23 May 2022
EMA/298712/2022

Complex clinical trials – Questions and answers

Version 2022-05-23

Draft agreed by Drafting Group experts (from EMA scientific committees, EMA working parties, EMA staff and Clinical Trials Coordination Group)	May 2022
Draft agreed by Clinical Trials Coordination Group	May 2022
Draft agreed by Clinical Trials Expert Group	May 2022
Adopted by ACT EU Steering Group	23 May 2022

Keywords	Clinical trial; complex clinical trial; clinical trial authorisation application; marketing authorisation application; trial design; trial analysis; Clinical Trials Regulation; master protocol; platform trial; biomarker; adaptive design; modifications; Bayes; control data; transparency

For questions related to this document, please write to ACTEU@ema.europa.eu.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands

Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Complex clinical trials – Questions and answers

Table of contents

Glossary

Platform trial	Broad term for a number of clinical trial (CT) designs characterised by a shared framework that allows for the investigation of multiple investigational medicinal products (IMPs) in a continuous manner, possibly in different diseases/conditions, with different IMPs 'entering' and 'leaving' the platform at different times based on pre-specified decision rules [see also ICH E8(R1)]; used in this document as a typical instance of a complex clinical trial (CCT).
Master protocol	A protocol describing the key features of a complex clinical trial that encompasses common elements to all its sub-protocols, that can allow for the investigation of multiple IMPs or diseases/conditions, and that specifies the shared framework across sub-protocols. This definition applies to trial protocols of CCTs with shared framework, such as trials called 'master protocol studies' as defined in ICH E8(R1) (see Q2).
Sub-protocol	A component of a complex clinical trial (such as described in a master protocol) that is specific to IMPs, to targeted populations, and/or to design features or other specificities not covered in detail in the master protocol. Under the EU CTR, sub-protocols can be implemented and authorised as separate clinical trials (each with a unique EUCT number) or part of the same clinical trial (see Q1.3).
Study (trial) arm	A pre-identified subgroup of trial participants to be assigned a pre-identified intervention, which is typically determined by randomisation.
Communication plan	To be included in the body of or in an annex to the protocol, see Q7.2
Status overview	Information on sub-protocols concerning recruitment (e.g., open or not), number of participants included and status (e.g., ongoing or terminated) per country, to be included in the cover letter of a substantial modification application (or initial application for a sub-protocol) and as applicable in other clinical trial applications (CTAs)
EUCT number	European Union Clinical trial number, either the EudraCT number or, in CTIS, the EU trial number. The EUCT number should be stated in all trial-related documents and regulatory submissions, in trial registries as well as in scientific and other publications
Adaptation	As per EMA Reflection paper on Methodological issues in confirmatory clinical trials planned with an adaptive design
Modification	As per EU CTR recital 23. Adaptations are examples of modifications. Where modifications have a substantial impact on the safety or rights of the trial participants or on the reliability and robustness of the data generated in the clinical trial, they should be subject to an authorisation procedure similar to the initial authorisation procedure (that is, substantial modifications (SMs) under the EU CTR or substantial amendments under the Clinical Trial Directive).

Scope

This Q&A document provides guidance and seeks to support sponsors, clinical trialists and applicants regarding scientific aspects and the planning, set-up, submission for obtaining CT authorisation (CTA), conduct, reporting and transparency, analysis and interpretation of complex clinical trials (CCTs) under the EU Clinical Trials Regulation (EU CTR) as well as their use in submissions for marketing authorisation. It complements and should be used together with relevant EU and ICH guidelines, in particular E6, E8, E9, E10, E16, E19, E11A and E20 (when available).

For the purpose of this document, the nomenclature follows the EU CTR, relevant ICH guidance, CTFG Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials (2019) and international common use as appropriate. Additional non-binding terminology conventions are described in the glossary to facilitate alignment between different sources of information and ensure consistent meaning.

This document aims to address challenges sponsors may face as regards scientific and operational aspects of CCTs and to encourage considering choices in development and implementation as early as possible, in order to generate useful evidence and inform clinical and regulatory decision-making. This document also refers to additional resources providing guidance for CCTs throughout the medicinal product lifecycle. The document is planned to be updated with evolving experience. Operational aspects related to the Clinical Trials Information System (CTIS) are not addressed in this Q&A.[1]

The scope of this document is to provide guidance and support for complex clinical trials which are defined as being non-conventional in the sense that they have elements, features, methods or combination thereof, including novel approaches, that confer complexity of their designs, conduct, analyses or reporting.

There can be a scientific rationale and motivation for a complex clinical trial in any phase of clinical development. Complex clinical trials add value to clinical development, including early decisions on further development, and are of particular interest where they have a potential to allow for more efficient and accelerated evidence generation for clinical development to advance public health and to support a marketing authorisation application. Complex clinical trials so far have been rather diverse, so that the balance of their value with their scientific and operational complexities needs to be considered starting from the planning stage. The robustness of data generated in a clinical trial, together with the rights, safety, dignity and well-being of participants, are the foremost principles stipulated in the EU CTR and they also apply to CCTs.

This Q&A document is not restricted to specific types of CCTs and applies also to other designs intended to address multiple research questions. This operational definition does not imply a legal categorisation or a need for sponsors or NCAs to demonstrate that parts of a CCT could in fact be handled as individual trials. This Q&A document recognises that CCTs can also include ATMPs as IMPs (see Q1).

Aspects of the modus operandi for clinical trial authorisation in the EU have consequences that sponsors and regulators have to be aware of and to accommodate. For a complex clinical trial, the structure of its results in a submission for marketing authorisation (MAA) may differ from that of its submission(s) for clinical trial authorisation (CTA). An example is a MAA submission that is based on an active and a control arm which had been submitted as different CTAs yet were part of

[1] For technical support with CTIS, go to https://euclinicaltrials.eu/support-info/.
Training and supporting materials are also available at https://euclinicaltrials.eu/training.

a shared scientific framework. A CCT builds on a scientific rationale at the level of a shared scientific framework across CTAs and thus across EUCT numbers. Regulators may have to handle an MAA with results of a CCT focusing on its scientific rationale and taking into account the necessities for choosing a submission approach that applied at the time of CTA. A complex clinical trial can thus refer to a trial with a single EUCT number (such as having a master protocol and sub-protocols within a common protocol structure, as one single protocol) or to several trials with different EUCT numbers linked by a common (master protocol) part. Choices for the submission approach for authorisation of CCTs are driven by the rule set for clinical trials in the EU. Since the shared framework of CCTs can span regions beyond the EU, consequences may affect the paradigm of corresponding identifiers in public trial registries between the EU and other regions and the MAA dossier in the EU.

Question 1: Important considerations for the planning and conduct of complex clinical trials

Q1.1: How to define in the protocol research questions, objectives, endpoints, assumptions and hypotheses when they are common and/or specific for sub-protocols?

Shared scientific framework (scientific rationale of the CCT)

In accordance with ICH E8(R1), "the essence of clinical research is to ask important questions and to answer them with appropriate studies". In practice, the research questions will therefore drive the overall purpose of the trial(s) and its objectives, thereby contributing to the rationale of the clinical trial. It should therefore be clear from the planning stage which scientific question the trial is going to address.

In this context, CTFG Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials (2019) refers to the need for an 'overarching hypothesis'. It is described in this document as 'scientific rationale' which is of particular relevance for complex clinical trials and is different from a statistical hypothesis. The scientific rationale defines the scientifically sound relationship(s) between the research questions of the (sub-)protocols.

This scientific rationale with its shared elements of the design and/or infrastructure common across sub-protocols can be described in the sub-protocols and the master protocol, with details on the relationship between sub-protocols in terms of efficacy and/or safety data collection, analyses, interpretation, and reporting.

Protocol design considerations

The rationale for the complexity of the design and conduct of a complex clinical trial needs to be explained in clear terms and justified in the protocol(s) and related documentation; such information should be made available to investigators, regulators, and provided in lay language to clinical trial participants. It should also be explained why the same objectives are not pursued using more conventional, non-complex designs.

For every (sub)protocol in a CCT, key elements of the trial protocol are listed in Annex I, section D and information to subjects in section L of annex I of the EU CTR; this section intends to highlight considerations of particular importance during the planning and set-up of CCTs:

- to consider the potential benefits, limitations, and challenges of applying complex design features versus more conventional approaches at the (pre-)planning stage.

- to justify the scientifically sound rationale for the complex design and the shared scientific framework.
- to address and mitigate potential challenges inherent to the choice of complex design elements, features, methods in the protocol (for example with respect to patient's safety and/or trial results reliability).
- to clearly and explicitly state in the relevant sections of the protocol the primary scientific questions and objectives depending on the overall design and submission approach (see Question 1.3), as well as, whenever relevant, specific sample size considerations, description of the population of interest as per the estimand framework (ICH E9(R1)), pre-planned comparisons, choice of control, the proposed randomisation method, and how multiple testing adjustment is addressed (see statistical hypothesis and Q1.3).
- to include additional schematics to describe the CCT design aspects and whenever relevant the overall CCT schedule in the relevant section(s) of the protocol(s).
- to include a detailed communication plan linked to the overall CCT schedule, describing for example the start and termination of sub-protocols or treatment arms (see glossary and Question 7.2 for details).
- to clearly describe how research questions, objectives and endpoints apply to specific or across sub-protocols in a CCT and to specify (preferably in a tabular format) which documents are to be considered for each sub-protocol and where they are located in the CTA structure.

Statistical hypothesis

It is a good research practice for any trial to address (a) clinical research question(s), to set clear and precise objectives and to pre-specify a statistical hypothesis. This equally applies to complex clinical trials that may address several research questions. However, while for confirmatory trials adherence to established standards for hypothesis testing should be followed, "the objectives for exploratory trials may not always lead to simple tests of pre-defined hypotheses" and a more flexible approach with changes in response to accumulating results could be applied (ICH E9). Yet, the more stringent these trials are, the more they can contribute to the total body of evidence.

Consequently, as any other clinical trial, CCTs require careful planning and pre-specification of their intended purpose. It is thus particularly important for a CCT, if it is intended or may eventually be used to provide the main clinical evidence to support a regulatory decision in the context of a marketing authorisation, to include pertinent assumptions and hypotheses; this should also be supported by having appropriate resources and measures in place to ensure a meticulous conduct of the trial to render the trial interpretable and to allow robust conclusions. In addition, this should also include considerations on replication of previous findings. Importantly when comparisons are intended, for example between arms or sub-protocols, these should be pre-specified and justified in the relevant (sub)protocols; The (sub)protocols should also address considerations on concurrency and/or randomised allocation (see also Q2 and Q4).

Operational feasibility

CCTs should be designed in a way that renders them operationally feasible, taking into account the trial logistics and data collection needs. Indeed, the main concern is that "complex trial designs translates into increased operational complexity due to the presence of several IMPs, populations, trial sites, multiple sponsors and/or manufacturers and contract research organisations (CROs)".

Consequently, complex clinical trials require intensive peer-level interaction and agreement between clinicians (community of investigators, clinical researchers), methodology experts (statisticians, biometricians, modelling and simulation experts) and project teams (organisation, performance of trial) about the choices in scope (subjects and conditions to be included), main design features (medicinal products, arms, endpoints) and adaptations. Such alignment is required because often there is no single or simple precedent for a CCT, and such trials are more unique than non-complex trials.

In addition, consultations with investigators and their communities, site personnel and patients early during protocol development and questions of conduct of the trial may result in better enrolment and retention, more efficient trial conduct and fewer protocol changes that may trigger substantial modifications. These groups of stakeholders and their engagement should therefore always be considered when planning CCTs. Of note, when patients are involved in the design of the clinical trial, a description of their involvement should be included in the protocol (EU CTR Annex I 17(e)).

The policy of analysis and publication of results of a CCT should be organized to comply with the EU CTR transparency requirements (see also Q7).[2]

Treatment allocation and change to randomisation ratio

Treatment allocation especially under the scenario encompassing multiple separate clinical trials (CTAs) under a shared framework should be clearly defined, pre-specified and documented for investigators to minimise bias.

In addition, in situations where standard of care may evolve rapidly, new IMPs are to be introduced and/or prevalence vary greatly in time or between countries, the potential for variations in the randomisation ratio at different period and/or between centres could occur. This should be taken into account during the analysis, e.g., by analysing the data for the two allocation periods separately. Please refer to the EMA Guideline on adjustment for baseline covariates in clinical trials (2015).

Q1.2: How to apply risk-proportionate approaches to CCTs?

Proportionate risk-based approaches should be applied for complex clinical trials, with risks to both trial participants and the reliability of trial results being addressed. A risk-based quality management system should include steps for risk identification, evaluation, control, review, communication and reporting.

Also, whilst onsite monitoring was described as the norm for CCTs in the CTFG Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials (2019), this may not always be required, and a risk-based approach should be considered (ICH E6(R2)). Besides, when elements of a decentralised trial (DCT) or DCT are planned, the recommendation on DCT elements[3] should be consulted.

Lastly, targeted training for site personnel and investigators should address in detail the complex features of the proposed trial and its critical-to-quality factors. In doing this, sponsors should consider the provision of continuous dedicated support to assist investigators and site personnel during conduct especially at the start of the trial or when modifications are planned.

[2] Additional clarifications in respect to how to submit data in CTIS to meet transparency criteria are under development and will be published when available in EudraLex Volume 10.
[3] Joint CTFG/CTEG/GCPIWG recommendation paper on decentralised trial elements – in development.

Please refer to "Risk proportionate approaches in clinical trials" (2017) that should be read in conjunction with ICH E8(R1) and ICH E6(R2) currently under revision.

Q1.3: Do I need to submit a CCT and its parts as one single trial or as separate clinical trials under the CT Regulation?

The CTFG Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials (2019) discusses two CTA submission approaches for a complex clinical trial. Both submission approaches may be used in the context of shared scientific framework for collection, analysis of data and regardless of the submission approach. Any potential inter-relationship (including for inferential purposes) between the individual trials should be addressed at planning stage, and recorded either in the individual sub-protocol and/or, where applicable, the common (master) part of the protocol (See Q1.4 in relation to emerging data). Applicants should however consider the potential consequences of both approaches in terms of conduct, analyses and assessment of complex clinical trials, primarily from a regulatory and scientific perspective; seeking advice at an early stage of planning is therefore strongly recommended and a detailed scientific rationale and robust justification for all aspects of the design are expected including at the time of scientific advice (see Q1.6). This is particularly relevant when a CCT is intended (or may be used) to provide the main clinical evidence to support a regulatory decision. Consequently, this section provides some preliminary considerations based on the current state of play, although these will likely need to be updated as further experience is gained with CCTs and scientific experience with such trials increases. The considerations below also need to be weighed against the scientific rationale for the trial(s) in terms of elements of agility being sought and against elements that lead to choose a given CTA submission approach such as intended regulatory purposes, nature of shared elements (e.g. master protocol, shared control, patient information sheet, etc), modalities of conduct in different countries, involvement of multiple sponsors/co-sponsorship, number of study arms/sub-protocols, potential introduction of new IMPs and requirements for reporting. In addition, under both submission approaches transparency requirements related to identification of the CCT, and publication of relevant dates and results should be followed (See Q7).

<u>Submission as a single trial/one EUCT number</u>

This single trial submission approach typically consists of several sub-protocols included under one CTA linked together by a clear scientific rationale (See Q1.1), encompassing the common protocol elements within the master protocol, and may include for example a common control arm as shared element. The following aspects should be considered when selecting such submission approach:

- The number of study arms/sub protocols included initially and subsequently, and timely implementation of a high number of cumulative substantial modifications, potentially with several changes planned in parallel, will impact the overall trial conduct. In addition, cumulative changes related to different sub-protocols potentially require preparing complex substantial modifications, which may lead to higher risk for refusal. For details on rules on submission of substantial modifications please see the CTR Q&A document.
- The intervention allocation procedure, including considerations about timing, will need to be sufficiently defined at the start of the trial (e.g., patients in Arm X enrolled between Month/Year M1/Y1 and Month/Year M2/Y2).
- Study arms/sub-protocols can be at different stages of conduct, so in the case where they may not be intended for the same regulatory submission, interim reporting is proposed or there

may be some information leakage from one arm, e.g., a shared arm, sponsors should ensure that study and data integrity is preserved (see Q7).

- Potential risk of bias introduced through deviations in conduct referred to as 'operational' bias (ICH E9).
- If different IMPs (or patient population) are introduced and evaluated at different periods of time, the choice of the " concurrent control group" needs to be justified since per ICH E10, "the test and control groups should be similar with regard to all baseline and on-treatment variables, except for the study treatment"; consequently, non-concurrency in time of the control and test arm(s) may affect the trial interpretability.
- The nature/type of IMPs and the potential impact of their intrinsic complexity (e.g., ATMPs, complex product-device combination) should be carefully considered for the design and operational feasibility of a CCT with such IMPs, especially when several IMPs are investigated from the start of a trial or planned to be added via substantial modifications.

Submission as separate trials/multiple EUCT numbers

A "multiple trial (CTA) submission approach" consists of requesting the authorisation of every sub-protocol as if it would be a standalone clinical trial. Under this submission approach, the following aspects would usually need to be considered:

- This multiple CTA submission approach brings more flexibility where some agility is needed for advancing development (e.g., future introduction of IMPs or trial population) via additional CTAs as scientific knowledge or standard of care evolves in a specific disease).
- The overall high-level scientific rationale linking each sub-protocol (CTA) specific rationale, objectives and potentially their positioning within the ongoing development programme (CCT) should be described in the common ("master") part of protocol (master protocol, in addition to the cover letter).[4]
- This approach brings more operational flexibility to implement substantial modifications.
- Compliance with transparency requirements is more efficiently addressed (see Q7).
- This multiple submission approach may however need pre-specification on whether/how external information will be used, affect the trial conduct ('operational' bias) and/or analysis.
- Scientific experience on this is still evolving and depending on the specific design on the platform and/or shared scientific framework, it may also be that the 'single trial submission approach' is a preferable choice.

Q1.4: What considerations are important when planning a complex clinical trial as a co-sponsorship?

Multiple co-sponsors, that can be an individual, a company, an institution or an organisation, are possible as per the EU CTR Article 71. Thus, a conduct of complex clinical trials (e.g., platform clinical trials) may be governed by a collaborative network of co-sponsors, for example by networks of researchers or research institutions within disease-focused consortia. The governance rules and structure to ensure oversight and timely decision-making need to be considered at the planning stage by means of establishment of relevant committees (e.g., overall, and sub-protocol-specific steering committees, data monitoring committees) and a communication plan (See Q7.4).

[4] The feasibility is being explored for submitting a master protocol with the first sub-protocol (CTA) as a reference trial to which subsequent sub-protocol CTAs can cross-refer. Pending the outcome, further guidance will be issued.

The responsibilities and the means to maintain the data integrity, confidentiality should be agreed in specific contract(s) and organised between co-sponsors (potentially with an involvement of a third party such as contract research organisations).

For questions regarding sharing responsibilities and delegating tasks/functions please refer to Question 5.2 in the CTR Q&A document.

Q1.5 What additional considerations, including for benefit-risk reassessment, need to be made during the conduct of CCTs?

Re-assessment of the benefit-risk in a CCT

Re-assessment of the benefit-risk should be performed at all critical steps throughout the clinical trial including but not limited to the modifications to main elements of the clinical trial design (e.g., the target population(s), IMPs, endpoints) as well as emerging data from any of the sub-protocols within the entire trial (independent of the way the CCT is submitted) that could affect benefit-risk in other sub-protocols whenever relevant.

To the extent possible, these potential modifications (e.g., introduction of new IMPs, treatment reallocation, sample size re-estimation based on results of an interim analysis) or criteria leading to such modifications should be described in the protocol. A difference should however be made between the flexibility for pre-planned modifications offered by a platform design and adaptations in the framework of an "adaptive design' (EMA 2007). In all cases however, the impact of such modifications on trial and data integrity, results reliability and potential inflation of type I error should be carefully considered and mitigated using a multidisciplinary approach. In particular, any potential risk for unblinding and its impact on data integrity should be mitigated.

All changes not addressed in the initial version of the protocol and affecting the trial conduct will need to be documented as protocol amendments and where necessary submitted as substantial modifications. It is also equally important to point out that modifications to one sub-protocol may entail modifications to the other sub-protocols, e.g., of the platform trial. It should be clear in each sub-protocol if and to what extent it is dependent on modifications of other sub-protocols.

Likewise, changes to the master protocol part may have an impact on all the sub-protocols, for example in case the benefit-risk change is relevant for the entire trial. Therefore, substantial modifications may be needed for all sub-protocols when there is a substantial impact on the safety or rights of the participants or on the reliability and robustness of the data generated in the clinical trial. Depending on the overall design of complex clinical trials, the same IMP may be investigated in several sub-protocols that are considered as separate clinical trials. In the future, when this functionality is developed in CTIS, sponsors are encouraged to submit these SMs in parallel as a single application to as many of the participating trials if certain conditions are met (see question 3.8 in the CTR Q&A document).

In addition, in situations where important events not necessarily foreseen arise that may impact the interpretability of the trial data e.g., one of the IMPs in a CCT becomes standard of care during the conduct of the trial, it is necessary to assess the impact of such changes on the benefit-risk relationship for trial participants and regarding interpretation and whether continuation of the trial is reasonable, or a new trial should be initiated.

As regards the management of urgent safety measures, please refer to the Q6.2.

Please also refer to the "Recommendation paper on the initiation and conduct of complex clinical trials" (2019) for further guidance.

Q1.6: Which specific aspects of CCTs would benefit from seeking advice?

CCTs need to be constructed to the benefit of multiple stakeholders' needs —patients, industry, site networks, disease scientists, regulators and HTA bodies. If the proposed CCT is not advantageous to one of these, the effort may be vain or unsuccessful; consequently, early engagement with patients, investigators, regulators and HTA bodies in trial design, and consistently throughout trial execution will be paramount to a successful outcome.

Early engagement with regulators and seeking advice is therefore highly recommended for any CCT and available for any sponsor, including academia and those acting as co-sponsors.

Examples of topics for such early engagement with the European Medicines Regulatory Network (encompassing EMA, NCAs and CTCG)[5] are listed below:

- Clinical design and methodological considerations when designing CCTs involving adaptive and/or seamless aspects, Bayesian approaches (see Question 3 for details), choice of control, including comparison across sub-protocols or external control, master protocols (e.g., in relation to description of treatment effects of interest and multiplicity aspects), and multiplicity control framework.
- Establishment of joint clinical trials between sponsors of similar or linked clinical trials, including advice on how to establish agreements to act as a sponsor or as co-sponsor.
- Choice of submission approach to get the CCT authorisation (e.g., one CTA vs multiple CTAs, see also Q1.3) and interrelationship between any design elements and implementation options of the proposed CCT (including CCTs transitioning from the EU Clinical Trial Directive 2001/83/EC to the EU CTR framework).
- Where a CCT is intended as main evidence to inform regulatory decision making for a given product, scientific advice is highly recommended in particular when data from across sub-protocols/CTAs are intended to be used; a detailed scientific rationale and robust justification for all aspects of the design are expected at the planning stage including at the time of scientific advice.
- Qualification of biomarkers (as single or multiple of) (see Q5).
- Novel methodologies, e.g., methodological approaches for platform trials (options include letters of support, scientific advice and qualifications).

When seeking advice, sponsors are encouraged to also share key operational elements (e.g., enrolment predictions, time to completion and input received from other stakeholders such as patients representatives and investigators in particular where there may be concerns associated with the trial design and complex features to enable a fully informed discussion and advice.

[5] The proposed optimisation of the scientific advice framework is one of the 10 priority actions under ACT-EU to ensure a strengthening of the coordination between scientific advice on CT approval and CT design as well as in the context of public health emergencies.

Question 2: Which additional considerations are needed for the design and conduct of master protocol studies?

Q2.1: How do requirements for clinical trial application and marketing authorisation need to be considered?

The requirements for CTAs and MAAs for scientifically sound rationales, designs and analyses of complex clinical trials are essentially the same. These include the generally accepted principles of sound trial planning that are noted in guidance documents such as ICH E6, E8, E9, E10, E17 and comprises e.g., the definition of the primary and secondary endpoints, a justification of the sample size and its planning assumptions, and a predefined, clearly outlined and detailed statistical analysis (plan). Decision rules (e.g. for a platform trial) should be clearly pre-specified. When comparisons are planned, these should be pre-specified. In addition, it will be of importance to understand the contribution of the trials within a development programme, including distinction between exploratory and confirmatory aspects, although both may be present within a shared framework. Depending on the complexity of the development programme, clear understanding of the regulatory purposes is needed (supportive, confirmatory as a single or as one of several pivotal trials) and/or there are inter-relationships between different sub-protocols.

Similarly, to conventional clinical trials, in the context of complex trial, it remains the sponsor's responsibility to ensure that the generated data is sufficiently robust and of high-quality to support future MAA.

It is of utmost importance to maintain trial and data integrity. During the submission either for CTA or MAA, the applicant is requested to discuss potential impact of design elements on the trial and data integrity, to justify that these will not be impaired (CTA) or have not been impaired (MAA). Importantly, such potential impacts should be considered already at the planning and during clinical trials conduct, in order that integrity is eventually not impaired. In particular platform trials are rather projects with multiple stakeholders involved, and their role and access to data needs to be considered carefully. Please refer to the Question 7 for further considerations.

Some aspects might be specific for CTAs and MAAs:

<u>CTA</u>

For authorisation of a clinical trial in EU, at least one investigational medicinal product should be included as per the EU CTR, Article 2.2.

At the time of the CTA, a description of the statistical methods to be employed needs to be available for the level of the platform/shared scientific framework as well as for each of the sub-protocols, if relevant, and included in the trial protocol (EU CTR Annex I 17(u)). As the protocol shall describe for the whole clinical trial the objective, design, methodology, statistical considerations, purpose and organisation, the specific protocol components for a complex clinical trial (e.g., master protocol part and sub-protocols) are considered as its integral parts.

Depending on the clinical trial design, its elements and features, the protocol structure and the content of the master protocol (e.g., common/shared elements of the design, procedures, infrastructure, standardised data collection) and sub-protocols (e.g., specific eligibility criteria for an IMP/combination or target population) might differ. The Master protocol part should be submitted simultaneously with at least one sub-protocols at the time of the initial CTA. It is expected that the master protocol and sub-protocols are interlinked seamlessly and free from inconsistencies. The description of all the linked sub-protocols, shared elements between them and their status is also expected in the cover letter. This also includes an overview of the anticipated

end of any of the sub-protocols and the reasons for it. Therefore, a graphical visualization depicting all closed, current and future planned sub-protocols/arms (e.g. status overview) is encouraged in the cover letter.

MAA

The assessment will benefit from a description of the overall evidence generation plan (e.g., when exploratory trials are included in a MAA) to be submitted at the time of MAA. It is expected to display the development strategy and any inter-relationship between different sub-protocols also graphically. Furthermore, it is important to understand the overall context and potential differences between the planning assumptions and the observed results. This might include other sub-protocols, whenever relevant. Such information can be included in the appropriate CTD Module 2 such as Clinical Overview(s) (module 2.5) and / or Clinical Summary(ies) (Module 2.7), whereas master protocol part and sub-protocols are expected to be submitted simultaneously in the Module 5 along with the SAP(s).

Q2.2: What additional information needs to be provided and/or clarified at the time of CTA and MAA submission?

Depending on the complexity of the trial and its design, scientific/statistical and operational aspects, the following non-exhaustive list of issues should be considered as to whether they impact on trial and/or data integrity. As this information might facilitate approval, it should be available if further clarification is sought at the time of CTA and/or MAA submissions:

- Rules/criteria behind treatment allocations (see also Q1.5), in particular where this is across sub-protocols
- Sponsorship and confidentiality agreements and contractual responsibilities of different stakeholders (i.e. (co-)sponsors, investigators, CROs) in the platform trial, as a consequence also oversight needs to be clarified (see also Q1.4)
- Access to data and means to maintain data and trial integrity
- Documents that describe the role of different relevant governance and/or oversight committees (as regards the Data Safety Monitoring Committee and the requirement of the DSMC charter submission, see also Q6)
- Safety management and overview
- Process of giving informed consent (e.g. in a Complex Clinical Trial that includes a dedicated screening part and a treatment part)

Q2.3: Where to include the pre-specified statistical analysis for sub-protocols and/or the entire trial?

In general, it is anticipated that there is an overarching protocol (master protocol) at the platform level and that there are trial-specific protocols (sub-protocols).

When the sub-protocols are self-standing, they should normally include the pre-specified statistical analysis (plan) for the respective trial (including a potentially overarching strategy of the Master Protocol whenever relevant). Sub-protocols should follow the principles of statistical guidance documents (e.g., ICH E6, E9) like any other trial protocol. The place and potential inter-relationship (or absence thereof) of sub-protocols in the overarching platform context still needs to be considered and described in the Master Protocol. It should outline principles or common elements that are applicable for the whole platform trial (shared scientific framework). Therefore,

a CT protocol consists of a master protocol part and a sub-protocol part, which covers the specific protocol elements for the IMP or target population.

There may be situations where this differentiation is not sufficient or feasible. This is the case when there is an interplay between the trials of the platform (e.g., related to the type 1 error, meta-analytic approaches, an analysis in one sub-protocol depends on another, etc.). All sub-protocols that are affected by such a situation need to contain all relevant information on the interplay with other trials at all times. This will require cross-referencing and re-assessing the need to update documents as soon as modifications within other sub-protocols become relevant. Ideally, modifications follow a pre-defined decision strategy (e.g., based on a pre-defined alpha-allocation strategy).

When applicable, the overarching testing strategy (for example information if data is to be pooled or not) should be described in the master protocol, and this should also include (if applicable) the conceptual testing strategy for the analyses in the individual sub-protocols. An analysis that includes data from more than one sub-protocol is recommended to be included in the master protocol part. Information about analyses that concern only one sub-protocol should be included in the protocol/analysis plan for that sub-protocol.

Question 3: How to describe and explain Bayesian approaches in complex clinical trials?

Bayesian approaches include a number of methodologies that can be used in clinical trials. In trials exploring pharmacokinetics and pharmacodynamics, Bayesian approaches have often been used to analyse data and to generate results, including empirical Bayesian approaches where prior distributions are estimated from the newly collected data, such as for population pharmacokinetic analyses. Bayesian approaches have also been used in the context of dose ranging, dose escalation and selection of a dose for further trials. Results from Bayesian work have subsequently been assessed in regulatory submissions and enabled inference on pharmacokinetic and pharmacodynamic parameters as well as dose selection. Bayesian approaches may in some situations also be used for inference on efficacy and safety from clinical trials, including trials for regulatory submissions. However, there are few precedents with notable or successful uses of Bayesian approaches and thus critical points encountered are flagged in this answer. Furthermore, Bayesian methodologies have evolved in recent years, so that early engagement with regulators is highly recommended as discussed under Q1.6.

This situation has already been recognised in the ICH guideline E9 (1998): "Because the predominant approaches to the design and analysis of clinical trials have been based on frequentist statistical methods, the guidance largely refers to the use of frequentist methods (see Glossary) when discussing hypothesis testing and/or confidence intervals. This should not be taken to imply that other approaches are not appropriate: the use of Bayesian (see Glossary) and other approaches may be considered when the reasons for their use are clear and when the resulting conclusions are sufficiently robust" with E9's glossary detailing that Bayesian approaches are "Approaches to data analysis that provide a posterior probability distribution for some parameter (e.g., treatment effect), derived from the observed data and a prior probability distribution for the parameter. The posterior distribution is then used as the basis for statistical inference."

Bayesian analyses for decision-making

The use and choice of frequentist or Bayesian approaches should be secondary to the pursuit of principles for quality in clinical trials as per section 3.1 in the guideline ICH E8(R1). This includes

that an appropriate number of data points needs to be collected, with appropriate duration and high-resolution endpoints, and appropriate controls are chosen, commensurate with the trial's objectives and the state of scientific and medical knowledge of reasonable stakeholders at that time concerning the disease, the investigational and other medicines. An inappropriately small sample size may be insufficient for any statistical approach. Bayesian approaches may appear to suggest lower samples sizes when compared to conventional frequentist power calculations, but adapted frequentist sample size calculations (e.g., non-conventional alpha threshold or power) can equally be agreed with regulators on a case-by-case basis. In addition, Bayesian approaches do not replace the need for a self-standing scientific discussion of the need for internal controls in a trial.

In complex clinical trials, Bayesian approaches are often used for specific trial activities such as, interim and final analyses (including for futility and for extrapolation), adaptations, pooling of data (active, control or external), or even using external controls, where any such activity needs a self-standing motivation, but this is not covered here. Bayesian approaches may then inform, facilitate or enable these activities. General scientific guidance on Bayesian approaches in specific situations of medicine development will be available in forthcoming guidelines (ICH E20 on adaptive clinical trials, ICH E11A on paediatric extrapolation).

In early clinical development, one challenge is to determine what substances are active enough to justify further patient exposure and motivate further development. For rare indications this is even more difficult, and it may then be strategic to formalise the decision making so that it is often predefined how much influence data from the most recent trial should have on this decision, and how prior information is distributed, for which Bayesian analysis may be a suitable tool. Bayesian analysis may also be useful to make decisions in futility analyses, by combining new data with prior information. For example, in a trial with multiple medicines, or multiple doses, the prior information on efficacy may differ between arms, and the futility criteria may therefor also differ.

With frequentist approaches, adjustment for multiple null-hypothesis significance testing (type 1 error control) is a central consideration in regulatory submissions for efficacy analyses of the main trial(s). When using a Bayesian methodology, it is of importance that the methodology allows for an evaluation of corresponding issues, including via simulation. The statistical inference from a clinical trial, whether based on frequentist or Bayesian approaches, informs the interpretation and decision-making, and neither approach replaces or limits these.

For regulators and stakeholders, the statistical methodology needs to be reasonably transparent and its results interpretable, considering that the results will also need to be used by non-statistician stakeholders to assess or discuss clinical trials. This is one of the reasons why simpler analyses may be preferred over complex ones, and, for example, why external data may be more readily useful in a text discussion of a trial's context than when included in modelling. However, complex methodology may in some cases also enable more interpretable results.

Complex clinical trials include platform trials, which "need to be constructed to the benefit of multiple stakeholders—patients, pharmaceutical companies, site networks, disease scientists, and regulators. If the platform is not advantageous to one of these, the effort may be unsuccessful" (Berry 2020). Thus, early engagement during the design stage of the complex trial is recommended between stakeholders and with regulators, see under Q1.6.

Documentation

To facilitate the scientific discussion and use of the proposed trial, sponsors should engage with stakeholders and regulators (see Q1.6) on the proposed Bayesian approach(es) in advance of a CTA and marketing authorisation and provide the following information:

- Rationale, clear reasons (see ICH E9) and purposes of the Bayesian approach (e.g., futility algorithm, formalisation of clinical thinking and assumptions, opening or closing arms, subgroup investigations), plans for statistical inference (including how chosen metrics will facilitate statistical interpretation), information on alternatives considered, how critical-to-quality factors are implemented
- Summary and relevant details of the approach and Bayesian workflow, description of the model(s) including in mathematical notation and of priors, the clinical and medicine development programme context informing the choice(s) for the model and for the type(s) of prior(s), e.g. functional, mixed, power, commensurate priors, hyperparameters, plans if any for model averaging or stacking
- Prior predictive simulations and, using synthetic or simulated data, posterior probability and posterior predictive distributions, simulations of the trial's operating characteristics, under a wide range of scenarios for the data that will be generated. Simulations and (after the trial) sensitivity analyses exploring, for any of the parameters or distributions that are necessary to be pre-specified for the models to be fitted, how treatment effect estimates and primary conclusions of the trial are affected when analyses are carried out based on alternative assumptions.

The purpose of the above information is to facilitate the case-by-case discussion and subsequent assessment of a clinical trial authorisation application or application for marketing authorisation.

Question 4: What are the considerations for planning, collection and use of control data from within a complex clinical trial for regulatory purposes?

Of various possible trial designs, this answer only addresses the situation where data generated within a complex clinical trial (in a shared framework, see Q1) are proposed for formal comparisons to inform safety and efficacy evaluations and decision-making.

The general principles involved in choosing a control group for clinical trials intended to demonstrate the efficacy of a treatment and related trial design and conduct issues are addressed in ICH E10 "Choice of control group and related issues in clinical trials". ICH E10 describes internal controls as a "group consisting of patients from the same population assigned to a different treatment" and reads, "A concurrent control group is one chosen from the same population as the test group and treated in a defined way as part of the same trial that studies the test treatment, and over the same period of time. The test and control groups should be similar with regard to all baseline and on-treatment variables that could influence outcome, except for the study treatment. Failure to achieve this similarity can introduce a bias into the study". In contrast, "An externally controlled trial compares a group of subjects receiving the test treatment with a group of patients external to the study". Randomised controlled clinical trials with an internal concurrent control arm are considered the standard in trial design where appropriate and feasible.

Platform trials are typically more complex than quoted from ICH E10; for example, they may introduce new treatments or new patient populations, at different timepoints, may have different

treatments allocated at different sites, may be implemented as either separate clinical trials (for sub-protocols) or as a single trial for reasons pertinent at the time of trial authorisation (see Q1.3), may utilise a common comparator arm, or may have rules to allocate treatment by randomisation to different sub-protocols (which may be separate clinical trials, or which may include subsequent treatment allocations or nested randomisations). These complex situations and potential comparisons within a platform trial represent additional sources of additional bias (of estimated treatment effects) so that advice and early interactions with regulators (see Q1.6) should be sought to discuss the potential impact, including for trial objectives and for concerns over trial integrity.

In a complex clinical trial, opportunities for its conduct should be in balance with trade-offs in bias and variance for stakeholders, including for regulators and considering the trial's clinical objectives and setting. The interactions with regulators (see Q1.6) can address this balance and can cover questions such as addressing sources of bias, operational provisions and mitigations.

To evaluate the extent to which data generated within a complex clinical trial can serve as control data, several attributes outlined below need to be considered together. It should be emphasised that no comprehensive list of attributes is to be provided, but they will be important for sponsors to address and discuss in interactions with regulators and stakeholders.

When a complex trial is submitted in separate CTAs (see Q1.3), the use of shared controls remains a valid and feasible option from a CTA submission and scientific point of view, after due consideration of attributes. When a common comparator arm is used, data from such shared controls (conducted prior or concurrently) should be available to allow a continuous benefit/risk assessment for trial participants.

The reality of every clinical trial, and in particular of complex clinical trials, is that changes and differences occur during its often years-long conduct, and these add bias (to estimated treatment effects), even if they are unobserved, subtle, unintended, or mitigated through the recommended application of standardisation. The sources of bias include but are not limited to selection bias, indication bias and ascertainment bias; further examples of potentially relevant biases are listed and discussed in Burger et al. (2021). Example attributes with particular relevance to complex clinical trials are discussed in the following points.

- Concurrency: the extent to which control and test treatment data are concurrently collected. The period from start to end of recruitment on the test arm is sometimes also used to select control data. This may be recommended for platform trials with a shared control arm. However, the course (rates) of recruitment over time and the options for treatment allocation to any other test treatment arms also need to be considered.
- Treatment allocation: Its standard is by means of randomisation, but in a complex trial randomised allocation may also be within sub-protocols or to different sub-protocols, or it may involve sequential allocation steps. The allocation ratio may vary or be adapted (see Q1.1) during trial conduct. In some complex clinical trials, non-random allocation is proposed in addition or as alternative to the standard, which may add bias.
- Similarity of the disease under study: between arms, and consistency or differences / changes over time (e.g., evolving infectious agents)
- Study population: inclusion and exclusion criteria (e.g., differences between sub-protocols, changing over time or different between sites/ countries)

- Study sample: characteristics of recruited participants (e.g., differences between sub-protocols or over time with respect to age, comorbidities, severity of their disease, previous treatment including in the concerned trial, screening, timeliness of diagnosis)
- Standard of care: may evolve over time and with experience of investigators, e.g., with respect to timely initiation, intensity and intention, use of diagnostic and supportive interventions, application across all participants.
- Investigators and other trial personnel: gather experience and may change behaviour over time, including in screening strategy and consent discussions, and may be exchanged in given sites
- Blinding: Its strength and completeness may overall vary (e.g., with different sub-protocols) and it at risk to decrease over time, given evolving experience and accumulation of information.
- Sites and countries: Changes in daily practicalities of trial conduct may occur within or between sites, as well as by adding or discontinuing sites
- Protocol: Modifications of the master protocol and / or sub-protocol(s) are often required to implement specific changes yet can lead to changes also in various other aspects of trial conduct.

This Q&A addresses neither scientific questions, nor the regulatory acceptance of no controls, nor if data collected outside the complex clinical trial can be used as control data. Considerations for the use of external control data are described elsewhere (in particular ICH E10) and below.

- It should be noted that including groups serving as external controls from outside a defined trial environment, e.g., from a non-interventional clinical study or from standard of care (SOC) registries, may not be deemed appropriate to generate the expected robust data on efficacy and safety required for benefit-risk evaluation of an investigational medicinal product even when quantification and mitigation methods mentioned above are employed. Absence of an internal concurrent control may hamper the continuous assessment of the benefit-risk for trial participants during the trial. These considerations are equally relevant in the context of complex clinical trials and need to be addressed when designing the trial. In addition, the use of an external control instead of an internal control in a complex clinical trial, if not scientifically appropriately documented as part of the CTA (e.g., in the scientific rationale) may prevent trial authorisation.
- Bias may increase, and be more difficult to detect (compared to situations above), when using control data collected outside the complex clinical trial. Additional quantification and mitigation methodologies need to be developed and applied, such as outlined by Burger et al. (2021), who emphasise the importance of eliminating bias to the extent possible, and addressing and discussing transparently all sources of bias to inform the interpretation of results. The usefulness of external controls may be much less than anticipated when sources of variability are appropriately recognised (Collignon et al. 2020). The guideline on registry-based studies (EMA/426390/2021) provides a structured framework for discussing these methodological issues. Reference is also made to the EMA guideline on clinical trials in small populations (CHMP/EWP/83561/2005).
- Potential strategies to develop, test and validate novel methodologies to gain regulatory acceptance are outlined by HG Eichler et al. (2019). Exercises are required in methodology development, by generating data that are separate from data generated for development of a

medicine, and it is strongly recommended to discuss this in the platform for qualification of novel methodologies (see Q1.6).

- External data that are used to support interpretation of trial results and/or marketing authorisation applications should be collected and maintained in a manner which would ensure data integrity and fulfilling principles of being attributable, legible, original, accurate, complete and consistent (ALCOA++). These requirements to assure data integrity should be maintained throughout the data life cycle (see also Q7.3).

Question 5: Which principles apply, and which regulatory pathways should be considered when using biomarkers and biomarker assays in complex clinical trials and consequently applying for marketing authorisations?

Q5.1 What are specific aspects of relevance for the use of biomarkers and biomarker assays in complex clinical trials?

Biomarker assays/IVDs, including multiplex biomarker assays, are frequently used in different contexts to measure biomarkers in CCTs, thus introducing an additional level of complexity. The development status of each biomarker assay should be considered at the planning stage to ensure compliance with the IVD Regulation (Regulation (EU) 2017/746, IVDR), also taking into account potential need for additional biomarker assays if there is plan for adding new IMPs to an ongoing CCT.

An assay is considered an IVD if the manufacturer assigns an intended purpose that fulfils the definition of an IVD according to IVDR Article 2. Notably, where the biomarker assay has a medical purpose of providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations in the context of the clinical trial such assay fulfils the definition of an IVD. Consequently, the evaluation of the biomarker assay within this clinical trial is considered a clinical performance study of an IVD, according to the IVDR. Sponsors of clinical trials should be aware the additional considerations apply when biomarker assays are neither in-house IVDs, nor CE marked, or CE marked as IVD/CDx for another intended purpose. However, when the IVDs/CDxs are CE marked for their intended purpose, no additional regulatory review of the assay is foreseen by concerned authorities.

For the information to be provided in the cover letter of the clinical trial application and for further guidance (e.g. responsibilities of a clinical trial sponsor) please refer to the "Q&A on the interface between Regulation (EU) 536/2014 on clinical trials for medicinal products for human use (CTR) and Regulation (EU) 2017/746 on *in vitro* diagnostic medical devices (IVDR)" (2022).

In the trial documentation, sufficient information needs to be provided to assess the appropriateness of the biomarker assay(s) in the context of the trial and for evaluation of the robustness of data to be generated. Where applicable, the version, class type and regulatory status of the medical device /IVD should be indicated. The parameters should be included in the IFU for CE marked devices.

In addition, where multiple biomarkers are used in complex clinical trials, the consequences of their interplay on the selected patient population(s) needs to be elaborated in the protocol.

Depending on the trial design, biomarker assays and related analyses (as function of their purpose and associated claims) may be described either in the common (master protocol) part or in the sub-protocols, per IMP(s) or target patient populations.

Protocols of complex clinical trials with interventions that target multiple biomarkers should contain a pre-specified plan for allocation of trial participants potentially eligible for more than one sub-protocol. Likewise, pre-specification for sub-protocol assignment is essential when allocating trial participants with more than one biomarker of interest or based on various combinations of biomarkers. Different allocation schemes might be used (e.g. pragmatic or random allocation), that need to be justified. Also, the consequences for the estimation of the treatment effects need to be addressed. In case of overlapping target populations (e.g. participants determined as biomarker-positive for two or more biomarkers), the impact on multiplicity should be considered and clearly addressed in the protocol and related documents (e.g. SAP).

When a performance study is conducted with IVDs, a performance study plan should describe the rationale, objectives, design methodology, monitoring, statistical considerations, organisation and conduct of the performance study. In the context of master protocols, the statistical analyses to support regulatory claims for a future CDx might also be specified in the respective parts of the protocol/sub-protocols in case of medicinal product/CDx co-development. It should be considered, for example, whether the effect of the medicinal product in patients selected by CDx is clinically and statistically significant or, for predictive tests, to test whether there is a differential treatment effect between marker-positive and -negative patients defined by the CDx.

As regards performance studies undertaken to establish or confirm the analytical or clinical performance of a device, please also refer to "General principles of clinical evidence for In Vitro Diagnostic Medical Devices (IVDs)".

Sponsors of clinical trials investigating medicinal products and, in parallel, IVDs are encouraged to consult national guidance documents and contact the respective National Competent Authorities for performance studies prior to clinical trial submission. A timely consultation is also encouraged when a particular biomarker assay is used for different purposes/intended uses and/or has different regulatory status in sub-protocols (e.g. CE marked when used for one intended purpose in one sub-protocol, while not being CE-marked for intended purpose in another sub-protocol).

In clinical trials, where the assay is not a device for self-testing or a device for near-patient testing, the applicant is recommended to perform the assay (e.g. immunohistochemistry assay) at a central laboratory to generate consistent and robust data. The laboratory should be adequately accredited and the IVDs used in EU laboratories have to comply with the IVDR.

Of note, procedures for sample procurement, transport and storage need to be proven to be suitable for the intended purpose in the clinical trial and tailored for local or centralised testing.

Of importance are the questions of the study site for the performance study and documentation of competences of facilities performing assays (e.g. in the clinical trial protocol). For this and other aspects, please refer to the "Q&A on the interface between Regulation (EU) 536/2014 on clinical trials for medicinal products for human use (CTR) and Regulation (EU) 2017/746 on *in vitro* diagnostic medical devices (IVDR)" (2022) and the "General principles of clinical evidence for In Vitro Diagnostic Medical Devices (IVDs)" (2022). For the potential later certification, the manufacturer of the IVD can choose the Notified Body (see https://ec.europa.eu/growth/tools-databases/nando/).

In addition, when an IVD is proposed as a CDx, the IVDR brings tightened requirements for clinical evidence and conformity assessment, including a consultation procedure between the selected Notified body and the relevant medicines regulatory authority (EMA/NCA) depending on the route of procedure for the medicinal product (see Q5.6).

Q5.2: How to integrate pre-screening and screening processes for biomarkers within the shared framework of CCTs?

CCTs have a potential to improve screening efficiency and increase screen success rate by using a common pre-screening process.

In all cases, specific considerations for pre-screening and screening processes in the context of complex clinical trials will depend on scientific rationale, objectives, timing/intention of exposure to particular IMPs and/or approved medicinal products within their respective indications and the regulatory status of the assays used.

A larger pre-screening process may occur for potential participation in complex clinical trials, for instance based on large-scale profiling for genomic biomarkers. Pre-screening generally means pre-selection of potential trial participants based on historical data collected independently of the clinical trial and already available to the investigator in the medical record. The results are not shared with the sponsor. Therefore pre-screening can be done before informed consent is obtained.

However when potential participants are actively evaluated for enrolment in clinical trials, such process is considered as screening. After participants' recruitment, assessment for eligibility according to specific criteria usually occurs during the enrolment period. The examinations during the screening are trial-specific measures, the results of which are shared with the sponsor. Therefore, these examinations require the consent of the trial participants. Stepwise screening may also occur in conventional clinical trials.

There might also be situations when potential participants with a particular disease (condition) are pre-screened not necessarily for a specific trial, but more generally for clinical trials that may open at a future timepoint. In the context of complex clinical trial designs, such investigations may have already been conducted according to specific requirements (e.g. ethical, data processing, consent) and data shared in the pre-screening phase before actual consent is obtained for a specific trial arm. Therefore, this would be considered a stepwise screening.

Generally, screening processes and relevant procedures are an integral part of clinical trials and are described in clinical trial protocols. By extension, the description of a screening process, also in a form of a screening platform in some cases, is expected to be provided within a clinical trial protocol at the time of CTA submission. This will allow an integrated assessment of a clinical trial and its procedures by all concerned MSs, at initial submission and for any further modifications. As per the CTFG Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials (2019), a shared screening process is usually described in the common (master protocol) part.

When a pre-screening process is performed for purposes of future enrolment in clinical trials, such a pre-screening process should also be described as a part of the clinical trial protocol.

Note: It is difficult to envisage a stand-alone pre-screening process as independent from a clinical trial when leading to a decision to allocate relevant IMP(s). Such decision is partially taken on the basis of the pre-screening results.

The regulatory status of the assays used within both scenarios needs to be taken into consideration from the perspective of applicability of a clinical performance evaluation.

Please refer to the EU CTR, the "Q&A on the interface between Regulation (EU) 536/2014 on clinical trials for medicinal products for human use (CTR) and Regulation (EU) 2017/746 on *in vitro* diagnostic medical devices (IVDR)" (2022) and the "General principles of clinical evidence for *In Vitro* Diagnostic Medical Devices (IVDs)" (2022).

Q5.3 What are the requirements with regard to the biomarker assays when results of complex clinical trials are submitted to support MAAs?

Beyond the need for a consultation procedure referred to in Question 5.2, in view of a future Marketing Authorisation Application (MAA) particularly if a companion diagnostic (CDx) is proposed, a discussion of the scientific rationale for biomarker selection (e.g. in the setting of a biomarker driven therapeutic indication) and methodology used for diagnosis is required. It is therefore strongly recommended to co-develop the assay for use in the pivotal phase of development. In this case the analytical and clinical performance/validation data, resulting from the pivotal clinical trial, should be made available for MAA assessment by EMA/NCAs, and for CE-Mark Application assessment by Notified Bodies in liaison with EMA/NCAs. In addition, information related to the different assays used during development and their concordance, as well as their analytical and clinical validity, and relevant cut-off values for patient selection may be expected.

When developing a medicinal product associated with an IVD, the following guidance (or any other relevant guidance) should be consulted together with the guidance referred to in Question 5.1 with regard to the biomarker assay:

- https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-methodological-issues-associated-pharmacogenomic-biomarkers-relation-clinical_en.pdf
- https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-co-development-pharmacogenomic-biomarkers-assays-context-drug-development_en.pdf

The guideline on the evaluation of anticancer medicinal products (EMA/CHMP/205/95 Rev.6, draft) addresses the recent designs in oncology (such as umbrella and basket trials, so-called master protocols) and the emergence of indications defined in the first place by a biomarker selective for a disease sensitive to the treatment.

As regards assessment of biomarker assays during MAA, please refer to guidance in Day 80 sections 3.6 (clinical efficacy) and 4.6 (clinical safety) and Day 120 assessment report templates (section 3.3.4.5 and 3.3.7.5, respectively) (available at https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/assessment-templates-guidance).

As regards such consultation procedure on the suitability of the device in relation to the medicinal product(s), please refer to the "Guidance on the procedural aspects for the consultation to the EMA by a notified body on companion diagnostics" together with other related documents (Q&A on practical arrangements, application form and Assessment Report template, available at https://www.ema.europa.eu/en/human-regulatory/overview/medical-devices).

Question 6: Safety, rights and well-being of participants

Q6.1: How to ensure adequate risk-based quality management, sponsor oversight and investigator supervision in support of subjects safety /positive risk benefit?

Quality should be built into the operational design and conduct of CCTs and is highly dependent on adequate oversight by investigators/sponsors and compliance with the protocol and principles of good clinical practice (GCP) according to ICH E6(R2). Risks for participants' safety should be identified and appropriate risk mitigation strategy should be proposed for the entire trial and for each of the sub-protocols, including risks related to the active substances and those related to the design and clinical operations. A risk-based quality management system should include steps for risk identification, evaluation, control, review, communication and reporting.

Operational feasibility at multiple trial sites should always be a major focus in the choice of CCT design, trial site(s) and investigator(s), including communication plan. Implementation of risk proportionate approaches and risk-focused oversight and monitoring are encouraged for the entire trial and sub-protocols. Increased sponsor oversight will not be sufficient to justify a CCT design if clinical feasibility at the investigator site is compromised. To optimise clinical operational feasibility, sponsors are recommended to select sites with relevant experience, provide additional site training, regularly obtain relevant information from the investigator sites concerning clinical trial conduct and ensure that investigators understand dynamically changing operational needs and are up to date with relevant changes to the protocol (opening/closing arms), potential safety issues and current risk mitigation strategies.

Risk assessment to propose mitigation strategies should normally include risks to participants' rights, such as those related to consent and protection of data, data access, rectification or withdrawal due to unfavoured circumstances or risks influencing their dignity or well-being.

Risk mitigation strategies could also include a continuity plan for the entire CCT covering i.a. crisis situation and unexpected impactful events with the aim to ensure fast and resilient response for identified threats.

Please refer to the CTFG Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials (2019) and Risk-proportionate approaches in clinical trials (2017) that should be read in conjunction with ICH E8(R1) and ICH E6(R2) currently under revision.

Q6.2: How to organise safety monitoring and reporting (including urgent safety measures, unexpected event changing benefit risk, serious breaches, corrective measures), in complex clinical trials with multiple responsible parties involved?

Safety reporting requirements are applicable to the entire protocol as well as to sub-protocols and sponsors need to set up specific procedures respectively. Risk mitigation plan should address measures for the sub-protocols and the entire trial across all sub-protocols irrespective if these are conducted with one or multiple EUCT numbers and also one or multiple sponsors.

Regular safety overview with recording, analysis (including updated benefit risk) and reporting of adverse events and adverse reactions and sufficient capability to make quick decisions and communication to avoid or at least minimize exposure of participants to an identified (potential) safety concern is required and the responsibilities remain unchanged for the sponsor and investigator.

To ensure fast and reliable access to safety data along entire trial and between sub-protocol/arm an implementation of adequate logistical infrastructure (e.g. validated IT tools) should be considered.

When undertaking a complex clinical trial, the Sponsor(s) should ensure that changes undertaken for urgent safety reasons are implemented without delay per Article 54 of the EU CTR and that appropriate structures are in place on the sponsor side. Such changes should be clearly communicated to investigators and via CTIS to all (concerned) Member States in which the trials are approved regardless of the approach selected for submission (See Q1.3). This includes clear documentation of what aspects of a (sub)protocol are being changed and whether this affects the master protocol and other (sub)protocols in a CCT setting.

Irrespective of the immediate implementation, in case the changes applied by an urgent safety measure impact the protocol or other CT document, the sponsor should request a substantial modification providing an updated version of the document with a new version date/number

together with the list of changes with respect to the authorised version in line with Annex II, Section D of the EU CTR.

In case an event in a sub-protocol may lead to changes in benefit risk, this need to be reported for the clinical trial, including appropriate risk management for the sub-protocol/s (and if applicable the entire clinical trial), as well as communication to investigators, co-sponsors and information to the trial participants should be adequately provided (also see Q7.2 communication plan immediate and rapid communication), as it is to be handled for any clinical trial.

Be aware that a corrective measure like suspension and revocation can only be done to the entire trial, not selectively to sub-protocols (EU CTR Article 77). While a request to modify the protocol could be sub-protocol(s)-specific. With regard to regular safety reporting (ASR, SUSAR):

In case of a CCT with several IMPs, the sponsor may choose to submit a single annual safety report (ASR) for the trial instead of several ASRs for the different active substances (EU CTR Article 43.2). In this case, several safety-assessing Member States (saMSs) will be assigned to the different IMPs for SUSAR assessments, and the reporting MS will carry out and/or coordinate the assessment of the ASR (reference to IR). Therefore, multiple saMSs may directly contact sponsors with RFIs related to the safety of the concerned IMPs.

In case an active substance used as IMP is only used in one or more sub-protocols in a CCT, which are all closed and therefore no clinical trial is ongoing in EU/EEA with this active substance, this has to be reported in the next ASR for this active substance in its own ASR or the one of the clinical trials.

Q6.3: Do I need to establish a data (safety) monitoring committee in all situations?

Generally, yes for a complex clinical trial. In order to ensure the safety for the participants it is strongly advised to establish an independent data monitoring committee when conducting a long lasting as well as complex clinical trial (see EMA guidance on first-in-human or early clinical trials and Q7.2). The expertise within such committee is to be adapted and potentially enlarged to allow adequate follow-up of safety profile for multiple IMPs and/or disease/conditions and associated extent of safety reporting. In addition to safety-related monitoring, interim analyses and possible modifications of the trial design based on unblinded interim data are grounds for setting up an independent data monitoring committee in CCT setting.

When the Data Safety Monitoring Committee is established, its charter (or its draft) should be provided (EU CTR Annex I).

Please refer to the EMA guideline on Data Monitoring Committees (2006), Questions and Answers on Data Monitoring Committees (2020) and CTFG Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials (2019) for additional guidance.

Question 7: Transparency (balance with integrity) and communication between regulators, sponsors and investigators

Q7.1: What is expected as "end of trial" for a complex clinical trial?

The clinical trial protocol defines and justifies the end of trial; either last participant last visit or an appropriate later time point. The same considerations apply to a complex clinical trial: in the case of a master protocol and several sub-protocols, there should be an end of sub-protocol date for

every sub-protocol, to comply with the transparency rules required in the EU CTR. This date should be defined as the last participant last visit in the sub-protocol or, if justified, should be defined otherwise in the sub-protocol.

In addition, the EU CTR definition of early termination of a clinical trial applies to any sub-protocol. Irrespective of the description of criteria for an early termination of the clinical trial in the master protocol or sub-protocol, should this circumstance occur, the sponsor will need to notify an early termination of the sub-protocol and the reasons for it, see Question 10.10 in the CTR Q&A document.

The definition of end-of sub-protocol should be indicated in every sub-protocol. However, when there is a common definition to all sub-protocols, e.g., last visit last subject, it could be indicated in the master protocol.

The end of trial date and the end of every sub-protocol date need to be submitted to CTIS for all of the following: per member state, at the level of the EU and at a global level. The end of sub-protocol will trigger the need for a summary of sub-protocol results unless it interferes with the trial integrity. The same requirements would apply in case of any premature end of a sub-protocol, see Q7.4 for more details.

Q7.2: How and what to communicate around and during the trial submission and conduct between authorities and sponsor, sponsors and investigators as well as investigators and participants?

In order to give full attention to the integrity of the trial as discussed in Q7.4, the protocol (master protocol in case of sub-protocol implemented as separate CTs) should include a communication plan to all relevant stakeholders (e.g. investigators, CROs, regulatory authorities, ethics committees, trial participants and sponsors when there are more than one) for the following:

- Opening and closing of sub-protocols or treatment arms to ensure a rapid communication
- Immediate communication of safety signals (and risk mitigation measures). Special considerations are to be taken into account in early clinical trials and first-in-human trials. Guidelines are to be found at the EMA website: Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (europa.eu)
- Trial results of sub-protocols, including interim analyses and results from early termination

The role of data monitoring committees and their communication with sponsors are addressed in the EMA Guideline on data monitoring committees (2006) and the Questions and answers on Data Monitoring Committee issues (2020).

When more than one sponsor is involved in the trial, a written contract should be set out to establish which responsibility as per EU CTR Article 72.2 is attributed to which sponsor, see the CTR Q&A document.

Confidentiality agreements between sponsors and/or with third parties may be needed in order to have access to personal data or commercially confidential information, see Q1.4 for more details.

If there are a master protocol and sub-protocols, the general approach for communication should be outlined in the master protocol, and if applicable, details can be included in the sub-protocols. Changes to the communication plan may trigger a substantial modification.

Q7.3: How should I organise the documents to facilitate understanding and communication?

It is necessary that all documents are identified with:

- A common identifier (e.g. an acronym) in the title to be used for the master protocol and all sub-protocols
- A specific identifier (e.g. a number) for each sub-protocol

These identifiers should also be used in the names of the documents. When submitting substantial modifications, reference should be made to relevant sub-protocol identifier(s).

In addition, any reference to a complex CT in the Investigator's Brochure, in a medical journal paper, or in a public registry should include the corresponding EUCT number(s).

It is necessary to include a status overview in the cover letter of a substantial modification application (or initial application for a sub-protocol) and as applicable in other clinical trial applications (linked with this CCT), holding information on sub-protocols concerning recruitment (open or not), number of participants included and status (ongoing or terminated) per country, together with an overview of the anticipated start and end of the separate (sub)protocols as mentioned in Q1.1. To that end, a graphical visualisation depicting all closed, current and future planned sub-protocols is encouraged. Such a description and visualisation should also be included in the submission for application for marketing authorisation or extension of indication (e.g., module 2.5).

In case the master protocol and sub-protocol(s) are provided as one document, a tabular overview which sections should be considered from the master protocol and which sections from the sub-protocol should be considered, where the latter refines or complements but cannot replace or contradict information in the corresponding master protocol section.

The protocol summary should give a clear view of the overall CCT, including diagrams as applicable.

In case sponsors decide to refer to an IMPD from a different trial, this needs to be described clearly in the cover letter. A letter of agreement from the sponsor of the cross-referenced trial needs to be obtained, see Question 3.8 in the CTR Q&A document.

If external data are planned to be used in the analysis, detailed documentation of the approach such as in consideration of the guideline on registry-based studies and of ICH E10 should be included in the concerned sub-protocol.

Q7.4: How to ensure balance between transparency and trial integrity when closing of sub-protocols and communicating the summary of sub-protocol results?

When the EU CTR applies, transparency requirements should be adhered to including justified exceptions e.g. to protect personal data or proprietary information (Article 81.4). Irrespective of the submission strategy for requiring the authorisation, the same transparency rules apply to sub-protocols, especially with respect to sub-protocol start or first subject included, temporary halts, premature ends and reasons for them as well as for the provision of trial results, including the submission of lay summary and, "where the clinical trial was intended to be used for obtaining a marketing authorisation for the investigational medicinal product" (Article 37), also the clinical study report. In this respect, articles 36, 37 and 38 of the EU CTR should be taken into account: "However, where, for scientific reasons detailed in the protocol, it is not possible to submit a summary of the results within one year, the summary of results shall be submitted as soon as it is

available. In this case, the protocol shall specify when the results are going to be submitted, together with a justification." In addition to transparency measures for clinical trials and its relevant components, the EU CTR requests that robustness and reliability of the data generated in the clinical trial is ensured in the recital 51 of the preamble.

These principles of robustness and reliability of the data, which equate to the concept of trial integrity should also be applicable to the data generated at intermediate and final stages for each sub-protocol.

In practice, the balance between transparency and trial integrity should be assessed both at a planning stage (see Q7.2) and at the time when the need for publishing data arises after the trial has been initiated. This assessment should be done by the sponsor and a proposal, as well as the rationale for it, should be in the publication policy of the protocol, either master or sub-protocol.

This section should include the following:

- The sponsor commitment to notify the actual relevant dates of the clinical trial and sub-protocol according to EU CTR transparency requirements (i.e. start or first subject included, temporary halts and end or early end dates per clinical trial and in cases where a complex CT includes several sub-protocols per sub-protocol within 15 days of their occurrence in relation to every member state concerned and globally (when it ended in all participating countries)
- The sponsor commitment to submit a summary report of the results per sub-protocol/CT as applicable within the year following to the end of sub-protocol date and any scientific reason to postpone such date, when applicable
- Any justification to defer the publication of a sub-protocol results in order to preserve the integrity of this or other ongoing sub-protocols or parts of the CT e.g. due to a potential inter-relationship between sub-protocols, or potentially negative impact on them with respect to enrolment, treatment adherence or blinding. It should include the expected timing of publication.

When a complex CT includes several phases in the design, transparency criteria for the highest phase will be applied.

Any restrictive change in the publication policy will require a prior authorisation as a substantial modification.

References

EU CTR, Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC Text with EEA relevance (2014) https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32014R0536

CTR Q&A document, Clinical Trials Regulation (EU) No 536/2014 Questions & Answers (2022) https://ec.europa.eu/health/medicinal-products/eudralex/eudralex-volume-10_en#set-of-documents-applicable-to-clinical-trials-authorised-under-regulation-eu-no-5362014, Chapter V

Expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use (2017) Risk proportionate approaches in clinical trials https://ec.europa.eu/health/medicinal-products/eudralex/eudralex-volume-10_en

CTFG (2019) Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials, https://www.hma.eu/ctfg.html#c4141

Medical Device Coordination Group (MDCG) (2022) General principles of clinical evidence for *In Vitro* Diagnostic medical devices (IVDs) MDCG 2022-02 https://ec.europa.eu/health/medical-devices-sector/new-regulations/guidance-mdcg-endorsed-documents-and-other-guidance_en#sec10

Medical Device Coordination Group (MDCG) and Clinical Trial Expert Group (CTEG) (2022) Q&A on the interface between Regulation (EU) 536/2014 on clinical trials for medicinal products for human use (CTR) and Regulation (EU) 2017/746 on *in vitro* diagnostic medical devices (IVDR) MDCG 2022-10 https://ec.europa.eu/health/medicinal-products/eudralex/eudralex-volume-10_en#set-of-documents-applicable-to-clinical-trials-authorised-under-regulation-eu-no-5362014

ICH (2017) Guideline E6(R2) Good clinical practice https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice

ICH (2021) Guideline E6 on good clinical practice: Draft ICH E6 principles https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-e6-good-clinical-practice-draft-ich-e6-principles_en.pdf

ICH (2021) Guideline E8(R1) on general considerations for clinical studies https://www.ema.europa.eu/en/ich-e8-general-considerations-clinical-studies

ICH (1998) Guideline E9 on statistical principles for clinical trials https://www.ema.europa.eu/en/ich-e9-statistical-principles-clinical-trials

ICH (2000) Guideline E10 on choice of control groups and related issues in clinical trials https://www.ema.europa.eu/en/ich-e10-choice-control-group-clinical-trials

ICH (2019) Final concept paper E20 on adaptive clinical trials https://www.ich.org/page/efficacy-guidelines

EMA (2006) Guideline on Data Monitoring Committees (EMEA/CHMP/EWP/5872/03 Corr) https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-data-monitoring-committees_en.pdf

EMA (2007) Reflection paper on Methodological issues in confirmatory clinical trials planned with an adaptive design (CHMP/EWP/2459/02) https://www.ema.europa.eu/en/methodological-issues-confirmatory-clinical-trials-planned-adaptive-design

EMA (2015) Guideline on adjustment for baseline covariates in clinical trials (EMA/CHMP/295050/2013) https://www.ema.europa.eu/en/adjustment-baseline-covariates-clinical-trials

EMA (2017) Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07 Rev. 1) https://www.ema.europa.eu/en/strategies-identify-mitigate-risks-first-human-early-clinical-trials-investigational-medicinal

EMA (2020) Question and answers on Data Monitoring Committee issues (EMA/CHMP/470185/2020) https://www.ema.europa.eu/en/data-monitoring-committees-issues

EMA (2021) Guideline on registry-based studies https://www.ema.europa.eu/en/guideline-registry-based-studies-0

EMA (2022) Guideline on the evaluation of anticancer medicinal products (EMA/CHMP/205/95 Rev. 6, draft) https://www.ema.europa.eu/en/evaluation-anticancer-medicinal-products-man)

Berry SM (2020) Potential Statistical Issues Between Designers and Regulators in Confirmatory Basket, Umbrella, and Platform Trials. Clinical Pharmacology & Therapeutics, 108: 444-446. https://doi.org/10.1002/cpt.1908

Burger HU, Gerlinger C, Harbron C, Koch C, Posch M, Rochon J, Schiel A (2021) The use of external controls: To what extent can it currently be recommended? Pharmaceutical Statistics, 20: 1002-1016 https://doi.org/10.1002/pst.2120

Collignon O, Schritz A, Senn SJ, Spezia R (2020) Clustered allocation as a way of understanding historical controls: Components of variation and regulatory considerations. Statistical Methods in Medical Research, 29: 1960-1971 https://doi.org/10.1177/0962280219880213

Eichler HG, König F, Arlett P, Enzmann H, Humphreys A, Pétavy F, Schwarzer-Daum B, Sepodes B, Vamvakas S, Rasi G (2019) Are novel, non-randomised analytic methods fit for decision-making? The need for prospective, controlled and transparent validation. Clinical Pharmacology & Therapeutics, 107: 773-779 https://doi.org/10.1002/cpt.1638