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SCIENCE MEDICINES HEALTH

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20 May 2025
EMA/138236/2025

Overview of comments received on ICH M11 technical specification during second consultation (EMA/CHMP/ICH/778800/2022)

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
EORTC	0	0	281	Trial Design Examples: The section provides a good overview of trial design but lacks specific examples of different trial designs (Section 4.1).	Include examples of different trial designs to provide clearer guidance.
EORTC	0	0	295	Rationale for Trial Endpoints: Include a discussion on the rationale for choosing specific trial endpoints (Section 4.2.1).	Discuss rationale for choosing specific trial endpoints.
EORTC	0	0	488	Summary Table of Assessments: Include a table summarizing key assessments and procedures to enhance clarity (Section 1.3).	Include a table summarizing key assessments and procedures.
EORTC	0	0	215	Long-term Effects: The section might include an assessment of potential long-term effects of the trial intervention (Section 2.2.3).	Add assessment of potential long-term risks and benefits.
EORTC	0	0	349	Contraceptive Use: Contraceptive use requirements should be split between men and women in clinical studies, based on local regulations (Section 5.4.2).	Contraceptive use by [men and women] should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. a.Male participants: b.Female participants:
EORTC	0	0	293	If applicable, describe any stakeholder (e.g., patient, healthcare professional and patient advocacy groups) involvement in the design of the trial and any suggestions implemented	Specific section on patient engagement and feedback mechanisms (more elaborate).
EORTC	0	0	0	Provide a visual example of the trial schema to demonstrate the required format and content.	
(Gilead Sciences)	0	0	N/A	I assume there will be training materials eventually provided that fully describe that the techinical specification in and how it should be implemented for a sponsor. While I conceptually understand the purpose, when you get into the document it is not immediately clear how and why this all alignes with the elements in the template whether headings or section contents. Had to do a lot of basic work trying to figure this out on my own.	

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA, company 6	0	0		General comment for multiple sections: It would make sense to not include user guidance when something is just a header and instead put the detailed guidance with the subsections to which the information pertains. For example see Section 5.4 (line 344) where the user guidance for the heading is "No text is intended here (heading only)". In contrast, see Section 1.1.1 (line 116) where the definition is indicated as heading, but detailed user guidance is provided. This same user guidance is already repeated in the relevant area (line 117), so recommend to remove it from line 116 and replace it with the statement "No text is intended here (heading only)".	
EFPIA, company 4				General comments about the structure and format of the document itself: •There could be some additional explanations in the Tech Spec to make it more "user friendly". For example, there are references given to controlled terminology like C181236 and CNEW, but no explanation of what these references mean or where to find the corresponding controlled terminology. The numbered codes can often be found elsewhere in the Tech Spec but CNEW is used repeatedly often to point to definitions that are "nearby" in the document. •It would be helpful to publish Tech Spec in alternate format that allowed selection or sorting say by field types so you could more easily see all "heading" variables or all mandatory vs optional variables, etc., and in general view the variables in different ways. It's difficult to read sequentially through a 280 page document like this. •The way different terms/variables are represented is non-intuitive. For example , for variables that have a fixed constant value the name of the variable = the value specified (e.g. the heading variable Full Title only takes a value of "Full Title") which make sense. But for variables that take different values the value specification repeats the field type, which I don't think is correct (or at least is not explained). For example, the variable <full title> (Item 14), is shown as having a Data Type = text and a Value = text. In my understanding the value is not "text" but rather the value is whatever title is stated for the specific protocol being specified.	
EUCROF	0	0		How should the subject key be specified? Yes, this is something specific to EDCs, but this is not trivial. The subject key should be generated in such a way that it will be unique within that study (not possible to duplicate), and its format should be specified: how many digits, numbers/letters, prefixes, does it change after enrollment, etc.?	Consider adding a section for generation of pseudo-ananomous yet unique identifiers.
EUCROF	0	0		The subject status conditions are not defined. "Enrolled" is used ubiquitously, but this variable is not defined.	Suggest guidance to define what "enrolled" will mean exactly within the protocol. Such as, randomized or signed informed consent (both are commonalities, which is why the industry needs more standardization with this term).
EUCROF	0	0		Units for collected data should be specified. It would save the industry a lot of time and math if we standardized the units when collecting data. For example, Celsius versus Fahrenheit for temperature, SI units for lab parameters, cm for height, kg for weight, etc.	Provide guidance towards standardized units, particularly for laboratory assessments (SI units), temperature, height and weight.
Syneos Health CRO	0	0	0	Overall, the Technical Specification was comprehensive in scope and will lead to fewer revisions, clarifications, and amendments. While comprehensive, the document mainly focuses on the requirements of late phase trials. In particular, Early Phase trials use endpoints rather than estimands.	It is recommended to include detailed guidelines for early phase trials, specifically addressing the use of endpoints rather than estimands.

2. Specific comments on text

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
LFB	1	781		Thank you for this technical specification document. In 2023 we submitted our comments on the M11 Technical Specification and the Protocol Template. It appears that our comments on the technical specification has been taken into account. As this is a technical document linked to the protocol template, LFB has no further comments.	
EORTC	5	5	331	Handling Vulnerable Populations: The document could benefit from additional details on handling vulnerable populations, such as children, pregnant women, and the elderly (Section 5.1).	Add details on handling vulnerable populations. There is no dedicated sections on diversity and inclusion.
EORTC	5	0	439	Specify who will be responsible for this decision.	In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted
(Gilead Sciences)	6	7	N/A	Some of the rows (eg, data type, cardinality, confirmance) should provide clear definitions of the options that will be seen in all of the entires similar to what is provided for business rules. For example - what does one to one, wone to version number and other options mean?	
EFPIA, company 3	6	7		Term=Value: ")" missing and "." at the end should be removed	
EFPIA, company 3	6	7		Term=Business rules: Value Allowed: First sentence need re-wording, meaning is not clear.	
EFPIA, company 5	26	26	Amendment identifier	Business rule not clear and misleading about the allowed value and what to set in case of originale protocol	Value Allowed: Yes; if Original Protocol = No; blank if Original Protocol = Yes Relationship: Table Row Heading, Sponsor Protocol Identifier Concept: CNEW
EFPIA, company 5	27	27	Amendment identifier	Business rule not clear and misleading about the allowed value and what to set in case of originale protocol	Value Allowed: Yes; if Original Protocol = No; blank if Original Protocol = Yes Relationship: Table Row Heading, Sponsor Protocol Identifier Concept: CNEW
EFPIA, company 3	32	33		Term=Value: it is not clear if Alpha 2 or Alpha 3 country codes should be used. Should be clarified.	
EFPIA, company 5	39	40	Trial phase	Value does not contain the option "other", whereas the preferred terms presented in the table line 40 does contain the option "Other" (code C17649). In addition, a bracket is repeated 3 times where only one is needed in line 39, section on value.	add "other" to the list of values in line 39, and correct a typo as a bracket is repeated 3 times: Early Phase 1 (C54721); Phase 1(C15600); Phase 1/Phase 2 (C15693) Phase 1/Phase 2/Phase 3 (C198366); Phase 1/Phase 3(C198367); Phase 2(C15601); Phase 2/Phase 3(C15694); Phase2/Phase 3/Phase 4(CNEW); Phase 3(C15602); Phase 3/Phase 4 (CNEW); Phase 4 (C15603))); Other (C17649)
Syneos Health CRO	40	40	0 (Page 15)	We would propose the definition to be as following: First-in-human trials, in a small number of participants, that are conducted before Phase 1 trials and are intended to assess new candidate therapeutic and imaging agents. The study agent is administered at a low dose for a limited time, and there is no therapeutic or diagnostic intent in patients or healthy volunteer participants (…).	

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Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA, company 4	45	45	Title page - Sponsor Legal Address (User guidance)	It would be useful if guidance clarified the sponsor legal address to avoid any confusion on if this refers to "head office" or the country affiliate address where the trial is being run.	May not require an update but question for clarification
EFPIA, company 5	45	45	Sponsor legal address	user guidance sections says "provid the legal name of the individual…", but this should be the legal address	modify to: Provide the legal ~~name~~ address of the individual or pharmaceutical or medical device company, governmental agency, academic institution, private organisation, or other organisation who takes primary responsibility for and initiates a clinical investigation. If more than one Sponsor, list the Primary Sponsor address in this field.
EFPIA, company 1	47	48		<Co-Sponsor Name> Since there could be more than 1 co-sponsor, please consider making this data element repeatable.	Please change the "Repeating and/or Reuse rules" from "no" to "Yes, repeatable for each co-sponsor." If this change is accepted by the EWG, a similar change is needed for the next data elements "co-sponsor legal address"
EFPIA, company 5	48	48	Co-sponsor legal address	user guidance sections says "provid the legal name of the individual…", but this should be the legal address	modify to: Provide the legal ~~name~~ address of the individual or pharmaceutical or medical device company, governmental agency, academic institution, private organisation, or other organisation who takes primary responsibility for and initiates a clinical investigation. If more than one Sponsor, list the Primary Sponsor address in this field.
EFPIA, company 1	51	51		<Local Sponsor Address> The previous data element "Local Sponsor Name" is repeatable for each local sponsor. The local Sponsor address also needs to be repeatable. Unless this is addressed by the cardinality "one to Local Sponsor" in line 51, the "Repeating and/or Reuse rules" should make this element repeatable	Please change the "Repeating and/or Reuse rules" from "no" to "Yes, repeatable for each local sponsor"

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