Clinical Trials Facilitation and Coordination Group CTFG

Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials

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Clinical Trials Facilitation and Coordination Group (CTFG) is a working group of the Heads of Medicines Agencies on clinical trials. This document is published on the CTFG webpage: http://www.hma.eu/ctfg.html.

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1. INTRODUCTION AND SCOPE

This document provides recommendations for sponsors regarding the authorisation and conduct of complex clinical trials. The document describes the current perspective of the Clinical Trials Facilitation and Co-Ordination Group (CTFG) on these trials and outlines the major issues that sponsors should address in the process of initiating and conducting complex clinical trials in the EU/EEA.

The document highlights differences between complex clinical trials and conventional clinical trials particularly with regard to clinical trial applications (CTAs) and requests for substantial amendments. These recommendations should be read in conjunction with current legislation regulating clinical trials.

Marketing authorisation applications are outside the scope of this guidance.

2. COMPLEX CLINICAL TRIALS - DEFINITIONS AND CONCEPTS

2.1. Descriptions and concepts of complex clinical trials

For the purpose of this guidance, a clinical trial is considered to have a complex clinical trial design if it has separate parts that could constitute individual clinical trials and/or is characterised by extensive prospective adaptations such as planned additions of new Investigational Medicinal Products (IMPs) or new target populations. In this document, the separate parts of a complex clinical trial design will be designated 'sub-protocols' and may be described by sponsors in separate protocols or within a common protocol as study cohorts or arms depending on the context.

Sub-protocols are characterised by sub-protocol-specific statistical analyses and are thus considered independent parts of the clinical trial design. In comparison, a study 'arm' will be used to describe study cohorts where statistical analyses depend on other cohorts such as comparison to a common control arm. Each sub-protocol may be composed of one or several arms.

Complex clinical trial designs may have a common operational framework that increases efficiency by optimising the use of operational resources and allocation of trial subjects to the most suitable sub-protocol or arm. The core of such complex clinical trial designs is often a common screening platform ensuring operational efficiency and facilitating patient recruitment. The screening platform and common operational framework may be described in a master protocol or be an integrated part of the clinical trial protocol.

The most common characteristic features of complex trial designs are thus sub-protocols, extensive adaptations and master protocols. Master protocols and extensive adaptations are described in more detail in sections 2.2 and 2.3 respectively. Section 2.4 provides examples of the most commonly used strategies in complex trial designs and describes how complex clinical trials with sub-protocol designs can be submitted as either individual clinical trials or as part of a single complex clinical trial (see section 5 for further regulatory guidance concerning submission).

2.2. Master protocols

A typical master protocol describes the overall clinical trial design including components and operational aspects applicable to all related sub-protocols such as the clinical trial rational, objectives, endpoints, benefit-risk assessment, shared procedures regarding safety monitoring and reporting, and a common screening platform dictating trial subject eligibility and/or treatment allocation. The master protocol should clearly describe how trial subjects are allocated to the individual sub-protocols or arms and should describe decision criteria for opening and closing of sub-protocols/arms as well as for re-allocating trial subjects from one sub-protocol to another, if applicable. Master protocols are often applied to particular study designs such as basket, umbrella, or platform designs (see examples in section 2.4).

2.3. Extensive adaptive features

Complex clinical trial designs often include prospective adaptations, that is, adaptations that are pre-specified in the protocol and are not made on an ad-hoc basis once the trial has started . Interim analyses are generally used to assess if adaptations are needed during the conduct of the trial based on safety and/or efficacy criteria.

Examples of adaptive features that are considered extensive and often characterise complex designs include:

- Addition of new IMPs and/or populations. This often results in addition of new sub-protocols or arms during the course of the trial. The initial CTA should include a rationale for planned additions and describe and list future trial populations, IMPs and combinations thereof.
- Closure of sub-protocols based on futility or safety analyses, which results in sub-protocol-specific results becoming available during the course of the trial. Criteria for closing sub-protocols should be clearly defined in the protocol.

2.4. Examples of complex clinical trial designs and description of submission models

Common examples of complex clinical trial designs are basket, umbrella, and platform trials. These designs are more commonly used in oncology, but they may be applied in other therapeutic areas if there is a good rationale and the design is appropriately justified. Basket trials generally investigate the safety/efficacy/effect of an IMP or combination of IMPs across a variety of populations. Umbrella trials investigate the safety/efficacy/effects of several IMPs in a single population. Whereas platform trials may test several IMPs in one or multiple populations in a highly dynamic design.

The typical structure of complex trial designs is the presence of either several sub-protocols (Figure 1) or arms sharing a common control arm (Figure 2).

Complex clinical trials with sub-protocols can be submitted either as one single complex clinical trial or as separate clinical trials shown in Figure 1:

- One single complex clinical trial (Figure 1a)
- Separate clinical trials: they can be linked together by the title of the trials (Figure 1b)

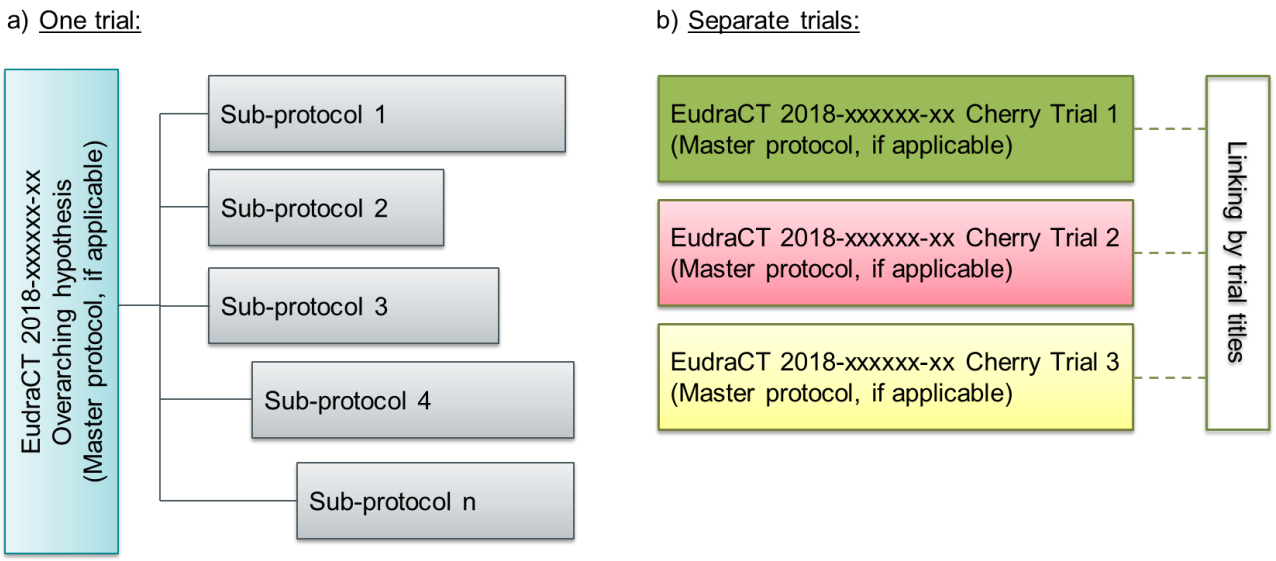

Figure 1: Example of complex clinical trial designs with separate parts. The separate parts can be submitted as one clinical trial with sub-protocols (a) or as separate clinical trials (b). If the clinical trials have a master protocol and are submitted as separate clinical trials (b), the master protocol should be submitted with each clinical trial application.

A master protocol can be used in any type of complex trial design. If it is used in separate trials the cover letters and protocols of each trial can refer to the common shared master protocol, which will be submitted with each protocol.

Whereas trials with several sub-protocols can be submitted as one or separate trials, a complex clinical trial with several arms sharing a common control arm must be submitted as one trial (Figure 2).

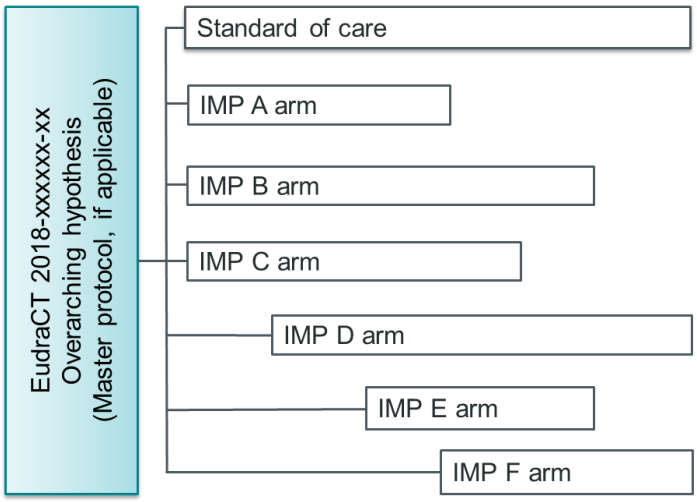

Figure 2: Example of a complex trial design with arms compared to a shared control arm. The design is characterised by extensive adaptations where arms with new IMPs are being opened and closed during the conduct of the trial via substantial amendments.

Further guidance regarding justification of the chosen trial design can be found in section 4.1. Recommendations regarding regulatory submissions are provided in section 5.

3. POTENTIAL OPPORTUNITIES AND CHALLENGES OF COMPLEX CLINICAL TRIALS

The area of precision medicine has greatly expanded during the past decade especially in oncology research, where enrichment designs target IMPs toward tumour-specific genetic alterations in complex trial designs. Precision medicine thus aims at investigating medicinal products only in the population expected to derive the greatest benefit from the treatment. Such biomarker-driven development is advantageous for both patients and sponsors because it aims to match patients with the expected best available treatment and could streamline clinical development.

However, complex trial designs also mean increased operational complexity due to the presence of several IMPs, populations, trial sites, multiple manufacturers and contract research organisations (CROs). Therefore, adaptations may cause challenges at both investigator and sponsor level and could jeopardise the safety oversight of the trials thus affecting the safety of trial subjects or the benefit-risk balance of the clinical trial.

Complex trial designs proposing extensive prospective adaptations such as the addition of new IMPs or populations also challenge the EU regulatory framework in terms of the definition of a clinical trial and data transparency, and they pose a challenge in terms of providing clear information particularly to the trial subjects.

According to the EU Directive 2001/20/EC, a clinical trial summary report will be made available to the competent authorities via the EudraCT database within one year of the end of the trial. A sub-set of the summary reports is made available to the public on the EU Clinical Trials Register. Data transparency is thus of great concern for complex clinical trials submitted as one clinical trial, since publication of sub-protocol results will be delayed until after the overall clinical trial is completed.

There are also concerns regarding the scientific value or outcome of complex clinical trials due to the parallel testing of several IMPs in small numbers of trial subjects, difficulties to control type I error, and challenges created by shared control arms, which need to be thoroughly addressed. In addition, complex trial designs raise concerns regarding data integrity as emerging data from closed sub-protocols may affect the conduct of the ones that are still ongoing.

4. KEY RECOMMENDATIONS FOR INITIATING AND CONDUCTING COMPLEX CLINICAL TRIALS

The EU Clinical Trial Directive 2001/20/EC and ICH E6 (R2) state that a clinical trial should be safe, scientifically sound and presented in a clear detailed protocol. The EU/EEA competent authorities support the conduct of innovative design trials provided that each clinical trial addresses a specific scientific hypothesis and the sponsor has adequate oversight of the safety and integrity of the entire clinical trial. When initiating and conducting complex clinical trials in the EU/EEA, sponsors should identify potential risks associated with the IMPs, trial populations and operational complexity. Sponsors should implement

appropriate risk mitigation strategies considering the following eight key recommendations that are further described in the following sections:

1. Clearly describe and justify design (section 4.1)
2. Maintain scientific integrity (section 4.2)
3. Ensure quality of trial conduct and optimise clinical feasibility (section 4.3)
4. Ensure safety of trial subjects (section 4.4)
5. Maintain data integrity (section 4.5)
6. Reassess benefit-risk balance at critical steps throughout clinical trial (section 4.6)
7. Validate companion diagnostics (section 4.7)
8. Consider data transparency (section 4.8)

4.1. Clearly describe and justify design

A clinical trial is a clinical investigation with a pre-defined objective aimed at addressing a precise hypothesis. Prospective planning of adaptations is crucial to avoid biases and the clinical trial design should be clearly described at the time of the initial CTA. For each clinical trial, the sponsor should describe and justify the proposed design considering the points below:

- The design should be thoroughly described with a clear description of all complex components such as the sub-protocol design, common comparator arm, master protocol, and planned possible adaptations.
- The protocol should describe all closed, current, and future planned sub-protocols/arms. Visual depiction is encouraged. Sponsors should discuss how many sub-protocols/arms are expected to be opened by submission of subsequent substantial amendments and when the whole trial is expected to end.
- A complex clinical trial submitted as one trial is expected to have an 'overarching hypothesis' defining the scientific objective(s) of the whole trial. The trial protocol should describe how the objectives specific to each sub-protocol contribute to the whole trial objective(s). The final clinical trial analysis should determine whether the overarching clinical trial objectives were met.
- The clinical trial rationale section should justify the choice of trial design including justification of features such as a master protocol, sub-protocols, platform, and/or future adaptation. For complex trials submitted as one trial, it should be discussed why a single trial should be preferred to several independent trials. This justification could be summarised in the cover letter.
  Sponsors should discuss the rationale of the specifically proposed clinical trial design and not the advantages of complex clinical trials in general. Increased operational efficiency and speed of development cannot be the only justification for choosing a specific trial design that may compromise scientific integrity, trial subject safety, or quality of trial conduct at the investigator and/or sponsor site.
- The clinical trial rationale section should include a detailed benefit-risk assessment. The benefit-risk balance should be positive both for the entire trial and for each sub-protocol.

- The protocol should clarify the relationship among the different sub-protocols and how changes in one sub-protocol may affect the other sub-protocols.
- The protocol should specify the criteria for allocating trials subjects to a specific sub-protocol/arm, the criteria for opening and closing sub-protocols/arms as well as for re-allocating trial subjects from one sub-protocol to another, if this is applicable.

4.2. Maintain scientific integrity

The scientific integrity of a trial should be maintained by ensuring that the initial hypothesis is scientifically sound and maintained throughout the clinical trial. Sponsors of complex clinical trials investigating several IMPs and/or populations are expected to consider the following points:

- The scientific hypothesis and primary objectives defined at the time of the initial CTA should not be changed during the conduct of the trial.
- Substantial amendments proposing extensive changes such as the addition of a new sub-protocol or arm investigating a new IMP or population should be clearly described, properly justified and in line with the clinical trial hypothesis defined at the time of the initial CTA. A new sub-protocol/arm will be considered a new clinical trial if the objectives are not in line with the initial clinical trial hypothesis.

4.3. Ensure quality of trial conduct and optimise clinical feasibility

Complex clinical trials enrolling several trial populations and/or investigating many different IMPs increase operational complexity and pose a challenge to sponsors as well as investigators. To assure quality of trial conduct, sponsors should:

- Implement a risk based system for quality management according to ICH E6 (R2).
- Ensure that the risk based monitoring plans are adapted to each sub-protocol as well as for the entire trial and that on-site monitoring is in place as appropriate for complex clinical trials. The risk based monitoring is expected to be defined and justified (for details see ICH E6 section 5.18.3 including addendum).
- Adopt a risk-adapted approach when proposing measures to identify and manage relevant risks and ensure implementation of proper risk-mitigation strategies. The risk management proposals should address risks that are specific to the trial as a whole as well as those specific to each sub-protocol. For more information, sponsors are referred to: Recommendations of the European commission expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use on “Risk proportionate approaches in clinical trials”, dated 25 April 2017.

Quality of trial conduct is highly dependent on investigator/sponsor oversight and compliance with the protocol and principles of good clinical practice (GCP) according to ICH E6 (R2). Clinical feasibility at trial sites should always be a major focus in the choice of trial design, trial site(s) and investigator(s) as well as implementation of risk proportionate approaches. Increased sponsor oversight will not be sufficient to

justify a complex clinical trial design if clinical feasibility at the investigator site is compromised. To optimise clinical feasibility, sponsors are recommended to:

- Select sites with relevant experience.
- Provide additional site training.
- Maintain good communication with the trial sites to obtain relevant information from the investigator sites concerning clinical trial conduct and to ensure that investigators are up to date with relevant issues and current risk mitigation strategies.

4.4. Ensure safety of trial subjects

Complex clinical trials are most often early exploratory trials where a limited amount of safety and efficacy data of the IMP(s) being tested is available. Also, clinical trials investigating an IMP in several study populations or several IMPs in one or more populations can be associated with an increased likelihood of mistakes due to the sheer complexity of the design. Adequate oversight together with early detection and immediate communication of safety signals are therefore crucial to protect the safety of the trial subjects in complex clinical trials with many IMPs, populations, and/or trial sites. To ensure trial subject safety, the following will be expected for complex clinical trials:

- A special focus on implementation of appropriate risk mitigation strategies with a focus on the safety of trial subjects in line with the principles described in section 4.3. Sponsors must identify potential safety risks affecting the whole trial and each specific sub-protocol/arm. Acceptable risk mitigation strategies with a focus on safety should include, but are not limited to specific eligibility criteria, prohibited medications, adequate wash-out periods, safety follow-up, and drug discontinuation criteria.
  A table summarising both identified risks and mitigations strategies should be included in the protocol. For more information, sponsors are referred to: Recommendations of the European commission expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use on “Risk proportionate approaches in clinical trials”, dated 25 April 2017.
- Generally, an independent data monitoring committee (IDMC) should oversee the safety of complex clinical trials in accordance with the EMA guideline on Data Monitoring Committees (EMEA/CHMP/EWP/5872/03 Corr). Other tasks of the IDMC may be assessment of efficacy and/or futility. Sponsors should ensure that the IDMC members are independent of the sponsor (e.g. no employees of the sponsor), external to the study and have the relevant expertise to perform their tasks. In particular, statisticians should be included in the IDMC of trials with interim analyses.
- The safety monitoring should be adequate to ensure early detection of potential safety signals, which will be managed and reported in compliance with the protocol and current legislation.
- The protocol needs to include a communication plan detailing how safety findings will be communicated in a timely manner to all relevant stakeholders (e.g. investigators, CROs, all relevant sponsor personnel, regulatory authorities, ethics committees and trial subjects). Sponsors are also reminded to set up procedures for reporting serious breaches and/or protocol deviations as per national clinical trial legislation.

Sponsors are reminded to follow all applicable guidance and recommendations regarding safety including information published by CTFG.

4.5. Maintain data integrity

When multiple questions are addressed through a complex trial design, special care should be taken to avoid multiplicity issues and false positive results in particular at later stages in the development program. The extent to which adaptive features are appropriate in a complex clinical trial depends on the purpose of the study. While adaptations may increase efficiency in an exploratory phase of development, the scientific value in a later development phase may be decreased. Also, it should be ensured that sample sizes are sufficient to provide conclusion on the initial trial hypothesis.

Data integrity is ensured by a sound statistical analysis plan (SAP) and protocol describing how the data collected during the conduct of the study will answer the clinical trial hypothesis. The protocol and SAP should be revisited as appropriate if the trial design is changed during the conduct of the trial.

As stated in Section 4.1, prospective planning before clinical trial initiation is critical to avoid introducing biases in clinical trials with extensive adaptations. To maintain data integrity during trial conduct, sponsors should:

- Describe the impact of the proposed adaptations on data validity. A summary of mitigation strategies should be provided in the protocol and summarised in the cover letter both at the time of the CTA and substantial amendments.
- Describe how they will control the type I error rate. Relevant issues include pooling of data between sub-protocols, futility analysis, and how inconsistent results between sub-protocols will affect the credibility of the results. Multiplicity issues specific to sub-protocols should be addressed in the sub-protocols and SAP.
- Be careful when planning how new treatment(s) will be compared against a common control arm (standard of care or placebo). Complex clinical trial designs where multiple IMPs are tested against a shared control arm may reduce the number of trial subjects assigned to placebo. However, the control arm is a fundamental part of the study design. The main issue is that concurrent control subjects will be more appropriate for comparison if there have been changes over time, for example in standard of care or biomarker testing. A discussion is recommended on the impact on the relevance of the comparison.

- Keep interim results confidential as knowledge deriving from opened and closed sub-protocols may affect the physicians and patient's attitude towards the investigational product. However, the protection of data integrity should not compromise data transparency as described in section 4.8. If a sponsor's representatives wish to review unblinded interim data the protocol must include a strong rationale and describe measures to maintain data integrity.

4.6. Reassess benefit-risk balance throughout clinical trial at critical steps

In complex clinical trials, information and data emerging from sub-protocols/arms may affect the conduct of the entire clinical trial. A process should be in place to ensure continuous re-assessment of the benefit-risk balance of individual sub-protocols as well as for the entire trial at critical steps in order to protect the safety and rights of the trial subjects. In particular, sponsors are advised to:

- Re-assess the benefit-risk balance at critical steps throughout the entire clinical trial such as events with potential safety signals or an impact on safety e.g. important adverse events as well as at submission of substantial amendments proposing major adaptations like closures of sub-protocols and addition of new IMPs/populations. When submitting the substantial amendment request, the protocol and/or cover letter should include a discussion of the updated benefit-risk balance that should be positive at both the global trial and sub-protocol level.
- Consider whether changes to patient information and informed consent form(s) (ICFs) are warranted based on a reassessment of the benefit-risk ratio and an assessment of the impact of the adaptations to the trial (closure/addition of sub-protocols or arms).

Due to the potentially increased complexity of a complex clinical trial with many sub-protocols or arms within one trial, sponsors are reminded that the information presented to a trial subject should be clear and relevant at any given time during the trial. Clarity could be improved by sub-protocol specific ICFs and/or staged consent for clinical trials with screening platforms. Sponsors are also reminded that re-consent is needed if trial subjects are re-allocated between sub-protocols as well as when the benefit-risk changes during the clinical trial. In the EU/EEA, the ethics committees (ECs) will review patient information and ICFs. Sponsors are recommended to contact the ECs for guidance in relation to patient information and ICFs, especially for trials with master protocols.

4.7. Validate companion diagnostics

Companion diagnostics are assays measuring biomarkers used to determine clinical trial eligibility, IMP assignment, safety management and/or outcome analyses. They have a significant impact on trial outcomes and appropriate treatment allocation of the trial subjects. It is the sponsor's responsibility to ensure that companion diagnostics are compliant with the applicable legislation and adequately validated in terms of both quality (sensitivity and specificity) and clinical relevance.

When using predictive or prognostic biomarker assays, sponsors should:

- Justify the relevance of the assay and the proposed cut-off values.
- Describe in the protocol/master protocol the proposed assay as well as the procedures for the acquisition and handling of biological samples.
- Specify how trial subjects will be allocated to a specific treatment in case they are positive for two or more biomarkers.

4.8. Consider data transparency

In the EU/EEA, data transparency is considered very important. In the interest of data transparency, the summary reports for Phase II-IV and paediatric Phase I trials are not only provided to competent

authorities, but are also published on the public EU Clinical Trials Register within one year of the end of the trial, and even earlier for paediatric clinical trials (6 months). For reference, see European Commission Communications 2009/C 28/01; Regulation (EC) No 1901/2006 and Commission Guideline 2012/C 302/03; Regulation (EC) No 726/2004 and Regulation (EC) No 1901/2006.

Data transparency may be compromised in complex clinical trials registered as one clinical trial, where data from each closed sub-protocol or arm will become available only after the end of the entire trial.

For complex clinical trials registered as one trial, sponsors are strongly recommended to:

- Include in the protocol a description of their "publication policy" regarding both interim results from closed sub-protocols/arms and final study results. In this section, sponsors should clarify how data transparency will be ensured in the trial.
- Include data from closed sub-protocols in the Investigator's Brochure, or if there is a need to keep data confidential from sites to protect data integrity data may be included in the clinical investigational medicinal product dossier (clinical IMPD). Provision of this data to competent authorities within one year following end of a sub-protocol is recommended. For paediatric trials, this data should be provided within 6 months of end of a sub-protocol.

5. REGULATORY CONSIDERATIONS AND COMMUNICATION

In the EU/EEA, each clinical trial is identified by a unique EudraCT number (EudraCT trial) and registered in the EudraCT database. The EudraCT number accompanies the trial from the first clinical trial submission and authorisation to the clinical study report and the marketing authorisation application. The EudraCT number is therefore crucial for monitoring regulatory and safety aspects of clinical trials.

Sponsors are encouraged to avail of the Voluntary Harmonised Procedure (VHP) when submitting complex CTAs. They are also recommended to seek advice from the relevant National competent authorities prior to submission of applications for clinical trials with an innovative complex trial design, e.g. from CTFG or the concerned member states as applicable.

In case of clinical complex trials where not all member states participate in all sub-protocols or arms, the sponsor must clearly state which sub-protocols/arms are running in which countries (a table is recommended).

Below we highlight some regulatory considerations concerning choice of submission models for complex clinical trials with a sub-protocol design followed by summaries of recommendations from section 4 to facilitate authority review by clear communication in cover letters (section 5.1) and of main issues concerning substantial amendments (section 5.2).

One or separate clinical trials

Clinical trials with several sub-protocols can be submitted either as separate trials or one single complex trial design as described in section 2.4. If submitted as one single EudraCT trial (Figure 1a) the trial will have

one or more separate sub-protocols that must be linked together by an overarching hypothesis. Opening or closing of sub-protocols will require a substantial amendment request.

The features which are shared by all the sub-protocols/arms can be included in a master protocol. As there is usually no IMP being administered within the master protocol, a master protocol cannot be considered a clinical trial with a medicinal product on its own and thus cannot be given a separate EudraCT number. However, the master protocol should have a unique sponsor ID and be version-controlled to ensure transparency across the sub-protocols. For complex trials submitted as separate trials, the master protocol must be submitted with each CTA. As a master protocol does not represent an independent trial, it cannot be submitted without a sub-protocol.

Sponsors can also choose to submit each sub-protocol, together with a shared master protocol if applicable, as separate trials identified by individual EudraCT numbers (Figure 1b, section 2.4). The individual trials can be linked by trial names as exemplified in Figure 1b and may share the same master protocol. The cover letter should list all the EudraCT numbers of clinical trials relevant to this 'platform'.

The choice of submission model should depend on the scope and scientific integrity of the trial. In case a complex trial is submitted as one single EudraCT trial, the sponsor is reminded that the scientific integrity of the trial must be maintained as described in section 4.1, also when new sub-protocols are added via substantial amendments.

Submission of separate EudraCT trials may thus be more appropriate for complex trials where there is no specific research hypothesis linking the sub-protocols. An example could be a platform trial investigating multiple IMPs in multiple populations where the independent arms are linked only for operational reasons.

Submission as separate trials is also recommended for complex trials where the potential IMPs or populations to be added are very poorly defined. For example, a phase 1/2 study investigating "X in combination with Y or other anti-cancer therapies" is not considered a trial with a strong rationale as the potential components of the combination are neither identified nor justified.

Complex clinical trial designs are generally considered appropriate primarily for phase I/II exploratory clinical trials.

While investigation of first-in-human (FIH) IMPs or combinations with very limited clinical experience requires robust justification at the time of the initial CTA, FIH IMPs or FIH combinations should not be added through substantial amendment requests. Due to the complexity and separate regulatory requirements for advanced therapy medicinal products (ATMPs), ATMPs without an EU marketing authorisation should also not be added to an existing complex clinical trial through substantial amendment requests.

5.1. Clear communication

Sponsors are recommended to use the cover letter to summarise the key features of a complex clinical trial design both at the time of initial CTAs and substantial amendment requests. For example, sponsors can use the cover letter to:

- Clearly state if it is a complex clinical trial with description of the main characteristics of the design such as “master protocol”, “sub-protocols”, and potential addition of new IMPs/populations, including the use of companion diagnostics, if applicable.
- Summarise the study rationale.
- Clarify whether new sub-protocols are expected to be added and if they will be submitted via substantial amendment requests or as new clinical trials.
- Provide relevant EudraCT numbers of clinical trials in the same ‘platform’ and/or previously authorised clinical trials with similar designs.
- Provide information about which sub-protocols/arms are running in which countries e.g. by a table.

5.2. Substantial amendments proposing addition/closure of sub-protocols or arms

When submitting a substantial amendment request proposing a major adaptation such as the addition of a new IMP/population, the sponsor is reminded to include the following:

- A statement in the cover letter that the amendment is proposing the addition of new IMP(s)/population(s).
- A rationale for why the changes are consistent with the overarching clinical trial hypothesis defined at the time of the initial CTA.
- A statement that the benefit-risk ratio has been re-evaluated and a summary of why the benefit-risk balance remains positive for each sub-protocol/arm and for the entire trial. New risk-mitigation strategies should be highlighted. For trials with a shared control arm, sponsors should discuss whether standard of care has evolved since trial initiation.
- Overview of the main design changes that have occurred from the trial initiation to the submission of the amendment requests including a list of closed and open sub-protocols/arms. Tables and visual depictions can be used to facilitate review.
- Interim safety and efficacy data. They could be included in the Investigator’s Brochure or clinical IMPD. Sponsors should clearly summarise and justify the early closure of a sub-protocol.
- A re-estimation of the number of trial subjects to be recruited and the expected end of trial date.

If a sub-protocol or arm is closed early by the sponsor due to a non-favorable benefit-risk balance, the end of such part of the trial should be communicated as an urgent safety measure or as a substantial amendment related to an urgent safety measure. The reason for the early termination and implication for the trial subjects, including description of any intended follow-up activities, should be provided in both cases.

6. REFERENCES

EU Clinical Trials Directive 2001/20/EC.

2008/C 168/02: Communication from the Commission regarding the guideline on the data fields contained in the clinical trials database provided for in Article 11 of Directive 2001/20/EC to be included in the database on medicinal products provided for in Article 57 of Regulation (EC) No 726/2004

ICH E6 Good Clinical Practice (R2: Integrated Addendum to ICH E6 (R1) Guidance for Industry).

EMA guideline on Data Monitoring Committees (EMEA/CHMP/EWP/5872/03 Corr).

“Q&A document - Reference Safety Information (RSI)” published on the CTFG webpage in November 2017.

Recommendations of the European commission expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use on “Risk proportionate approaches in clinical trials”, dated 25 April 2017.

2012/C 302/03: Commission Guideline — Guidance on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006.

European Commission Communications 2009/C28/01 Guidance on the information concerning paediatric clinical trials to be entered into the EU Database on Clinical Trials (EudraCT) and on the information to be made public by the European Medicines Agency (EMEA), in accordance with Article 41 of Regulation (EC) No 1901/2006.