouraged to submit higher quality data and documents

Work still ongoing…

Collaborate has continued work on analysing problems and proposing aligned solutions since May 2024 for remaining identified issues, i.e. major and minor problems

Outside additional topics related to CTIS, these issues include combined studies, parallel GMO applications, how to ensure that PIP and scientific advices are taken into consideration, low-intervention clinical trial simplifications, complex clincal trials, special trial scenarios, e.g. handling of vaccine studies with updates in manufacturing because of new virus strain, exchange on national appeal procedures and trial application decision letters as well as how to handle diverging views from ethics committees and different national requirements on patient-facing documents and language requirements

Thanks for your attention!