Recommendation paper on frequent issues identified during assessment of Part I and Part II

Outcome of the feedback received by Member States (national competent authorities and ethics committees)

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This recommendation paper is a dynamic and evolving document, subject to periodic updates to reflect on the experience gained with ongoing assessments of Parts I and II, incorporating current regulatory insights and feedback to address identified issues.

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Important notice: The views expressed in document are not legally binding. Ultimately, only the European Court of Justice can give an authoritative interpretation of Community law. This document aims at informing on the technical aspects of Clinical Trials Regulation (EU) No 536/2014 with a view to facilitating its implementation.

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1. Introduction

This document has been developed to support the improvement of Clinical Trial Applications (CTA) and to enhance the efficiency and consistency of their assessment across Member States. It presents a curated list of the most frequent and relevant considerations raised during the evaluation of Part I of CTA.

The considerations included in this guidance are the result of a targeted selection process based on feedback collected from national competent authorities (NCAs) and ethics committees (ECs) through a dedicated survey. The aim was to identify common issues that frequently lead to delays or additional queries during the assessment process. To ensure broad applicability and practical value, only considerations of general relevance were selected. In general, considerations that simply reiterate requirements already clearly addressed in published guidance documents, reflection papers, or that request compliance with the Clinical Trials Regulation (EU) No 536/2014 (CTR) were excluded from this compilation.

This document is intended to serve as a practical tool for sponsors when preparing their CTA, helping to anticipate and address common concerns proactively. By doing so, it contributes to a more streamlined and predictable assessment process, ultimately supporting the timely initiation of clinical trials.

Sponsors are strongly encouraged to consult and adhere to all applicable regulatory guidance documents and legal requirements. In cases where deviations from established guidance occur, a clear and scientifically justified rationale should be provided within the application. Ensuring alignment with existing standards—or transparently justifying any discrepancies—is essential to maintain the quality, integrity, and ethical standards of clinical research.

2. List of frequent issues identified on Part I assessment

2.1. Investigational Medicinal Product Dossier (IMPD)

2.1.1. When the sponsor refers to published pharmacokinetic (PK) data from a licensed product containing the same active pharmaceutical ingredient (API) but with a different excipient composition, they are required to provide robust evidence demonstrating that the excipient differences do not affect the absorption of the API or alter the expected clinical exposure.

Recommendation: A scientifically sound rationale should be added to justify the use of reference data from the approved product to support the efficacy and safety/toxicology profile of the investigational medicinal product (IMP). This rationale should be retained in all subsequent updates of the Investigator's Brochure (IB).

2.1.2. Provide latest stability data for long term and/or accelerated stability tests for investigational medicinal product (IMP) batches used in the study. (Often in time of an IMPD assessment actual stability data can influence acceptability of product proposed shelf life).

Recommendation: Sponsors should always submit the most current and complete data available for the IMP batches intended for use in the clinical trial. To facilitate a more efficient assessment process

and minimize review time, the most relevant data should be presented in a clear and structured format—preferably in a dedicated table.

Providing up-to-date data allows assessors to evaluate the IMP characteristics, ensuring that the IMP remains safe and effective throughout the study duration. This proactive approach reduces the likelihood of additional information requests and supports a smoother, faster regulatory review.

2.1.3. If authorised medicinal products are used as IMP and those are labelled trial specific (and not used in their market packaging / labelling) there is often no information on the manufacturing sites where (re)packaging, labelling and batch release of these IMP's are performed.
A typical consideration is IMP xyz is labelled / packed specifically for this trial, but no information is given which manufacturer(s) perform(s) the packaging / labelling and the batch release of the product. Please provide for IMP xyz an S-IMPD which states the manufacturing sites involved and provide a copy of the manufacturing authorisations from these manufacturer(s).

Recommendation: For authorised medicinal products, an S-IMPD should be provided, clearly identifying the manufacturing sites responsible for (re-)packaging, labelling, and batch release. Additionally, copies of the manufacturing authorisations for these sites should be uploaded in the good manufacturing product (GMP) section.

2.1.4. Indicate the changes made between the manufacturing process of clinical batches from the previous phase and the clinical batches that will be used for this trial. Provide and discuss the comparability data for batches produced according to these processes unless otherwise justified.

Recommendation: A comprehensive history of all batches produced should be provided in a clear tabular format. This should include details on batch numbers, their intended use (e.g. clinical, stability, validation), and any changes made to the manufacturing process or product composition over time. A comparability exercise must be conducted to evaluate the impact of any changes by comparing pre- and post-change batches. All data should be thoroughly discussed to demonstrate consistency and product integrity, unless a valid scientific justification is provided for any omissions.

2.2. Investigator's Brochure (IB)

2.2.1. Safety margins (*AUC and Cmax - if applicable both unbound in addition*) are not included, or low and not discussed in relation to relevance for human safety and the risk management plan.

Recommendation: Sponsors should consistently provide detailed information on safety margins, including area under the curve (AUC) and maximum concentration (Cmax) (if applicable both unbound in addition) values, and a clear rationale for dose selection. This information should be contextualized in terms of its relevance to human safety and integrated into the overall risk management strategy.

Compliance with this recommendation greatly enhances the efficiency of the assessment process. When safety margins are transparently presented and justified, assessors can more readily evaluate the adequacy of the proposed dosing regimen and its alignment with safety objectives. This reduces

the need for additional clarification requests and iterative reviews, thereby streamlining the evaluation timeline and supporting faster, more informed regulatory decisions.

2.2.2. Translatability of nonclinical findings are not evaluated, discussed or linked to clinical trial risk mitigation procedures. Should be addressed in the documentation

Recommendation: Sponsors should always provide a thorough discussion on the applicability of non-clinical findings to the proposed clinical trial. This includes evaluating the relevance of observed toxicological, pharmacological, or safety signals in non-clinical studies and clearly linking them to the clinical context, including risk mitigation strategies outlined in the protocol and the risk management plan.

Addressing translatability ensures that potential risks are appropriately anticipated and managed in the clinical setting. It also enables assessors to better understand the scientific rationale behind the trial design and safety measures. This proactive approach reduces the likelihood of follow-up questions and delays, thereby improving the overall efficiency and predictability of the assessment process.

2.2.3. For the non-clinical studies conducted, the methods of analysis and their sensitivities aren't adequately described in the Investigator's Brochure (). The Sponsor is requested to provide information regarding the methods of analysis used for the analysis preformed for the non-clinical studies. This information should also be included in the next version of the IB.

Recommendation: Sponsors should ensure that comprehensive details on the analytical methods used in non-clinical studies—including their sensitivity, specificity, and validation status—are clearly documented. This information is essential for assessing the reliability and interpretability of the non-clinical data.

Inclusion of this information in the IB not only supports scientific transparency but also facilitates a more efficient and informed assessment process. It enables reviewers to evaluate the robustness of the data and reduces the need for additional clarification requests. Sponsors are therefore encouraged to provide the requested information promptly and to commit to updating the IB in a timely manner to reflect these details.

2.3. Protocol

2.3.1. Study treatment (comparator/placebo). The sponsor is requested to update the protocol including a justification for the use of placebo.

Recommendation: Sponsors should ensure that protocol of clinical trial includes a dedicated section discussing the rationale for the use of placebo. This section should address the ethical considerations, scientific justification, and relevance to the study objectives. It should also explain why a placebo is appropriate in the context of the indication, patient population, and available standard of care. Particularly, the standard of care in the country must be considered. A suboptimal treatment in the control arm must be avoided.

Providing a well-reasoned justification for the usage of placebo, enhances the transparency and scientific integrity of the trial design. It also facilitates a more efficient assessment by enabling

reviewers to quickly evaluate the ethical and methodological soundness of the proposed approach. This reduces the likelihood of delays due to requests for additional information or protocol amendments.

2.3.2. Given the availability of authorised products for the condition under study, the sponsor is requested to update the inclusion criteria. Specifically, the protocol should clarify that subjects may be enrolled in the study only if they are not eligible for, or do not have access to, the authorised treatments (e.g., due to safety, tolerability, compliance issues, or based on the investigator's clinical judgement).

Recommendation: Sponsors should include in the protocol a clear and comprehensive discussion of the potential benefits of patient enrolment, particularly in scenarios where approved therapeutic alternatives exist for the same indication or setting. When applicable, the inclusion criteria should explicitly state that participation is limited to individuals who are either ineligible for, or unable to access, authorised treatments.

This approach ensures that the trial population is ethically selected, and that patient participation is justified. It also supports informed decision-making by investigators and ethics committees and demonstrates that the study design respects the principles of clinical equipoise. Including this information in the protocol facilitates a more efficient and transparent assessment process by addressing potential ethical concerns upfront and reducing the need for additional clarifications.

2.3.3. The protocol does not currently include criteria for clinical trial termination. These criteria should cover scenarios such as unacceptable risk to participants, a negative shift in the risk/benefit assessment, requests from a concerned Member State (e.g., regulatory authority or ethics committee), or insufficient recruitment rates.

Recommendation: Clinical trial protocol should include clearly defined and justified criteria for trial termination or suspension. These criteria should outline the specific conditions under which the trial may be halted.

Including these criteria ensures that the trial is conducted with appropriate safeguards and ethical oversight. It also provides transparency for investigators, participants, and regulators, and facilitates timely decision-making in response to emerging issues. From a regulatory perspective, the presence of well-defined termination criteria supports a more efficient and confident assessment process, reducing the need for protocol amendments or clarification requests. There should be mechanisms in place to avoid prolonged treatment in case of toxicity and lack of efficacy.

2.3.4. The current protocol proposes administration of the Investigational Medicinal Product (IMP) for an unlimited duration or for a period of XY years at a specified dose, as outlined in protocol section XX. However, there are no clinical data available to support this treatment duration or dose. The sponsor provided only limited data from study phase I or data from study phase I are not available.

Recommendation: Sponsors should provide adequate clinical safety and, if available, efficacy data from previous phase trials—particularly phase I studies—to justify the proposed treatment duration and dosing regimen in the current trial. This includes data on tolerability, adverse events, dose-limiting toxicities, and any emerging safety signals.

Such data are essential to support the transition to a higher-phase clinical trial, especially when long-term or indefinite administration is proposed. Including this information ensures that the risk/benefit profile is appropriately assessed and that participant safety is safeguarded. It also facilitates a more efficient and confident regulatory review by reducing the need for additional data requests or protocol amendments.

2.3.5. The protocol does not currently specify the planned treatment and medical follow-up of patients after the end of the study. It also lacks clarity on how patients who withdraw early from the study will be followed up therapeutically.

Recommendation: Sponsors should ensure that the clinical trial protocol includes a detailed plan for a medical follow-up of all participants after the study concludes. Additionally, protocol should clearly outline how patients who discontinued the study prematurely will be managed, including any safety assessments or therapeutic support they will receive.

Providing this information is essential for ensuring participant safety and ethical oversight. It also supports regulatory and ethics committee evaluations by demonstrating that appropriate care is planned beyond the formal study period. Including these details in the protocol will contribute to a more efficient and transparent assessment process, reducing the need for follow-up queries or amendments.

2.3.6. Protocol does not provide sufficient details about the statistical analysis methods, including methodology for testing primary and secondary endpoint

Recommendation: Clinical trial protocol should include a comprehensive and well-justified statistical analysis section.

A clearly defined statistical analysis section in the protocol ensures that the study's objectives are appropriately addressed and that the results will be scientifically valid and interpretable. Including this information in the protocol enhances the transparency and credibility of the trial design and facilitates a more efficient regulatory review by reducing the need for follow-up questions or protocol amendments.

2.3.7. Any deviation from the recommendations outlined in the EMA Guideline on Data Monitoring Committees should be explicitly explained, including how patient safety and data integrity will be ensured through alternative measures. Additionally, if you establish a DSMB, it is requested to include the work procedure or document containing the list of members (roles, names and qualification of the members) as well as the frequency of meetings and how they will monitor the security data.

Recommendation: Sponsors are recommended to provide clear and well-founded justifications in cases where their approach diverges from the recommendations outlined in the EMA Guideline on Data Monitoring Committees. Such justifications should be included in Clinical Trials Information System (CTIS) part I, specifically within the protocol information placeholder, under the Data Safety Monitoring Charter subsection. In particular cases (i.e. paediatric clinical trials), sponsors should provide a justification for not establishing a DSMB, including a description of the risk profile of the clinical trial and the patient population, as well as the purpose and nature of a planned interim analysis (especially regarding safety monitoring). Alternative safety oversight mechanisms, such as an internal safety

review team or medical monitor, should be described, including how safety data will be reviewed and adverse events reported. Additionally, the sponsor should confirm their willingness to establish a DSMB, and provide a DSMB Charter that includes the names, qualifications, and roles of the members, the frequency of meetings, and the procedures for monitoring safety data.

2.3.8. Criteria for treatment discontinuation and for withdrawing trial participants from the clinical trial should be clearly defined in the protocol.

Recommendation: The request to clearly define criteria for treatment discontinuation and trial participants withdrawal in a clinical trial protocol is essential to ensure participant safety, ethical conduct, and regulatory compliance. According to the CTR, the protocol must provide sufficient detail to allow national competent authority and ethics committee to assess whether the trial adequately protects participants. Clear criteria for patients withdrawing help prevent unnecessary risks, ensure consistent clinical trial conduct, and support the generation of reliable data. They also guide investigators in making informed decisions and ensure transparency in managing participant involvement.

2.4. Safety

2.4.1. The reporting of serious adverse events (SAE) by the investigator is restricted without any justification to the time period of 30 days after last dose of trial treatment or initiation of another therapy

Recommendation: Sponsors should provide a clear and scientifically justified rationale for the selected SAE reporting period. In cases where the SAE reporting period is restricted, the justification should be explicitly documented in the protocol. This ensures that safety monitoring is aligned with the characteristics of the IMP and that participant protection is maintained throughout the relevant risk window. Including this information also facilitates a more efficient and informed assessment by regulatory authorities and ethics committees, reducing the need for follow-up queries or protocol amendments.

2.4.2. The protocol lacks specific information regarding the volume of blood samples to be collected per subject and per visit in the paediatric population. This information is required in accordance with guidance for the ethical considerations regarding the minors. If the proposed blood volume exceeds the maximum allowable limits (e.g., per single draw or over a 4-week period), the protocol must specify the measures to minimise blood volume and prioritise laboratory assessments.

Recommendation: Sponsors should clearly detail the planned blood sampling volumes in the clinical trial protocol, particularly for paediatric participants (i.e. volume of blood to be collected per visit and over the course of the study, justification for the sampling schedule and volume, reference to applicable ethical guidelines and limits, mitigation strategies if volumes exceed recommended thresholds).

Providing this information is essential to ensure the ethical conduct of the trial and the protection of vulnerable populations, such as paediatric subjects (please refer to the guidance "Ethical considerations for clinical trials on medicinal products conducted with minors (2017)" for further details). It also facilitates a more efficient and transparent review process by enabling regulators and ethics committees to assess the appropriateness of the sampling plan without requiring additional clarification.

2.4.3. In chapter XY it is listed that safety/laboratory results that could unblind the study will not be reported to investigational sites or other blinded personnel until the study has been unblinded. Sponsor is asked to specify these results and elaborate if not providing them to investigator is not in conflict to standard practice and could not jeopardize patient's safety in the clinical trial, because per declaration of Helsinki, patient must not get worse treatment and medical care in the clinical trial than in the standard clinical practice and investigator is responsible for all medical decision related to patient.

Recommendation: Sponsors should clearly identify which specific safety or laboratory results have the potential to unblind treatment allocation. If such results are withheld from investigators, the protocol must include a robust justification. This justification is particularly important considering the Declaration of Helsinki , which states that trial participants must not receive inferior treatment or care compared to standard clinical practice. Investigators remain fully responsible for the medical care of their patients and must have access to all relevant safety information to fulfil this duty.

Ensuring patient safety must remain the highest priority throughout the clinical trial. Any restrictions on data sharing must be carefully balanced against the ethical obligation to provide appropriate medical oversight and care.

3. List of frequent issues identified on Part II assessment

3.1. Participant Information Sheet (PIS)/Informed Consent Form (ICF)

3.1.1. The Participant Information Sheet (PIS) is excessively lengthy, inadequately written (or translated), and not appropriately adapted to the national context. Acronyms are not defined, and certain elements are redundant. A thorough revision is necessary to ensure the document is comprehensive, concise, clear, relevant, and understandable to a layperson (CTR, Article 29(2). This document is not a generic template, but a specific document intended to inform participants. Particular care must be taken in the presentation of the trial's objectives and procedures. The anticipated benefits, risks, burden and constraints must be presented in a fair and transparent manner. It should also describe in a clear concise way the trial participant should do in case of a trial related injury.

Recommendation: Sponsors should use the national template PIS/ICF (if available) and draft the PIS according to the instruction. This will enhance the participants understanding and facilitate concise, clear, relevant and accessible information to participants in alignment with CTR, Article 29(2). See the overview "Part II requirements per Member States" on the MedEthicsEU website for further information on national templates and instructions per Member States.

3.1.2. The current documentation does not include any age-appropriate information for minors, nor does it provide a version Participant Information Sheet (PIS) and Informed Consent Form (ICF) for participants who reach the legal age to consent during the clinical trial.

Recommendation: Sponsors should prepare age-appropriate information specifically designed for minors, with content adapted to their cognitive and developmental level. These documents should be distinct from the consent forms signed by parents or legal representatives and should be tailored to different age groups (e.g. young children, adolescents). Additionally, as soon as a minor participating in a clinical trial reaches the age of legal competence (as defined in national law, which varies between 12 and 18 years), a separate PIS/ICF should be provided to allow them to give informed consent independently. This ensures that their continued participation is based on their own understanding and

voluntary agreement, in accordance with ethical and legal standards. See also question 9.4 of the Commission Q&A published on Eudralex volume 10.

3.2. Secondary use of data and/or biological samples

3.2.1. It is unclear if the data and/or surplus biological samples collected for the purpose of the clinical trial will also be used for future research with other/new purposes. If this is the case, please describe the handling of these data and/or biological samples, inform the trial participant about the intended scope of any future research and make the consent for such future research optional for the trial participant

Recommendation: Sponsors should clearly define the intended scope of any future research involving the collected data and/or biological samples. The PIS/ICF (in the main SIS/ICF or as a separate PIS/ICF which vary per each Member State) should include clear information on the potential future use of data and/or biological samples for the purpose of other clinical trials and for the purpose of the scientific research conducted in the public interest. It should contain information about the purpose and scope of future use, the retention period for biological materials and data, the voluntary nature of consent for future use, the participant's right to withdraw consent at any time without affecting their participation in the main trial. If the scope of future research is not yet defined, sponsors should indicate that participants will be re-contacted to provide specific consent should new research purposes arise.

The collection, storage and future use of personal data and/or biological samples must be in compliance with the requirements of the CTR, General Data Protection Regulation (GDPR) EU No 2016/679 and relevant national legislation. Also, international guidance (e.g. WMA Declaration of Taipei on ethical considerations regarding Health Databases and Biobanks, 2016) may be applicable. Since the requirements may vary per each Member States, the sponsor should contact the Member State as indicated in annex III of the Commission Q&A published on Eudralex volume 10

3.3. Arrangements for post-trial provisions to study medication

3.3.1. The sponsor has made arrangements for post-trial access to the study medication for participants who have responded well on the study medication and might benefit from continued access after the end of trial but the information in the Participant Information Sheet (PIS) is not sufficiently clear about these arrangements , especially the duration of the post-trial arrangements and access to the medicine after this period has ended.

Recommendation: Sponsors should have post-trial provisions arranged before the start of the clinical trial to take care that trial participants can continue the use of the study medication if this has been identified as beneficial and safe and whenever the trial allows it. If post-trial access to study medication is foreseen, specific information about these provisions must be disclosed to participants as part of the informed consent process. This approach aligns with ethical principles outlined in the Declaration of Helsinki.

4. General Recommendations

4.1.1. Comply with the Clinical Trials Coordination Group (CTCG) and Commission guidelines and the Clinical Trials Regulation (i.e. Annex I D17, CTCG guidance on contraception, Recommendation paper on principles of good laboratory practice (GLP).

4.1.2. **Provide all the relevant documentation (i.e. MIA/GMP certificates, latest IB version, data from previous studies, full paediatric investigation plan (PIP) when available). Please provide a list of the document submitted in the cover letter.**

4.1.3. **Provide rationale for changes applied in a substantial modification application and for not following previous scientific advice.**