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Overview of comments received on ICH M11 guideline (EMA/CHMP/ICH/778799/2022)

Please note that comments will be sent to the ICH M11 EWG for consideration in the context of Step 3 of the ICH process.

1. General comments – overview

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ACRO (Association of Clinical Research Organizations)	0	0		The Association of Clinical Research Organizations (ACRO) represents the world's leading clinical research and technology organizations. Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices, from pre-clinical, proof of concept and first-in-human studies through post-approval, pharmacovigilance and health data research. ACRO member companies manage or otherwise support the majority of all biopharmaceutical sponsored clinical investigations worldwide and advance clinical outsourcing to improve the quality, efficiency and safety of biomedical research. ACRO welcomes the opportunity to comment on the ICH M11 Guideline.	
ACRO (Association of Clinical Research Organizations)	0	0		ACRO would welcome an additional section with guidance on a suitable transition period to use of the new template. This should cover guidance on ongoing clinical trials, those in set-up and new trials. Suggested timelines are given in column G.	Suggested additional new text: Clinical trials which are in set-up or ongoing, at the time of publication of the guidance may continue with existing protocol formats. Clinical trials to be submitted for regulatory approval from 1st January 2025 onwards should use the new template.
CSL Behring	0	0	general comment	Section 2.2 of this guideline briefly discusses technical specifications, and it is unclear how, in practice, the technical specifications associated with the clinical electronic structured harmonized protocol are going to be applied and made functional in the template. Is ICH planning to integrate the technical specifications into the template (for example, as macros and a toolbar?) or is it the intent of ICH that integration is going to be left to Sponsors to implement in their templates. Please clarify this issue for reference.	
CSL Behring	0	0	general comment	Section 3 of this guideline notes, with respect to template conventions and design, that "unnecessary repetition is eliminated wherever possible". It is our opinion that the multiple sections of the template add repetition throughout the document.	

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EUCROF - EU CRO Federation	0	0		EUCROF is welcoming the opportunity to provide comments on the ICH M11 (CeSHarP) Guideline and Template. We support the ICH M11 Initiative as standardization of clinical trial documents has proven to contribute to the quality of clinical trials a great deal. Examples are ICH E2F, ICH E3, ICH E6 Chaper 6, ICH E6 Chapter 7. EUCROF is wondering, however, why the CeSHarP Initiative was put under section M (Multidisciplinary) in ICH and not under section E (Efficacy). The topic is a clinical topic and so far, documents for clinical trials are addressed in section E (see above). Maybe this is also the reason why the dissamination of the public consultation did not reach the clinical community as it should have. Many clinical stakeholders were/are not aware of ICH M11.	
EUCROF - EU CRO Federation	0	0		EUCROF is of the opinion that the CeSHarP template is not serving early phase trials in the same way as it does later phase trials. For early phase trials, multiuple sections of the template are not applicable whereas standard early phase protocol sections are not represented in the template. For example, for early phase trials the following sections are needed in order to comply with the European Medicine Agency's "Guideline on strategies to identify and mitigate risks for first-in-human early clinical trials with investigational medicinal products" (EMEA/CHMP/SWP/28367/07 Rev.1: •Graphical overviews, e.g. of trial design and PK/PD modelling •Dose/exposure selection; Dose/exposure escalation rules; trial progression rules •Minimum safety data requirements and rules for Safety Review Committees •Risk mitigation tables •Adaptive study design features and their boundaries •Adverse reaction rules including rules for trial specific adverse effects that need to be prepared for, e.g. hepatic, renal, haematological, cardiac, dermatological, cytokine release related, including rules for Adverse Effects of Special Interest (AESI). Early phase trials are underrepresented in the template. For further comments on early phase trials, we would like to refer to the comments provided by Richmond Pharmacology. Richmond Pharmacology is an Associated Member of EUCROF and specialised in early phase clinical research.	
Jo Haviland, Pragmatic Clinical Trials Unit, Queen Mary University of London	0	0		Where sections aren't applicable for a specific trial should all section headings be retained and N/A indicated, or headings removed & remaining sections renumbered accordingly?	
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	0	0	general comment	We welcome the initiative of the ICH Assembly to develop a guideline for the structure of a trial protocol. This will lead to better structured and more complete protocols.	

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KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	0	0	general comment	The guideline states: "To date, no internationally adopted harmonised standard has been established for the format and content of the clinical protocol to support consistency across sponsors and for the electronic exchange of protocol information". That means that the regulatory bodies involved in the guideline drafting did not consider the SPIRIT Initiative (Standard Protocol Items: Recommendations for Interventional Trials, https://www.spirit-statement.org/). SPIRIT consists of the following main resources: - SPIRIT Statement Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin JA, Doré CJ, Parulekar WR, Summerskill WS, Groves T, Schulz KF, Sox HC, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013 Feb 5;158(3):200-7. doi: 10.7326/0003-4819-158-3-201302050-00583 - Explanation and Elaboration Chan AW, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleza-Jeric K, Laupacis A, Moher D. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ. 2013 Jan 8;346:e7586. doi: 10.1136/bmj.e7586. Checklist - as well as a protocol template which is available online. The SPIRIT 2013 Statement provides evidence-based recommendations for the minimum content of a clinical trial protocol. SPIRIT is widely endorsed as an international standard for trial protocols. The minimum content of a clinical study protocol, as described be the SPRIT initiative, should be considered for this guideline as well. The SPIRIT initiative should be discussed, and relevant publications should be cited.	
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	0	0	general comment	It is described that the ICH M11 Guideline is not intended to supersede other guidelines, nor "to characterize a well-crafted final protocol". However, this will lead to the fact that this template will be not sufficient depending on the national/regional requirements.	

2. Specific comments on text

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	3	4	1,1	The clinical trial protocol does not only describe processes and procedures for the trial conduct and analysis but also provides details on the trial purpose and design. Suggest to expand the explanation of the purpose of the clinical protocol.	The clinical protocol **provides details on trial purpose, objectives, design and its rationale and** describes the processes and procedures directing the conduct and analysis of a clinical trial of medicinal product(s) in humans.
ACRO (Association of Clinical Research Organizations)	4	6	1,1	ACRO welcomes the inention to have an internationally adopted stanadrd for the format and content of the clinical trial protocol to support consistency across sponsors. ACRO members work with multiple sponsors and harmonisation will enable efficiencies in clinical development.	
EUCROF - EU CRO Federation	13	13			Add sponsor representatives or designee as one of the audiences for the guideline and template of Protocol, such as CROs.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ACRO (Association of Clinical Research Organizations)	35	42	1,3	ACRO notes the applicability of the protocol template across all phases of interventional clinical trials and all therapeutic areas. ACRO also notes the use of the term "medicinal product" to refer to any therapeutic, prophylactic, or diagnostic agent including pharmaceuticals, biologics, vaccines, cell or gene therapy products, as well as drug-device combination products when registered as a drug.	
CSL Behring	39	40		Section 1.3 Scope discusses that the terms “medicinal product” in the guideline and “trial intervention” in the protocol template appear to be used interchangeably. It is unclear to us why two different terms are being used between documents when these refer to the same information. Please clarify the relevance of maintaining two terms or consider harmonising the terms across both the guideline and the protocol template.	Proposed change (if any): n/a
EFPIA	39	42	1,3	The definition of "medicinal product”and “trial intervention” refers to drug-device combination products when registered as a drug. This excludes drug-device combinations where the drug component is in development simultaneously with the device component.	Proposal for rewording: '…and drug-device combination products when ~~registered~~ **classified under relevant regulations** as a drug.'
CSL Behring	56	56		Revise the sentence at Line 56 to remove reference to the word ‘design’.	The Template design represents…
ACRO (Association of Clinical Research Organizations)	69	71	2,1	ACRO notes the intention of the template to incorporate recommended and optional text to maintain flexibility. This will be important to ensure the specific needs of any particular clinical trial and/or geography can be sufficiently described.	
EFPIA	81	81	2,2	"Develop a data model based on specifications"	Meaning unclear as written. Do the Tech Specs define this data model, or is the user to create their own data model? If so, would that lead to different dtat models across sponors? Please clarify what is meant here.
EUCROF - EU CRO Federation	89	89			Add sponsor representatives or designee as one of the audiences for the guideline and template of Protocol, such as CROs.
Stephen Bremner	287	288	1,1	For MAMS designs or platform trials, maximum number of arms may not be known	Allow space for a brief note.
Stephen Bremner	289	300	1,1	Statistician not in list roles to blind	Include statistician
Thomas Hamborg, Pragmatic Clinical Trials Unit, Queen Mary University of London	431	431	4,1	The expected number of participants is not an element of the study design and not referred to again in the subsequent more detailed suggestions in this section	Suggest deleting 'the expected number of participants'
Richard Hooper, Pragmatic Clinical Trials Unit, Queen mary University of London, UK	450	452	4,1	The CONSORT statement elaboration document says the following regarding the terms "single blind" and "double blind": "This research shows that these terms are ambiguous and, as such, authors and editors should abandon their use. Authors should instead explicitly report the blinding status of the people involved for whom blinding may influence the validity of a trial."	Guidance should ask authors to explicitly report the blinding status of the people involved for whom blinding may influence the validity of a trial, rather than recommneding the terms "single blind" and "double blind".
Thomas Hamborg, Pragmatic Clinical Trials Unit, Queen Mary University of London	450	452	4,1	The instruction to describe level and method of blinding in given within the suggestions for Method Of Assignment to Trial Intervention. Blinding is indepdent of assignment method and should be described separaetly from assignment within Trial Design	Move lines 450 - 452 to after line 455
Thomas Hamborg, Pragmatic Clinical Trials Unit, Queen Mary University of London	683	699	6,6	The ratio with which participants are allocated to different treatment arms is a key component of the randomisation procedure. Yet the template does not include a requirement to specify the allocation ration anywhere.	Suggest adding instruction to specify allocation ratios to each trial arm. Section 6.6.2 seems most suitable to me.
Jo Haviland, Pragmatic Clinical Trials Unit, Queen Mary University of London	793	797	7,4	Should the Trial Stopping Rules section also refer to formal interim analyses (that use stopping rules) specified elsewhere in the protocol?	Add reference to section where formal interim analyses with stopping rules are described in the protocol

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Jo Haviland, Pragmatic Clinical Trials Unit, Queen Mary University of London	868	875	8.4.3 & 8.4.4	Should the measurement tool for capturing AEs be reported in this section (e.g. CTCAE, as appropriate), or would this fit better in Appendices 12.3 & 12.4?	
Richard Hooper, Pragmatic Clinical Trials Unit, Queen mary University of London, UK	1006	1007	9	I don't understand what kinds of circumstances should be described here, or why a separate statement is required here at all, when the rest of section 9 expands on the primery analysis. The example suggested in the guidance is "The analysis will be conducted on all participant data at the time the trial ends", which would be common in many trials but seems unnecessary to state. What alternatives might be specified instead? Is this section getting at the possibility that e.g. only a subset such as "compliers" would be included in the primary analysis? But this has to do with estimands, and needs more careful description in the relevant subsections of section 9.	Either remove the guidance saying "Provide a statement with regard to when the primary analyses will be conducted. For example: The analysis will be conducted on all participant data at the time the trial ends", or provide cleareer guidance and more examples if this statement is still essential to include at the start of Section 9.
Richard Hooper, Pragmatic Clinical Trials Unit, Queen mary University of London, UK	1010	1011	9,1	What is an "analysis set"?	Provide more guidance on what an analysis set is.
Stephen Bremner	1010	1011	9,1	Unclear exactly what information is expected here	Add headings/table e.g. file name, location & date
Jo Haviland, Pragmatic Clinical Trials Unit, Queen Mary University of London	1013	1070	9.2 - 9.6	Although the explanatory text under the section 9.2 heading states that this section "*introduces* the Statistical Analysis Plan" the contents suggested under the sub-headings suggest very detailed information should be given. Presumably it isn't the intention that the protocol contains the full SAP?	Suggest add a sentence (possibly under secion 6 heading) to the effect that full details will be included in the full Statistical Analysis Plan.
Thomas Hamborg, Pragmatic Clinical Trials Unit, Queen Mary University of London	1055	1055	9.2.5	Description of Supplementary Analysis is very brief. Further guidance might be helpful	Explanation of Sensitivity Analysis (9.2.4) was copied from the Glossary of ICH E9(R1) addendum on estimands. Suggest doing the same for the Supplemenary Analysis section
Thomas Hamborg, Pragmatic Clinical Trials Unit, Queen Mary University of London	1094	1100	9,8	Sufficient information should be provided so that the sample size calculation can be reproduced. For comparions between arms a key component is the assumed difference between arms in terms of the primary outcome (usually MCID). A justification for this or reference to where this justification can be found should be provide.	Add sentense to instruct providing a reference to the assumed between group difference where applicable.
Jo Haviland, Pragmatic Clinical Trials Unit, Queen Mary University of London	1184	1208	12	See my comment for sections 8.4.3 & 8.4.4 above. Should the AE / SAE measurement tool be described in the appendix? (e.g. CTCAE etc)	