	CTCG Q&A on submission Complex Clinical Trials in CTIS, vs 1.0, dd 14 March 2023		
Nr	**Question**	**Answer**	**References**
	Important considerations for the submission of complex clinical trials(CCT) in CTIS		
1	Do I need to submit a CCT and its parts as one single trial or as separate clinical trials under the CT Regulation in CTIS?	Both submission approaches are acceptable. Question 1.3 of the Q&A on complex clinical trials addresses several factors to be considered for submission (under one EU CT number or several EU CT numbers). Regardless of the approach, at least one IMP should be investigated, e.g. the master protocol should be submitted simultaneously with at least one of the sub-protocols (e.g. IMP-specific) under the same EU CT number at the time of the initial submission.	https://health.ec.europa.eu/system/files/2022-06/medicinal_qa_complex_clinical-trials_en.pdf https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2019_02_CTFG_Recommendation_paper_on_Complex_Clinical_Trials.pdf
2	In case the sponsor of a clinical trial is not the product owner (PO) of the IMP and should not have access to the quality IMPD (IMPD-Q) in order to protect commercially confidential information or associated considerations/RFI, what options do exist for the PO and the sponsor?	The several options are described in question 2.15 of the Q&A CTR published on Eudralex volume 10.	https://health.ec.europa.eu/system/files/2022-06/medicinal_qa_complex_clinical-trials_en.pdf
3	What is specific for a CCT as regards the cover letter, the protocol summary, the titles of the master and subprotocols and naming of these documents?	To facilitate the overview and communication, unique indentifiers ensuring the coherence between the master protocol and subprotocols are needed. Question 2.1 and 7.3 of the Q&A on complex clinical trials specifies this in more detail. For naming of documents, see also the CTCG recommendations on naming of documents in CTIS .	https://health.ec.europa.eu/system/files/2022-06/medicinal_qa_complex_clinical-trials_en.pdf 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
4	Can the master protocol and/or sub-protocols contain country- or region specific information ?	If it is valid/applicable for all subprotocols, such information can be included in a harmonised/consolidated master protocol or its appendix; if information is specific for subprotocols only, it can be included in the respective harmonised/consolidated sub-protocol or its appendix.	https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2018_05_CTFG_Best_Practice_Guide_for_sponsors_of_transition_multinational_clinical_trials.pdf
5	Does the sponsor of the master protocol have to be the same for all subprotocols?	No, article 71 of the CTR states that a clinical trial can have more than one sponsor. In case of co-sponsorship, all co-sponsors shall in prinicple have the responsibilities of the sponsor. This implies that they are jointly responsible. However, co-sponsors can jointly determine to split the responsibilities of the sponsorship by a contractual agreement. This allocation of responsibilities and tasks between co-sponsors can be different between the different subprotocols. Further details are provided in Q1.4 of the Q&A on complex clinical trials and Q5.2 of the Q&A on CTR published on Eudralex Volume 10.	https://health.ec.europa.eu/system/files/2022-06/medicinal_qa_complex_clinical-trials_en.pdf https://health.ec.europa.eu/document/download/bd165522-8acf-433a-9ab1-d7dceae58112_en?filename=regulation5362014_qa_en.pdf
6	What are the transparency rules if the CCT is submitted in CTIS as a single trial and subprotocols are falling in different categories of trials (1, 2 or 3) for deferrals of publication in the public domain of CTIS?	The subprotocol which falls in the highest category will determine the category. For example, one subprotocol falls in category 2 (deferrals up to 5 year after the end of the clinical trial) and another subprotocol falls in category 3 (deferrals up to one year after the end of the clinical trial), the trial will be treated in line with category 3. If the clinical trial is not submitted as a single trial but as separate clinical trials with different EU CT numbers, each clinical trial can have their own category with its respective deferral rules. In case there are different categories of master protocol and subsprotocols, the sponsor is responsible for aligning these different deferral rules to keep the integrity (e.g provide master protocol with shortest deferral time). More information on the protection of publication of commercially confidential information and personal data is provided in the Appendix on Disclosure Rules, to the “Functional specifications for the EU portal and EU database to be audited – EMA/42176/2014” and the associated Q&A .	https://www.ema.europa.eu/en/documents/other/questions-answers-protection-commercially-confidential-information-personal-data-while-using-ctis_en.pdf https://www.ema.europa.eu/en/documents/other/appendix-disclosure-rules-functional-specifications-eu-portal-eu-database-be-audited_en.pdf

7	What are the general principles of a complex clinical trial transition from the CTD to the CTR and submisstion in CTIS?	The general principles for transition of a clinical trial are given in chapter 11 of the Q&A on CTR published on Eudralex volume 10. The sponsor is generally required to have a harmonised or consolidated master protocol and its sub-protocols approved under the CTD by each of the MSC prior to transitioning. Such harmonisation/ consolidation at the time of transition and subsequent submission to CTIS should be exceptional and agreed by all MSC where a CCT will be ongoing under CTR. The sponsor should contact the national contact points of the proposed RMS and MSC before transition to have an agreement of all MSC for this exception for CCT on the general rule. In any case, no substantial modifications can be made for a clinical trial in transition.	https://health.ec.europa.eu/document/download/bd165522-8acf-433a-9ab1-d7dceae58112_en?filename=regulation5362014_qa_en.pdf
8	If a CCT has been authorised under CTD as one single trial and I want to transition this CCT to CTR, should this submmission approach be maintained in CTIS?	Not necessarily, the sponsor has the option to submit the CCT under one or several EU CT numbers in CTIS. See also question 1. In addition to the considerations mentioned in Q1.3 of the Q&A on complex clinical trials, the approach also depends, among others, on the MSs involved in the approval and status of different sub-protocols, an interrelationship between subprotocols, safety reporting requirements, the expected number of substantial modification (overall and per subprotocol), etc.	https://health.ec.europa.eu/system/files/2022-06/medicinal_qa_complex_clinical-trials_en.pdf
9	How to proceed if a master protocol and one sub-protocol were authorised under CTD under one number (as a single trial) in one MSC and the entire CCT (master protocol and all sub-protocols) was authorised under CTD in more than one MSC with a different number?	The general principle is that the master protocol and subprotocols need to be harmonised/consolidated before a CCT can be transitioned. See also question 4. The sponsor should justify the submission approach and consider different relevant aspects (see question 1, 5 and CCT-Questions and anwers). In this particular case submission under several EU CT numbers could be preferable.	https://health.ec.europa.eu/system/files/2022-06/medicinal_qa_complex_clinical-trials_en.pdf https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2019_02_CTFG_Recommendation_paper_on_Complex_Clinical_Trials.pdf
10	Is it needed for a transition of a CCT to submit both part I and part II documentation for subprotocols which have no active sites at the time of transition?	No, part I documentation has to be submitted for all sub-protocols which are still ongoing in at least one MSC and part II documentation has to be submitted only for subprotocols with sites which are still recruiting or having trial participants. In any case, the clinical trial application for transition CCT will require all application files (Part I and II) to be submitted in CTIS; a partial submission according to the article 11 of CTR is not allowed for transition trials.	https://health.ec.europa.eu/document/download/bd165522-8acf-433a-9ab1-d7dceae58112_en?filename=regulation5362014_qa_en.pdf