EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000
An agency of the European Union

24 May 2023
EMA/CHMP/ICH/778801/2022

Overview of comments received on ICH M11 template (EMA/CHMP/ICH/778801/2022)

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 notes that the Template reflects the standard requirements for protocol contents as noted in Part D of Annex I of the EU Clinical Trial regulation.	
ACRO (Association of Clinical Research Organizations)	0	0		ACRO would welcome provision of an editable version of the template for ease of implementation.	
Boehringer Ingelheim	0	0		Template does not include an investigator's agreement signature page.	Include investigator's agreement signature page, or propose a specific section for a signature page.
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	0	0	0	Limited space to the description of monitoring activities. no mention of auditing activities.	suggest describing in detail the methods of monitoring and auditing during the clinical trial
CSL Behring	0	0		Within the Protocol Template section 0.3 (Template Conventions and General Instructions), the table outlines 'Fields' as a type of text. It is not clear from the 'Typeface Details' column if once a particular selection option or free text has been selected for a field, if all other fields of the same type are then auto populated. Please clarify if the template will be set up to auto-populate information fields.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
CSL Behring	0	0		The draft template document refers to 'Trial' throughout e.g., Trial Objectives, Trial Design etc. We suggest that the document be updated to refer to 'Study' in place of trial for consistency throughout the entire document.	
CSL Behring	0	0		As a general observation, it appears that the ICH expert working group does not plan to include example/recommended text blocks in this template. From a Sponsor's perspective, the availability of examples of text that would be considered appropriate can be helpful when drafting clinical study protocols (CSPs). Thus, would ICH consider generating a full "model CSP" including example text to be used as a guide for sponsors when drafting CSPs?	
CSL Behring	0	0		In general, we understand that Level 3+ headings are intended to be able to be modified, deleted etc. as they may not always be applicable to a particular clinical study protocol. Assuming this to be the case, shouldn't these headings all appear in blue font text throughout the template, to clearly denote that they are optional fields?	
CSL Behring	0	0	1,1	Section 1.1 Protocol Synopsis, commencing from Line 255, discusses committees in some detail. Section 10.2 of the template also discusses committees in the context of general considerations relating to regulatory, ethical, and trial oversight. As a general comment, we question why the guidance in the synopsis section 1.1 is more detailed than the guidance presented in the section that is specifically relevant to 'committees' and suggest the drafting team may wish to revisit this.	
EFPIA	0	0		[Minor] Recommendation to check for consistent use of group vs arm, and unless there is a strong rationale why one is preferred over the other, please consider flexibility in the use of arm vs group in the required text, as long as the protocol uses one or the other consistently throughout. It will create significant difficulties for sponsors that need to update standards, and all participant facing materials to align.	
EFPIA	0	0	0	There are several "required" sections per the technical specification that may not be applicable to all trials. The guidance text in some of those sections state "if applicable....", so it seems these sections would be blank if they are mandatory sections. Should they instead be optional if they are not applicable to the trial? As one example (although there are many), all the medical device sections and sub-sections (chapter 8) are in black text in the template and are listed as required in the conformance field of the technical specification.	
EFPIA	0	0	0	Should details about interim analysis in the synopsis? Not currently included.	
EFPIA	0	0		ICH E9(R1) provides a framework to align planning, trial design, conduct, and analysis (+interpretation).	Consider adding instructional text to remind authors that trial design aspects (eg, in Sections 4, 6.3, 6.7, 6.8, 7.1) as well as the description of how to perform the statistical analysis (Section 9) need to be aligned with the estimands defined in Section 3.
EFPIA	0	0	0	In section 0.3, Level 3 except 8.4 is described "Do not delete" and black font text should appear in all protocols. But, most of Lebel 3 section titles are used black font. Therefore, all L3 section titles should be changed to blue font.	All Level 3 section titles except 8.4.x change to blue font
EFPIA	0	3	0	It is a well-structured guidance and template document. We understand that the intent of ICH M11 protocol template is to present the format and structure of the protocol (including the table of contents, common headers, and contents). We like the structure and flexibility of the template, that can be applied across all phases of clinical trials and across therapeutic areas. However, we think some sections are missing and will add value to bring them as part of protocol structure (e.g., analysis plan for demographic/baseline characteristics, treatment exposure, pregnancy testing assessment). In addition, we believe that some instructional text could be more informative to make the template more informative for users. For example, estimand related sections can benefit from more instructional text on how it ties to trial objectives and analysis (given this is a new concept to non-statisticians).	
EFPIA	0	0		Overall positive that the template is not too detailed so it allows for flexibility and for sponsors to tailor it to own needs.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	0	0		We request changing to the use of 'study' instead of 'trial' to align with ICH E8(R1), and to ensure clarity on the broad scope of this template. We question the choice of the term 'trial' instead of 'study' to denote interventional studies. 'Study' is clearly the broader term and is needed to reflect the many types of studies that are in scope for this template, if it is to cover 'all phases of clinical research and all therapeutic areas' as stated in section 0.2. The use of 'trial' is far more restrictive in its meaning. In ICH E8(R1) from 2021, the term 'study' is used throughout, including in the Annex, where the many types of interventional studies are characterised (e.g. clinical pharmacology studies, exploratory studies, dose finding studies, safety studies, etc. all of which are meant as interventional.	Please use 'study' instead of 'trial' throughout.
EFPIA	0	0		Please clarify more clearly what is considered mandatory in the template and what is considered as recommendations. This applies to both the Title page information (including the sequence of rows), as well as the headings and texts within the document. There are numerous inconsistencies in the use of the various fonts, and that leads to lack of clarity.	
EFPIA	0	0		The Template Conventions are not used consistently throughout the document. Examples are provided in the detailed comments. Since the interpretation of the template is highly dependent on clear and consistent use of the various 'typeface details', they need to be used consistently.	
EFPIA	0	0		It is unclear whether non-integral medical devices that do not fall under 'drug/device combinations intended to be registered as drugs' are included in the scope of this template. There are several mentions of 'investigational devices' that would indicate that, including the reference to EUDAMED on the Title Page, but from the scope under section 0.2 only drug/device combination products registered as drug are in scope. Please clarify further and resolve the discrepancies.	
EFPIA	0	0	M11 Template	Context: expanded use of non-traditional data sources (e.g., EHRs/EMRs, Digital Health Tech., Direct Data Capture, etc.) As RWD becomes more common to support protocol data collection procedures/activities, we suggest mentioning or including a section that allows for a consistent description and design of those items. For example, the use of RWD using tokenization methodologies and the provenance of such data from the provider/producer and its use within the clinical trial. The content to be included should be flexible to accommodate as much detail as required to ensure transparency and clarification of such data sources and their processing activities (e.g., standardization mappings, transformations, etc.). Note: Existing sections to support this can include, but are not limited to, 11.3 Source Data, as part of 9 Statistical Considerations, or via a new Appendix.	
EFPIA	0	0	M11 Template	Context: electronic reporting outcomes and clinical assessments We suggest including a consistent sub-section under 8.3 Safety Assessments and Procedures pertaining to ePROs, eCOAs, etc.	
EFPIA	0	0	Protocol Title Page	Protocol Title page envisages two version numbers: protocol version number and amendment number. It is unclear how these numbers are to be used in conjunction.	It would be important to establish clear and unambiguous versioning standards. Is it not sufficient to either use protocol version, i.e. protocol v1 upon first amendment becomes v2. For the local amendments, they become V1-country suffix, and upon first global amendment all local amendments are incorporated in global protocol v2. There is no need in this case to separately list amendment number. Or, alternatively, we keep protocol number - without version - for the original protocol instance, and then only number subsequent amendments.
EFPIA	0	0		Bookmarks would be really useful for the navigability of this document.	Please add bookmarks to the document.
EFPIA	0	0		Will this template and the TransCelerate common protocol template be aligned, particularly with regard to information that is currently in appendices in the common protocol template.	
EFPIA	0	0		The terms "treatment group", "trial intervention" and "trial arms" are use interchangeably. Please pick one convention to use throughout or provide instruction on how to choose the appropriate one.	Please harmonize the convention used for describing trial intervention.
EFPIA	0	0		This template is mostly focused on the concept of confirmatory trials including estimands. Pilot studies are only mentioned in Section 9.8, Sample Size Determination. Please consider adding a paragraph in the beginning of the document to talk about the requirements for Phase 1 studies.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA/EFSPI Estimand Implementation Working Group	0	0	-1	General comment: Thank you very much for the opportunity to review ICH M11. The EFPIA/EFSPI Estimand Implementation Working Group and the EFPIA/EFSPI Regulatory ESIG greatly appreciates having a standard template with a sufficient level of flexibility, which the current template offers to sponsors. We have four major concerns: 1) A clinical/regulatory rationale for the primary and key secondary estimands should be included in the protocol 2) Section 9 should include a level 2 section named e.g., "General Considerations" where topics that apply across objectives can be described 3) Not all trials will do hypothesis testing. Some trials aim for estimating a treatment effect to support decision making, so terminology like "hypothesis testing" should not be assumed 4) The template should accommodate different understandings of what the "Analysis Sets" section should include and where to describe data points selection Details on each of the four main topics can be found in the specific comments below.	1) The instructional text in section 3 should be updated with a request to provide a rationale for the primary and key secondary estimands 2) Add a section 9.1 section named "General Considerations" with instructional text recommending level 3 sections on different topics that are common across objectives, e.g., the details of how intercurrent events and the chosen strategies impact estimation methods (may include discussion around analysis sets, selection of data points and handling of missing data), type 1 error control, decision criteria, etc. 3) Replace the wording "hypothesis testing" in section 9.1.2 with a more neutral terminology, e.g., "decision criteria" 4) Data points selection should be included as a topic, allowing for flexibility in terms of where this is discussed; it could be in the analysis sets section, whilst discussing how intercurrent event strategies align to estimation methods (in Impact of Intercurrent Events Strategies sub-section of General Considerations section or in the analysis section itself). Instructional text should be added in all three parts of the statistical considerations section to allow for that
EFPIA/EFSPI Estimand Implementation Working Group	0	0	-1	General comment: Change in structure is proposed in Section 9 Original Structure: 9.1 Analysis Sets 9.2 Analyses Supporting Primary Objective(s) 9.2.1 Statistical Model, Hypothesis, and Method of Analysis 9.2.2 Handling of Intercurrent Events of Primary Estimand(s) 9.2.3 Handling of Missing Data 9.2.4 Sensitivity Analysis 9.2.5 Supplementary Analysis 9.3 Analysis Supporting Secondary Objective(s) 9.4 Analysis of Exploratory Objective(s) 9.5 Safety Analyses 9.6 Other Analyses 9.7 Interim Analyses 9.8 Sample Size Determination 9.9 Protocol Deviations	9.1 General Considerations 9.1.1 Decision Criteria 9.1.2 Multiplicity Adjustments 9.1.3 Impact of Intercurrent Event Strategies 9.1.4 Handling of Missing Data 9.2 Analysis Sets 9.3 Analyses Supporting Primary Objective(s) 9.3.1 Endpoint Derivation(s) 9.3.2 Main Analysis (Estimand Label) 9.3.3 Sensitivity Analysis (Estimand Label) 9.3.4 Supplementary Analysis 9.4 Analysis Supporting Secondary Objective(s) [9.4.1-9.4.4 subsections as required.] 9.5 Analysis Supporting Exploratory Objective(s) 9.6 Safety Analyses 9.7 Other Analyses 9.7.1 Subgroups 9.8 Interim Analyses 9.9 Sample Size Determination
Estimand Review team	0	0		The text should be written consistently in British English or all in American English.	
Estimand Review team	0	0		Estimands should be part of Section 1	See our proposals
Estimand Review team	0	0		Several Guidelines are mentioned throughout the document, for example ICH E9 and E9(R1). Maybe add "..., current version" to make sure that M11 referes to the latest version in case of future updates?	
EUCROF - EU CRO Federation	0	0			Suggest addition of a Pharmacodynamic section. See also general comment on early phase trials.
EUCROF - EU CRO Federation	0	0	Section 10.3	It would be helpful to also suggest text here regarding the possible need for an ICF for Pregnant Partner Follow-up since that is often needed.	Add instructional text as per cpmment.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUCROF - EU CRO Federation	0	0			Add a section in the Protocol template to refer to publication of trial results (final and /or interim), irrespective of trial outcome, depending on local or regional requirements.
Eva Degraeuwe, Ghent University, BPCRN	0	0	0	For the interpretation of the guideline, it would be advisable to include a template protocol that is completed according to standards, to that there is less confusion in regards to wording as well as to increase efficiency.	
Eva Degraeuwe, Ghent University, BPCRN	0	0	13,3	13.3 discusses country/region specific difference however for the reporting almost all countries have a different procedure. It would be advisable to include a recommendation for sponsors to collect this information beforehand and how it will be collected, rather than having them think on it at the end of the protocol (including an example).	
Eva Degraeuwe, Ghent University, BPCRN	0	0	0	The collection of SAE's - to include information how this will be tracked from a sponsors perspective: software date and location of licensing, GDPR protection, disclosure information	
Freeline Therapeutics	0	0	Title page	Suggest do not use 'CESHarP' as it is a contrived nickname and the words that have been thought up to fit it creates a cumbersome title. A nickname is not needed for a document like this.	Use the title 'Protocol Template'.
Freeline Therapeutics	0	0	13,4	Include a table for every amendment, including the current amendment, to provide a cumulative record of the amendment history in 1 complete protocol document which will streamline the Clinical Study Report (only need to include 1 document in CSR Appendix 16.1.1). As noted above, these amendment history tables should be all together in an appendix not as part of the title page and a numbered section.	Include a table for every amendment, including the current amendment. Move all amendment information into an appendix.
Freeline Therapeutics	0	0	NA	We would usually have a Level 1 section on Data Mnaagement (the collection and processing of data ie describe how data will be collected; state which, if any, data will be recorded directly onto the CRF and so is to be considered be be the source data in itself. Is this section 11.2? It is not clear and anyway would be better placed before Statistics section in a logical flow of trial activities.	Consider if a Data Management section is needed.
Freeline Therapeutics	0	0	0	Should Sections 10 or 11 include: monitoring at the site, publication policy (CSR;manuscripts), insurance/indemnity, financial disclosure, retention of records at site, audits/inspections.	Consider if Sections 10 or 11 (or preferably 1 combined 'General Considerations' section) should include subsections on: monitoring, publication policy, insurance/indemnity, financial disclosure, retention of records, & audits/inspections.
Interpharma, Association of Switzerland's research-based pharmaceutical industry	0	0	0	It is a well-structured guidance and template document. We understand that the intent of ICH M11 protocol template is to present the format and structure of the protocol (including the table of contents, common headers, and contents). We like the structure and flexibility of the template, that can be applied across all phases of clinical trials and across therapeutic areas. However, we think some sections are missing and will add value to bring them as part of protocol structure (e.g., analysis plan for demographic/baseline characteristics, treatment exposure, pregnancy testing assessment). In addition, we believe that some instructional text could be more informative to make the template more informative for users. For example, estimand related sections can benefit from more instructional text on how it ties to trial objectives and analysis (given this is a new concept to non-statisticians). Please see the following line comments with details on suggested modifications.	
Interpharma, Association of Switzerland's research-based pharmaceutical industry	0	0	0	After the section where all the analyses are presented, it would be good to have a section detailing the plans for publication of the data. This should include: - Plans to publish data at congresses and in journals - Plans to make datasets available to the (scientific) public - Plans to prepare layman summaries for participants and the interested general public	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	0	0	general comment	We miss the following items, that are described by the SPIRIT initiative for evidence-based recommendations for the minimum content of a clinical trial protocol: 28: Declaration of interests 29: Access to final data set 31: Dissemination policy These items should be mandatory for trial protocols and should be included in this template. Additionally, we are missing statements on the following: Publication policy, patient participation, participation in more than one clinical trial, inclusion of dependent individuals, rationale for sex and age distribution. These should be considered to be included in the ICH M11 protocol template, as well.	
LFB Biotechnologies	0	0	6	It is not clear if AxMP should be treated as a trial intervention in sections 6.1 to 6.5 or in Section 6.8.4 other therapy	Clarify or split 6.1.1. IMP and 6.1.2 AxMP
LFB Biotechnologies	0	0	8.4	Special situations (abuse/misuse/medication error/occupational exposure) are not cited	would be interesting to add a paragraph for special situations (in section 8.4: for instance 8.4.11 Special situations: abuse, misuse, medication error, occupational exposure)
LFB Biotechnologies	0	0		There is no section regarding the handling and the management of the data during the clinical trials and record keeping. It could be interesting to add a short section to precise how the data will be collected, which tools will be used, that the tool should be conform to the requirement of the standard industry, that the data will be validated, reviewed, coded, reconciled in accordance with GGP-ICH-E6, what will be the format of the datasets after the database lock for statistical analysis.	The following section could be proposed after Statistical section to describe briefly how the data will be managed '10.6- Data collection and management responsabilities'.
LFB Biotechnologies	0	0	8.4	Art 41 4. If the investigator becomes aware of a serious adverse event with a suspected causal relationship to the investigational medicinal product that occurs after the end of the clinical trial in a subject treated by him or her, the investigator shall, without undue delay, report the serious adverse event to the sponsor	add a section for the description of the reporting of Serious Adverse events related to IMP occured after the end of the trial
LFB Biotechnologies	0	0	cover page	sponsor Name and address' According to Reg (Eu) 536/2014, there is a possibility of co-sponsorship (ART 72 _ "where a clinical trial has more than one sponsor, all sponsors shall have the responsibilities of a sponsor set out in this Regulation, unless the sponsors decide otherwise in a written contract setting out their respective responsibilities") in this particular case where no contract is in place, it cannot possible to list 'primary sponsor'	the sentence 'if more than one Sponsor, list the primary Sponsor in this field' could be replaced by 'if more than one Sponsor, list in this field, the primary Sponsor or all sponsors if responsibities not determined in a contract"
LFB Biotechnologies	0	0		No clear section to mention the participation of a potential CRO	suggest to mention it after chapter 1 or in the section related to the trial organization
LFB Biotechnologies	0	0	9	There is no mention of baseline descriptive analyses in the statistical section, but it could be part of secion 9.6, "Other analyses" (lines 1068, 1069)	For the sake of clarity : "Describe Other Analyses such as Subgroup analyses, Adjusted analysis, Baseline descriptive analyses if needed"
PTC Therapeutics, Inc.	0	0	0	For clarity, it is important to have the protocol version number on every page.	PTC recommends to include version number in the header or footer of all pages as a mandatory field.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Quotient Sciences	0	0	0	In general, the template (particularly the summary) is much better suited to large, late phase trials rather than complex-multi-part phase 1 trials in healthy volunteers, such as first in man trials comprising single and multiple ascending dose parts, a food effect part and parts to assess the effect of age, sex and ethnicity. To accommodate early phase multi-part trials, more flexibility is needed to allow meaningful information to be presented in the summary. In addition, based on many years' experience, it is essential for first in man trials that all stopping criteria - participant dose stopping criteria and withdrawal criteria; dose escalation stopping criteria; and trial stopping criteria - be located in a single clearly labelled section. Having dose esclation stopping criteria remote from other stopping criteria hinders compliance. It is also essential that there be a clearly labelled section (Dose Escalation Criteria) that contains all dose escalation criteria for a first in man trial. The rules for escalating the dose must be clear, together in one place, and easy to locate, or compliance may be compromised.	Please consider the needs of complex, multi-part phase 1 trials in healthy volunteers. Dedicated sections containing all stopping criteria and criteria for dose escalation are essential for first in human trials.
Quotient Sciences	0	0	0	Some level 3 headings won't be applicable to phase 1 healthy volunteer trials. Where some level 3 headings under a single level 2 heading are applicable and some are not, should all level 3 headings be retained with 'Not applicable' entered under irrelevant headings? Or can we delete some of the level 3 headings (which would result in renumbering of the remaining level 3 headings)?	Please clarify whether *some* level 3 headings under a single level 2 heading can be deleted.
Quotient Sciences	0	0	0	There is very limited contact information in the protocol template. ICH E6 specifies that the protocol should include name and contact details of the sponsor's medical expert, and the name and address of the monitor, clinical laboratories and other medical and/or technical departments/institutions involved in the trial.	Please confirm whether ICH E6 will be updated to specify that those additional contact details should be documented outside the protocol.
Quotient Sciences	0	0	0	Investigational Medicinal Product' ('IMP') would be preferable to 'Trial Intervention'. It is more descriptive, as it clarifies that the products are experimental and that they are intended to provide medical benefit. All of the examples given in the Terminology section (lines 38-43) could be described as investigational medicinal products.	Replace 'Trial Intervention' with 'Investigational Medicinal Product' throughout the template.
Rebecca Leary, Newcastle University	0	0	0	It is helpful to specify core items to include in a protocol but linking to vocabularies would increase data harmonization.	
Richmond Pharmacology Dr Jörg Täubel Dr Ulrike Lorch Dr Andrew Stokes Dr Edward Jackson Dr Saqib Mir	0	0		I. Introduction Richmond Pharmacology appreciates the opportunity to offer feedback on the ICH M11 (CeSHarP) protocol template currently being developed. As an organization owned and managed by very experienced and distinguished Principal Investigators and Co-investigators, we are experts in early phase clinical research. Many of the trials we perform are first-time-in-human (FTIH), including healthy and patient participants, the latter often with rare diseases. The investigational medicinal products (IMP) researched in our trials are mostly biologicals and advanced therapies, including in-vivo genome editing therapy. The sponsors of our clinical trials are mainly based in all regions of the founding regulatory members of ICH. Our comments and proposals stem from three decades of continuous practical experience as early phase investigators. We are training a new generation of early phase investigators who will see many advances in clinical research. We wish to train and guide this next generation of investigators to safely respond to such advancements with flexibility and ingenuity.	To enable us to continue designing and performing safe and innovative early phase trials that provide fast patient access to new and advanced therapies, we request that the EWG considers the following three potential solutions: 1. Exemption: Should ICH wish to continue developing the template in its current format and content, we would request a clear statement in the ICH M11 guideline that exploratory early phase clinical trials are explicitly exempted from the use of the proposed protocol template. 2. Creation of a platform using conditional formatting and input to distinguish between exploratory and confirmatory trials: Rather than developing a one-size-fits-all template, ICH could, in collaboration with subject matter experts, develop an electronic platform that allows conditional input of protocol sections required for the two main categories of trials. Using appropriate filters, the platform would ensure that only those sections are presented that collect and collate data appropriate for the category of trial. There could be mandatory sections that are presented for all trials once the relevant category has been selected, and optional modules that can be opened and completed as needed.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Richmond Pharmacology Dr Jörg Täubel Dr Ulrike Lorch Dr Andrew Stokes Dr Edward Jackson Dr Saqib Mir	0	0		We fully support some of the aims of the ICH M11 initiative. However, we are deeply concerned about ICH's concept of achieving these aims with one protocol template that should be used globally for all categories of interventional clinical trials, and for all phases of clinical research. Such a concept is likely unhelpful for the design and conduct of most early phase clinical trials. Consequently, many parts of the proposed template are either superfluous to what early phase clinical trials need or, even more disconcertingly, the template is missing many essential sections required to ensure participant safety and feasible practical conduct of early phase trials. A distinction should be made between the two categories of early phase/exploratory and later phase/confirmatory trials. Confirmatory trials may benefit from a template as suggested in the draft guideline. Exploratory trials should do just as their name says: they need a much greater degree of flexibility, in addition to specific risk management modules to deal with unexpected findings.	3. Creation of a publicly accessible library of best-practice modular protocol sections, from which stakeholders can choose those that are relevant for a clinical trial, and which are kept up to date by all relevant subject matter experts. This would be the most adaptable, collaborative, up to date, and least prescriptive approach. It could be compared to the very helpful initiatives and guidelines provided the Heads of Medicines Agencies' Clinical Trials Coordination Group (CTCG), e.g. on contraception and complex clinical trials. We provide the rationale for our proposals in the following sections of the response, focusing on key themes presented by the ICH Expert Working Group in the draft ICH M11 guideline, and during the presentations given at a public webinar on 26 January 2023: i. Electronic transferability of modular protocol sections ii. Time and cost savings during drug development to improve patient access iii. Practical use of an "off-the-shelf" protocol to investigators iv. Compliance of protocol design with the "quality by design" principle
Richmond Pharmacology Dr Jörg Täubel Dr Ulrike Lorch Dr Andrew Stokes Dr Edward Jackson Dr Saqib Mir	0	0		II. Comments and solutions: i.Electronic transferability of modular protocol sections Comments: We fully support a level of standardisation in terms of the modular organisation of protocols to promote ease and completeness of design, review and practical implementation. A protocol is a document to be put into clinical action, it must be coherent and readable, but above all it must be safely practicable. An IT tool or solution to aid submission/review should not build-in redundant information or reduce the quality and safety of a protocol by missing essential sections, just for the ease of review/submission. We should strive to promote ease of understanding and consistency whilst bringing regulatory oversight and electronic transferability into the next decade. IT systems already exist that allow electronic transfer of protocol sections/modules into review and approval systems. Generally, it is possible to transfer/export any information from various sources into portals of shared information. IT solutions should follow user specifications, rather than users being forced into templates dictated by IT solutions. We are confident, that the pace of development of new IT solutions fully supports flexible and modular protocol designs for each type and category of clinical research.	Proposed solutions: We suggest that IT solutions should be found to match user needs. Specifically, for exploratory research, we suggest that they should be exempted from using a template that is designed for confirmatory trials. Instead, we propose conditional (2) and modular (3) solutions outlined above. We have been making use of such modules in our protocols for many years for areas we describe in more detail later in this document. Usually, these modules are presented as tables or algorithms that are visually intuitive and easily implemented. This would align with the ICH M11 proposal by maintaining a "modular view of the protocol" to facilitate electronic data exchange.
Richmond Pharmacology Dr Jörg Täubel Dr Ulrike Lorch Dr Andrew Stokes Dr Edward Jackson Dr Saqib Mir	0	0		II. Time and cost savings during drug development to improve patient access Comments: There is an abundance of evidence confirming that the use of adaptive and flexible protocol designs significantly reduces the number of substantial amendments/modifications, saves cost and time, and improves patient access. In contrast, there is to our knowledge no evidence to support the use of a single global multiphase protocol template for this purpose, and there was no data presented during the webinar to support this claim. We support the idea of creating core common content to save time and costs. We agree, a poorly designed protocol can lead to substantial amendments and delay. However, a single global multiphase protocol template would lead to a lack of flexibility and adaptability in design. This would jeopardise safety and practical implementation, inevitably leading to substantial amendments/modifications, wasting time and resources.	Proposed solutions: The proposed ICH M11 template has some good headings and subheadings, but different and additional ones are required for early phase researchers and investigators. We suggest that - either via a conditional input platform or via a library of best practice modules - tables, figures, and algorithms for individual sections are provided, which can be used as required for each specific (category of) trial. All sections and modules should reflect current best practice and contain and be suitable for complex and adaptive early phase trial design. For early phase trials we often need the following modules in keeping 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:

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Richmond Pharmacology Dr Jörg Täubel Dr Ulrike Lorch Dr Andrew Stokes Dr Edward Jackson Dr Saqib Mir	0	0		ii.Time and cost savings during drug development to improve patient access Comments: There is an abundance of evidence confirming that the use of adaptive and flexible protocol designs significantly reduces the number of substantial amendments/modifications, saves cost and time, and improves patient access. In contrast, there is to our knowledge no evidence to support the use of a single global multiphase protocol template for this purpose, and there was no data presented during the webinar to support this claim. We support the idea of creating core common content to save time and costs. We agree, a poorly designed protocol can lead to substantial amendments and delay. However, a single global multiphase protocol template would lead to a lack of flexibility and adaptability in design. This would jeopardise safety and practical implementation, inevitably leading to substantial amendments/modifications, wasting time and resources.	- 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) Providing a useful array of practical and pragmatic protocol sections/modules presented in a structured, visually attractive format (tables, figures, algorithms) that allows easy comprehension and implementation of complex topics, would benefit the early phase research community and regulators.
Richmond Pharmacology Dr Jörg Täubel Dr Ulrike Lorch Dr Andrew Stokes Dr Edward Jackson Dr Saqib Mir	0	0		iii. Practical use of an “off-the-shelf” protocol to investigators Comments: In the webinar, the EWG members explained that one aim of the initiative was to provide an “off-the-shelf protocol” for all phases of clinical research that would aid writing and practical implementation. As outlined above, we fully support the aim of establishing core content to share best practice in a collaborative way, to provide practical help for those less experienced with protocol writing/design and for electronic transfer of key information. The proposed template currently does not meet the standards of “an off-the-shelf” product that is fit for purpose, and neither do we think it will ever work equally well for all phases of research. If, for a specific trial protocol, one would keep all unnecessary sections, add all additional essential sections, and deal with amendments in the way suggested, the document would get very large, unwieldy and practically very difficult to implement. It would require extensive administrative and operational resource to bring it into a condition that is understandable and practically useable. It is quite possible that protocols would need to be transferred into another internal document that can be worked with. This cannot be the spirit of ICH. Crucially, for early phase trials the template does not comply with essential requirements of the EMA’s guideline for risk management in early phase clinical trials (EMEA/CHMP/SWP/28367/07 Rev.1).	Proposed solutions: Clinical trials should be safe, scientifically sound and presented clearly in a detailed protocol. A platform or library of protocol sections or modules could act as source of best-practice protocol content and could be tailored to the phase/category of a trial and the nature of the IMP and trial design. Change should be made as easy as possible for early phase clinical trials. It is imperative that a protocol can safely respond to unexpected challenges which come to light during a trial rather than adhering to an inflexible template protocol which may no longer be safe.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Richmond Pharmacology Dr Jörg Täubel Dr Ulrike Lorch Dr Andrew Stokes Dr Edward Jackson Dr Saqib Mir	0	0		Protocols need to be written with sufficient adaptability to respond to emerging trial results. This is particularly pertinent for complex innovative trials where adaptability is not only sought but, in many cases, required extensively (CTFG: Recommendation paper on the initiation and conduct of complex clinical trials and FDA: Adaptive designs for clinical trials of drugs and biologics guidance for industry). The suggested ICH M11 template does not have the structure or content for this. It is not clear why public consultation for this template was not sought earlier, including all relevant stakeholders. Protocol design and writing is a complex and collaborative process between Investigator and Sponsor. Regulators also contribute through scientific advice and their responses to submissions. Individual Sponsors may utilise templates, which are designed to not only follow regulatory guidance, but also adhere to their company policy. Similarly, as Investigators, we have our own systems regarding the content and structure of a protocol. Guidance should be used to facilitate a collaborative approach; it is important to consider all stakeholder perspectives and to simplify processes as much as possible. Early phase clinical research is fast moving, and having one multi-phase template which already seems superseded in parts and non-compliant with other regional guidelines, does not seem logical. As a research community, we are constantly striving to improve protocol design and thereby improve study conduct, safety, and the quality of research.	Consistent placement of content would be helpful but does not necessarily need to be top priority. IT systems are capable of handling relevant information, irrespective of their place. Consequently, we do not see the merit in adding key information to appendices. The need for appendices would be greatly reduced with the use of modules that consist of tables, figures and algorithms to concisely present information within the body of the protocol. From a practical perspective it is better for Investigators to read a protocol without having to continually refer to appendices. Appendices should be used to supplement, not replace, information within the body of the protocol.
Richmond Pharmacology Dr Jörg Täubel Dr Ulrike Lorch Dr Andrew Stokes Dr Edward Jackson Dr Saqib Mir	0	0		iv. ompliance of protocol design with the “quality by design” principle Comments: We appreciate that the current proposal of ICH is intended to achieve quality by design. In reality, introduction of a protocol template for all phases would potentially make protocols less safe than they should be.	Proposed solution: In early phase trials, processes and protocols need to be futureproofed to allow them to adapt, to flexibly support safe, dynamic, novel, exploratory research. It would be much easier to do this by adopting a more modular approach, either by using a conditional protocol platform to accommodate the choice of exploratory or confirmatory trials, or by using a library of best-practice modules. The library of best-practice modules option is the most adaptable, because individual modules can be kept up to date by small groups of experts on an ongoing basis.
Richmond Pharmacology Dr Jörg Täubel Dr Ulrike Lorch Dr Andrew Stokes Dr Edward Jackson Dr Saqib Mir	0	0		III. Conclusion: Please can you reconsider your current proposal for implementation of a clinical trial protocol template across all phases and categories of clinical research and consider the three alternative options we propose.	
Richmond Pharmacology Dr Jörg Täubel Dr Ulrike Lorch Dr Andrew Stokes Dr Edward Jackson Dr Saqib Mir	0	0		IV. Useful links to relevant manuscripts: 1. Three steps to writing adaptive study protocols in the early phase clinical development of new medicines Lorch, U., O’Kane, M. & Taubel, J. BMC Med Res Methodol 14, 84 (2014). https://doi.org/10.1186/1471-2288-14-84 2. Practical risk management in early phase clinical trials Coates, S., Täubel, J. & Lorch, U. Eur J Clin Pharmacol 75, 483–496 (2019). https://doi.org/10.1007/s00228-018-02607-8 3. Efficient Design of Integrated and Adaptively Interlinked Protocols for Early-Phase Drug Development Programs Coates, S., Pohl, O., Gotteland, JP. Täubel, J. & Lorch, U. Ther Innov Regul Sci 54, 184–194 (2020). https://doi.org/10.1007/s43441-019-00044-y	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Ronald Cornet, Amsterdam UMC. The opinion here is his personal/professional reflection and not "endorsed" by his organisation	0	0	0	519 (parts of) attributes are specified, of which 20 are pick lists. It seems that this is a fully, or at least largely, free-text specification, without any linking to existing vocabularies to represent the items or the values. This seems to be a missed opportunity to come to further standardization: - Using vocabularies for the data elements / attributes would enable better cross-linking with other domains - Using vocabularies for the values would enable better harmonized (!) specification thereof, and would enable more flexible searching. E.g., "Population Diagnosis or Condition" now relies on a text value, which makes systematic searching, including use of different levels of granularity in description and retrieval, impossible.	Recommendation: develop a solid schema in an broadly accepted schema language with rigorous semantics (JSON-LD; ShEx; ShaCL; LinkML), and rely on controlled vocabularies as much as possible. If and where needed, consider (co-)development of such vocabularies.
TransCelerate BioPharma Inc.	0	0	0	There is a lack of clarity on how the FDA guidance "Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials" should be implemented in the protocol.	Recommend that FDA and other regulators consider what guidance should be in the protocol and where it would be best placed.

2. Specific comments on text

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	3	3	0,1	Instead of uniquely identifying the template revisions by the date only, please consider also labeling with a version number.	add a column called 'version number' in between the colum 'date' and 'description of Revision'.
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	4	10	0.2	Since the M11 protocol template is not sufficient regarding national/regional requirements, it should be added to Section 0.2 "Indendend Use of Template", that country or region-specific requirements for protocol contents, such as EU Regulation 536/2014 (Annex 1), are not included and must be additionally taken into account.	In the description, it should be added: "Country or region-specific requirements for protocol contents, such as EU Regulation 536/2014 (Annex 1), are not included and must be additionally taken into account."
CSL Behring	5	6		We propose revision of the first sentence of section 0.2 for consistency with the language used in the draft guideline.	This template is intended for interventional clinical trials of drugs, vaccines, and drug/device combinations intended to be registered as drugs pharmaceuticals, biologics, vaccines, cell or gene therapy products (when applicable), as well as drug-device combination products when registered as a drug.
CSL Behring	7	7		Reference is made to ISO 14155 in this draft document; however, this standard is not referred to in the guideline where it is most appropriate. Propose to remove the reference to the ISO standard from the template document.	Existing ICH Guidelines and ~~ISO 14155~~ were considered in its development.
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	11	15	0.3	Template Conventions and General Instructions: The use of different fonts is unnecessary. The use of different font colours suffices and would ensure a clean visual impression of the text.	
EFPIA	12	12	0,3	For consistency, propose to add bolded subheading 'Text Structure and Flexibility' to match the 'heading structure and flexibility' (line 16) and other headings further down in this section.	Text Structure and Flexibility
EUCROF - EU CRO Federation	14	14	0.3 Template Conventions and General Instructions	Table below Line 14: There are different Typeface Details for Instructional text (Calibri) and Suggested text (Century).	Keep all typeface as Times New Roman 12 pt., as shown for the universal font to avoid the chance that when the text is removed/revised that it will leave behind another typeface that cannot be seen or goes unnoticed.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUCROF - EU CRO Federation	14	14	0.3 Template Conventions and General Instructions	Table below Line 14: Instructional text is usually done as hidden text (i.e., only visible with the show/hide feature is on).	Do not add instructional text as hidden text to avoid the chance that it will not be removed at finalization. It should be visible at all times and removed as the writer fills in each section.
EFPIA	14	14	0.3	It is unclear how 'Suggested text' is being used in the document. Is this entirely optional to use, or is it the expectation that it will be used in some form, when applicable? For example, on the Title Page the field for 'Amendment Number' is blue, but it is stated that for the original protocol to 'indicate Not Applicable' (rather than deleting the field). Please clarify the expectations on fields in Blue Century more clearly.	
EFPIA	14	14	0.3	The description of the use of braces for variable text does not reflect the way they are used in the document. Currently [square] and {brace} brackets are used. It should be one or the other not both.Please align.	
EFPIA	14	14	0.3	Please clarify what square brackets WITHOUT grey shading mean, since this is used several times throughout the document (e.g. page 10 line 67-70 and page 21 line 310+314).	
EFPIA	14	14	0,3	The font of "trials" and "trial" is different from the other.	change to calibri font like other.
EFPIA	14	15	0,3	If universal text is Times New Roman and variable text is Century, then the protocol text would have two differnent fonts unless the medical writer changes it afterwards. Line 57 addresses this point but do not believe much is gained by using two fonts.	Could just use the color code to distinguish between the two types of text.
TransCelerate BioPharma Inc.	14	14	0,3	In the template conventions typeface details, {braces} are used for variable text and [brackets] are used for fields. However, the use of these throughout the document appears to be inconsistent as some text may be both variable and a field. Consistent identification of variable fields is important to avoid user misinterpretation as well as for clear programming of the electronic version.	Ensure consistent use of braces and brackets throughout the document.
EUCROF - EU CRO Federation	16	16	Heading Structure and Flexibility	In “Addition” column, “Add L2 headings, if needed, at the end of the higher-level section to preserve the established L1 and L2 heading structure” spans both the L2 and L3 rows in the table.	This text should only apply to the 1.1 Level 2 (L2) row in the table.
EFPIA	16	22	0,3	Level 4 headings is the maximum. No numbering for additional headers is allowed for in the text, which means they are not so easily found.	Proposal to allow numbered section headings below level 4. Please provide guidance to allow for Level 5 and 6 headings as well
Freeline Therapeutics	18	19	0,3	Addition/deletion/modifications of Level 2 headings must be allowed to ensure the protocol is presented effectively for the reader and is relevant to the trial. Redundant headings (with 'Not Applicable') or additional sections forced into inappropriate existing headings make the document less streamlined. eg Section 7.1 Discontinuation of Trial Intervention is irrelevant for gene therapy where it is a one-time treatment therefore cannot be discontinued.	Amend note to say that addition/deletion/modifications of Level 2 headings are allowed.
EFPIA	21	21	0.3 (1.1.1)	Please provide the following clarification as Section 8.3 is also about safety: Do not delete or modify Level 3 safety subheadings in Section 8.4 (adverse events). Other Level 3 headings may be deleted or modified as needed'	Add clarification: Do not delete or modify Level 3 safety subheadings in Section 8.4 (adverse events). Other Level 3 headings may be deleted or modified as needed'
EFPIA	21	22	0,3	In the table about heading structure and flexibility, column 'Addition': there is a box spanning L2 and L3 that specifies that L2 headings can be added, but it does not mention L3 headings can be added.	Add L2 and L3 headings, if needed, at the end of the higher-level section to preserve the established L1 and L2 heading structure
EFPIA	21	22	0.3	Please remove bold completely in the columns 'Modification or Deletion' and 'Additions' or make it consistent.	remove bold for 'Level 3 safety subheadings (Section 8.4). Other Level 3 headings may be deleted or modified as needed'

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	21	22	0,3	Level 3 - States Safety level 3 is not to be deleted but all other level 3s can be deleted or modified. Envision this execption to the rule may be very hard to universally maintain.	Can the safety L3 be elevated to a L2?
TransCelerate BioPharma Inc.	21	21	0,3	The text currently states that level 3 headings may be deleted or modified, but does not specify if they may be added. In the CPT experience, level 3 headings are frequently added by sponsors to capture sponsor- and study-specific details.	Ensure it is clear Level 3 headings can be added anywhere in the document, including Section 8.4.
EFPIA	24	24	0,3	Please add guidance on numbering paradigm for numbering tables and figures that aligns with section header.	
EFPIA	24	24	0,3	It states that tables should include a title and figures should have a caption. It is unclear why a difference is being made. Consider giving both tables and figure a caption.	Tables and figures should be numbered and include a ~~title or~~ caption.'
CSL Behring	34	34		It is stated that the term 'Participant' is used rather healthy volunteer, however in the synopsis section, the term "healthy volunteer" is actually proposed as a selection option under "population type". Please check if that is correct, given this statement here.	n/a
EFPIA	34	37	0,3	For pediatric participants who have yet to reach the age of majority, consent is provided by the parent or guardian. Only "assent" can be provided by the pediatric participant.	The text should be expanded to reflect this nuance - refer to ICH E11 or ICH E11 R1 for contextual background in devleopiong the appropriate text.
EFPIA	34	37	0,3	We agree that 'participant' should be used consistently in the protocol, CST and SAP as the preferred term as Health Authorities prefer this term, even for oncology studies.	
Interpharma, Association of Switzerland's research-based pharmaceutical industry	34	37	0	For pediatric participants who have yet to reach the age of majority, consent is provided by the parent or guardian. Only "assent" can be provided by the pediatric participant.	The text should be expanded to reflect this nuance - refer to ICH E11 or ICH E11 R1 for contextual background in devleopiong the appropriate text.
EFPIA	38	38	0,3	"Trial intervention" encompasses both IMP and AxMP. It would be helpful to specify this here, or at least to refer to an appropriate section to differentiate them with their respective definitions to avoid any confusion.	Specify that "Trial intervention" encompasses both IMP and AxMP and refer to an appropriate section to differentiate them with their respective definitions to avoid any confusion.
EFPIA	38	40	0,3	The definition of "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. Is also inconsistent with wording in section 0.2 (line 5) "This template is intended for interventional clinical trials of drugs, vaccines, and drug/device combinations intended to be registered as drugs. "	Proposal for rewording: '…and drug-device combination products when ~~registered~~ classified under relevant regulations as a drug.'
EFPIA	38	38	0.3	Please provide a consistent definition of 'trial intervention'. The way in which this term is used within the template varies from section to section, and is often in conflict with the definition provided on page 5. According to the definition, trial intervention is equivalent to the former IMP, meaning 'the agent being tested or used as a control. 'Diagnostic agents' would often fall outside this category, but are listed as part of the definition. This leads to uncertainty aleady within the definition. Later in the document, 'trial intervention' is often used to mean 'test drug' (in contrast to control), whereas control is part of the definition - see e.g. line 612. Then in section 6, auxiliary medicinal products (AxMPs) are introduced (line 599) as part of 'trial intervention', which conflicts with the main definition on page 5, since these are neither test products nor controls. Later on the same page (line 603) the AxMPs are described as 'additional products'. It needs to be very clear whether or not trial intervention also includes 'auxiliary medicinal products'. Please ensure a clear definition is established and used consistently throughout.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	38	43		It is problematic for the template to define "intervention" in a limited manner as "any therapeutic, prophylactic, or diagnostic agent including pharmaceuticals, biologics, vaccines, cell or gene therapy products and drug-device combination products when registered as a drug.". According to the World Health Organization (WHO), "intervention" is a broad term that includes "drugs, cells and other biological products, surgical procedures, radiological procedures, devices, behavioral treatments, process-of-care changes, preventative care, etc." It is important for sponsors to be able to use the term "intervention" according to the broader WHO definition. For example, during the period between study entry and initiation of the study drug, sponsors communicate the need for sites to report serious adverse events caused by a protocol-mandated intervention (e.g., biopsy, discontinuation of medications during washout period). In such cases, "protocol-mandated intervention" is referring to any intervention except use of a therapeutic, prophylactic, or diagnostic agent. Also note that the limited definition of "intervention" proposed for the M11 template will not be readily apparent to the average reader (e.g., site personnel). In addition, the accompanying Informed Consent Forms should use the term "treatment" rather than "intervention." "Treatment" is a term that is familiar to a layperson and is recognized as something a study doctor might prescribe to treat an illness or condition, while "intervention" will not carry that meaning for most people.	Retain "study treatment" rather than "study intervention" in the template accordingly with global standards and for harmonization purposes (ref WHO).
EFPIA	38	43	0,3	The term "trial intervention" or "study intervention" as used in Transcelerate CPT is being confused with the study procedures. It leads to a lot of discussions with study teams. Can the term "study product" or "trial product" be used instead? The procedures on participants can be referred as "study procedures".	"Study product" or "trial product" refers to any therapeutic, prophylactic, or diagnostic agent including pharmaceuticals, biologics, vaccines, cell or gene therapy products (when applicable), and drug-device combination products when registered as a drug. "Study product/trial product" include the agent being tested or used as a control (for example, placebo or active comparator).
TransCelerate BioPharma Inc.	38	43	0,3	The definition of "trial intervention" used in this document appears to include all interventions used in a trial, including NIMP/AxMP. However, differentiation is often needed in a protocol for investigational intervention as there are separate requirements for handling of investigational intervention vs. authorized NIMP/AxMP. This needs to be closely aligned with the EU CTR requirements.	Suggest including a definition of "investigational intervention" as a subset of trial intervention, and the terms used consistently throughout the document. TransCelerate has been successful with this use and definition in the CPT.
CSL Behring	40	42		Terminology relating to 'trial intervention' refers to the agent being tested or used as a control as being in scope. It is not clear whether "trial intervention" also includes pre-defined other treatments such as pre-medication, rescue medication, etc.? These may either be an inseparable part of the intervention or a potential confounder that needs to be considered as an intercurrent event when defining an estimand. Please clarify. Furthermore, when the template is finalised, it will likely be adopted across the major ICH regions. We suggest the drafting team consider if the PMDA's "Drugs Used in Clinical Trials (DUC)" concept is adequately reflected in the template.	n/a
EFPIA	40	40	0.3	In many cases the drug-device combination will not yet be registered. Please modify 'registered as a drug' to 'classified as a drug' or similar.	Please modify 'registered as a drug' to 'classified as a drug' or similar.
EFPIA/EFSPI Estimand Implementation Working Group	40	43	0	The definition of trial intervention is unclear. The wording suggests that only the interventions to be tested or used as control are included, i.e., IMPs and not e.g. rescue and background interventions. According to section 6.1 NIMPs and AxMPs are also covered by the terminology. Please align.	Append text: Trial interventions include the agent being tested or used as a control (for example, placebo or active comparator) as well as background and rescue interventions
EFPIA	44	45	0,3	"While blinding is the more commonly used term, masking is an alternative term which may be used in certain situations." This is too vague. It is unclear whether "blinding" and "masking" are interchangeable. What are the "certain situations" where masking may be used? Note that TransCelerate Common Protocol Template uses "masking." One example: In retinal programs 'masking' is used in the protocols since there is sensitivity around the term 'blinding' in studies for eye diseases causing blindness.	
Estimand Review team	44	45	0,3	Explain the term masking better	Consider adding "(i.e. like in eye diseases trials)"

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
CSL Behring	46	46		The title of the section “Suggestions for Publishing a Paper or.pdf Document” does not reflect the content of the section, where the instructions relate to formatting of word template documents. We propose a revision to the section title to better reflect the content.	Suggestions for Word document finalisation before Publishing a Paper or .pdf Document
SÚKL CZ	52	52		There should be "navigation panel" - type correction	put "navigation panel" instead of "navigation pane"
Freeline Therapeutics	52	53	0,3	Suggest including that no more than 4 heading levels are included in TOC per FDA requirements	Include note that no more than 4 heading levels are included in TOC per FDA requirements.
EFPIA	53	53	0.3	Please remove the single closing bracket.	
EFPIA	54	55	0,3	add: "(except in Section 8.4)" to clarify that Level 3 headers in that section should be kept.	Clarify that Level 3 headings in section 8.4 must be kept.
EFPIA	57	57	0.3	"Example" text is not described in template conventions. Please either delete here or insert explanation in table on type of text	
CSL Behring	60	61		The content of lines 60 and 61 relate more to confidential commercial information (CCI) than to the formatting points listed above within the section. As the information appears to be out of place, we suggest mentioning it elsewhere in the template, e.g., as a completely separate subheading under list of abbreviations, e.g., “Considerations for Transparency and Disclosure”.	n/a
EFPIA	60	61	0,3	The reminder about protocols being publicly disclosed is critical. This location may not be optimal in the template.	Consider moving this alert/reminder to a more prominate location, possibly on the Title Page and using a larger more visible fint style.
Estimand Review team	62	62	0,4	Consider adding further abbreviations for Safety	Consider adding the following terms: "SAR" - "serious adverse reaction" and "SUSAR" - "suspected unexpected serious adverse reaction" and "RSI" - "reference safety information"
SÚKL CZ	62	62	0.4	Add CTIS = Clinical trial Information system to list of abbreviation	Add CTIS = Clinical trial Information system to list of abbreviation
SÚKL CZ	62	62	0.4	Add SAR = Serious Adverse reaction and AR= adverse reaction to list of abbreviation	Add SAR = Serious Adverse reaction and AR= adverse reaction to list of abbreviation
SÚKL CZ	62	62	0.4	Add SUSAR to list of abbreviation	Add SUSAR to list of abbreviation
CSL Behring	62	62		IVRS (interactive voice response system) and IWRS (interactive web response system) are terms used as abbreviations within the table appearing within section 0.4 of the template. Proposes that this information be combined into a broad category of IRT – interactive response technology.	IVRS – Interactive Voice Response System ~~IWRS – interactive Web Response System~~ IRT – Interactive Response Technology
EFPIA	62	62		Acronym, recommend using CDISC/NCI standard for controlled terminology for trial phase.	
EFPIA	62	62	Abbrv.	IVRS and IWRS are today mostly referred to as IxRS. Otherwise consider RTSM (randomisation and Supply Management)	Use "IxRS" instead throughout the protocol
EFPIA	62	62	0,4	Instead of including the list of abbreviations as an instruction, consider moving it to Section 14 as optional text.	
EFPIA	62	62	0,4	We prefer including the list of abbreviation at the beginning of the protocol as provided in this template.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	62	62	0,4	Suggest deleting "NIMP" from the abbreviation list - it is being replaced by "AxMP"	
TransCelerate BioPharma Inc.	62	62	0,3	In the table of abbreviations, both NIMP and AxMP are included. A selection of one of these terms for global use would be more efficient and preferred rather than using both terms interchangeably. The CPT still uses AxMP and NIMP interchangeably, but as AxMP becomes increasingly preferred, sponsors are unsure if NIMP is still used by some countries or will become obsolete.	Recommend that ICH determine if AxMP can replace NIMP globally or if both terms need to be maintained.
EUCROF - EU CRO Federation	63	63	Table on Page 8		Could this table have a section title for bookmarking purposes?
EUCROF - EU CRO Federation	63	63	Table on Page 8	Compound Number/Name row: “Compound” does not match any other term in the protocol.	Change to “Trial Intervention” to be in line with section 6 of the template.
EUCROF - EU CRO Federation	63	63	Table on Page 8	Short Title row: No suggested character length is given.	Add suggested character length.
EUCROF - EU CRO Federation	63	63	Table on Page 8		Specify that WHO number is Universal Trial Number (UTN).
Estimand Review team	63	63	0,4	Typo for jRCT	Replace jRCT with JRCT
Quotient Sciences	63	64	Title page	Amendment scope - it should be possible to delete this option for single-centre trials.	
Quotient Sciences	63	64	Title page	Compound Number(s) - please can this refer to 'Compound Code' instead of 'Compound Number' - most IMPs are referred to by codes comprising letters and numbers.	Change 'Compound Number(s)' to 'Compound Code(s)'
Quotient Sciences	63	64	Title page	Trial phase - please add 'Phase 0' as an option.	Add 'Phase 0' as an option
Quotient Sciences	63	64	Title page	Manufacturer Name and Address - please clarify in the title that this refers to the manufacturer of a device and not an IMP, because some studies involve both IMPs and devices.	Change 'Manufacturer Name and Address' to 'Device Manufacturer Name and Address'
Quotient Sciences	63	64	Title page	Regulatory Agency Identifier Number(s) - please add IRAS ID to the list (primary identifier of UK trials).	Add '[IRAS ID:]'
SÚKL CZ	63	63	protocol full title	For clarity every page of protocol must be identified with protocol number (EU number/EudraCT no if applicable), version and approval date	Add an information: "Protocol should contain study identification on each page + numbering of the pages throughout the whole document + version and date."
SÚKL CZ	63	63	Version	The version should be obligatory, not optional, since both the original version and updates/amendments must be properly chronologically identified - i.e. by version number + date of its release. It should also be specified that the version number is suppososed to increase with each amendment.	Protposed text: "Mandatory field. Version and updates/amendments must be properly chronologically identified"
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	63	63		According to SPIRIT item 1, the instruction regarding to the protocol title should be more specific: "Descriptive title identifying the study design, population, interventions, ..."	The description should be adapted to: "Protocol Full Title: The protocol should have a descriptive title identifying the study design, population, interventions, the scientific aspects of the trial sufficiently to ensure it is immediately evident what the trial is investigating and on whom, and to allow retrieval from literature or internet searches."
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	63	63		Protocol Number: A unique alphanumeric identifier for the trial, designated by the Sponsor is not available for academic clinical trials. The description should be therefore adapted: "A unique alphanumeric identifier for the trial, designated by the Sponsor, is a standard part of trial data, and should be included for most trials but not mandatory for academic clinical trials."	The description of the protocol number should be adapted to: "A unique alphanumeric identifier for the trial, designated by the Sponsor, is a standard part of trial data, and should be included for most trials but not mandatory for academic clinical trials."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	63	63		Regulatory Agency Identifier Number(s): This section should comprise all applicable trial identifiers from WHO approved trial registries, not only those from regulatory agencies. The header should be changed accordingly: "Regulatory Agency Identifier Number (s)/Trial Registry Number(s) (WHO approved)"	The header should be changed to: "Regulatory Agency Identifier Number (s)/Trial Registry Number(s) (WHO approved)"
CSL Behring	63	63		Within the table, 'Version' appears with the description "An optional field for use by the Sponsor at their discretion". It is not clear how this row is expected to be used in practice, given that the field immediately below is for the protocol 'Amendment Number'. As such we find it confusing, and a Sponsor could use "Version 2" instead of more accurately recording "Amendment 1". We	n/a
CSL Behring	63	63		Within the 'Trial Phase' field, the options for acceptable entries appear to be somewhat restrictive. Mirrored as per CT.gov, there are also multiple trials in the CT.gov database that use sub-phases such as "2a" or "3b". We propose amending the language of the instructional text to afford greater flexibility.	Acceptable Recommended/preferred entries are:
CSL Behring	63	63		Within 'Sponsor Name and Address', instructional text notes that in some countries the clinical trial Sponsor may be the local affiliate company (or designee). It is not clear what will happen if, for a global clinical trial, additional countries join the study after the initial protocol has been approved and without any protocol amendment. Please clarify the expectations around this regarding the template.	n/a
CSL Behring	63	63		Within 'Sponsor Approval Date', it is not clear if the approval date is the same as the Sponsor signature date appearing directly below (ref: Line 65 – Sponsor Signatory) or if it is the date of any electronic approvals that may occur in the sponsor's document management system. A protocol is only considered approved when the last signatory (per SOP or other requirements) has approved it. Typically, multiple team members approve the document on different dates. Once approved it is not possible to change anything in the document. It is our opinion that the text here is too specific and the action suggested are not possible to do in practice.	n/a
EFPIA	63	63	0,4	Suggest replacing "Version:" with "Edition:" - "edition" is the correct terminology for a document	
EFPIA	63	63	0,4	Suggest deleting "EudraCT" from the list of RA identifiers - since 1 February, it is "EU Trial Number" (CTIS)	
EFPIA	63	63	0,4	For Trial Phase, clarify if use of an alpha character acceptable (ie, Phase 2a). If so include in the picklist.	
EFPIA	63	64	Title page	The title page should be identified as such.	Insert an object that generates a bookmark "Title page" in the navigation pane.
EFPIA	63	63	title page	Consider adding character limits for Full title and short title in-line with registry requirements	Add character limits for compliance with Ctgov
EFPIA	63	63	0,4	The term "Other" in the Trial Phase definition is not a specific value and provides no valuable information. The use of "Other" should be avoided in as much as possible. Consider replacing 'Other' here with 'N/A', which is consistent with guidance at https://prsinfo.clinicaltrials.gov/definitions.html	Replace 'Other' with 'N/A'
EFPIA	63	63	0,4	Consider including the confidentiality statement in the footer rather than the middle of the cover page.	Include the confidentiality statement in the footer rather than the middle of the cover page.
EFPIA	63	63	Table	Please clarify whether the order of rows in the table on page 8-10 is mandatory or can be modified. And if mandatory, please consider what the optimal order should be. For example, it seems illogical to place the confidentiality statement in the middle of all the information that identifies the trial (protocol title, number, version). It would be preferable to place it at the end, since it is independent of the rest. Similarly it would make sense to keep the Protocol Full Title, Acronym and Short Title together.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	63	63		Consider bookmarking this table as 'Protocol Title' page for easy retrieval and to ensure it shows up in the Table of Contents.	
EFPIA	63	63		The 'Amendment Number' is in blue font (suggested text), which implies it can be deleted if not applicable. However, the instructions state 'If this is the original instance of the protocol, indicate Not Applicable'. In case of an original protocol, please clarify whether the line 'amendment number' should be deleted or should be kept with a statement of 'Not Applicable'. Although the line 'Amendment Number' can be 'Not applicable', the line 'Amendment Scope' is in black font (required text). Please clarify whether the line 'Amendment Scope' can be deleted in case of an original protocol.	
EFPIA	63	63	Table	If "Amendment Number" is blue, presumably "Amendment Scope" should also be blue. Please modify.	
EFPIA	63	63		If there's a character limit for the protocol title or short title, it might be relevant to mention this in the instructions.	
EFPIA	63	63	Table	According to the template conventions, shouldn't the acceptable entries for trial phase be listed in this field in braces instead of red instructional text? Please clarify or modify.	
EFPIA	63	63	Table	Under Short Title, consider to revise 'plain language' to 'layperson language' which is the commonly used term.	
EFPIA	63	63		Please consider not including address of sponsor and address of manufacturer. This level of detail might lead to amendments and could rather be included in other documents.	
EFPIA	63	63		Regulatory Agency Identifier Numbers: Please consider adding Clinical Trials Information System (CTIS) number.	
EFPIA	63	63	Table	Since the text on Device Manufacturer relates to 'investigational devices' please clarify whether this includes the device part of a drug-device combination product, or only durable devices that are independent of the drug. It would seem from the scope in section 0.2 that only 'drug-device combinations to be registered as drugs' are in scope.	
EFPIA	63	63	Table	The EUDAMED database is not in scope for drug-device combination products, which is the scope of this template. Please either clarify the use of this or consider deleting.	
EFPIA	63	63	Table	It is assumed that the new ICH M11 protocol template, once released, will only apply for new protocols, not protocols for ongoing trials. Since the EudraCT number will no longer be effective for new protocols, please delete or else clarify the circumstances where this should be used.	
EFPIA	63	64	title page	Recommend indicating the Phase of the trial near the top of the page. This is a key piece of information.	
EFPIA	63	64	title page	"Study number" is more holistic that "Protocol number". "Study number" implies the actual study, while with "Protocol number" could be the version number of the protocol that accompanies the version date. "Study number" is also widely used and discrepancies of naming/definitions between different documents should be avoided	Change wording "Protocol Number" to "Study Number"
EFPIA	63	64	title page	Trial Phase: Recommend to use terminology that will be used in the datasets that explain the trial phase to ensure consistency in terminology. Currently used phase terminology is PHASE 0 for pre-clinical trials, PHASE I TRIAL, PHASE II TRIAL, PHASE II/III TRIAL, PHASE IIA TRIAL, PHASE IIB TRIAL, PHASE III TRIAL, PHASE IIIA TRIAL, PHASE IIIB TRIAL, PHASE IV TRIAL, PHASE V TRIAL	Use established CDISC terminology
EFPIA	63	64	title page	Acceptable entries for phase of trial should be "Phase 2/3" or "Phase 1/2" when there it goes across several phases. This would be more consistent with current practice.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	63	63	M11 Template	Context: Sponsor Approval Date The existing instructional text "Use the CDISC date format (dd/mmm/yyyy, for example 07/JUN/2015) to indicate the date the protocol (or amendment) was approved by the Sponsor." The purpose of referencing a CDISC date in this document, including the date format representation, is unclear. In CDISC, the standard format, e.g., in SDTM, would be ISO 8601.	We suggest removing the CDISC reference and use ISO 8601 or preferred format to ensure a standardized representation of dates. Note: Please also consider remaining agnostic to any specific standard/guidance outside of ICH and ISO, where appropriate.
EFPIA	63	64	M11 Template	Context: master protocol reference tracking In order to have consistency and traceability when a master protocol is used, an explicit reference to that protocol should be included where the line # is referenced. This would ensure a uniform location to identify such cases when reviewing a sub-protocol in consideration of a master protocol. It should be a permissible field in this case. Note: The reference to a master protocol is included only under section 4.1 Description of Trial Design as instructional text.	
EAHP	63	64		Linked to the "Manufacturer Name and Address (page 9), EAHP suggests adding the address of the warehouse that will be responsible for sending the experimental drugs.	Add address of warehouse
PTC Therapeutics, Inc.	63	63	0,4	The proposed format for dates is not inline with CDISC and ISO8601. Given global variance in date presentation, PTC recommends to use DD MON YYYY format, or at minimum, DD MON YYYY if shortened form is preferred.	PTC recommends use of DD MON YYYY format for global clarity.
PTC Therapeutics, Inc.	63	63	0,4	Use of version number and amendment number can lead to confusion, especially if country-specific amendments are involved.	PTC recommends to make amendment number an optional field.
PTC Therapeutics, Inc.	63	63	0,4	PTC would like clarification of the purpose of the field "Manufacturer Name and Address" (for investigational device). It is our understanding that the goal of this guidance is for countries to share the protocol electronically and global file. Regulatory status of the device can be different globally (for example, investigational is one county but 510K approved in US).	PTC proposes that the field is optional/removed.
Agios	63	63	N/A	The 'sponsor approval date' is placed far under the 'amendment number' in the table, though these are often found together.	Suggest to move rows 'Amendment Number' and 'Amendment Scope' to end of table above 'Sponsor Approval Date' to group them together.
Agios	63	63	N/A		suggest to capitalize the first letter for "Global" under 'acceptable entries for amendment scope'
Freeline Therapeutics	63	113	0,3	It is not clear if these lines are meant to constitute the protocol title page? The following comments relating to these lines assume that this is indeed the title page.	Include a heading to state what these lines are presenting.
Freeline Therapeutics	63	113	0,3	Consider re-ordering the rows more logically, keeping the same types of information together and the most important first to improve flow and readability, e.g., the short title should follow the full title; the protocol number should follow the title (full and short); Amendment Scope & Confidentiality rows at the end of the title pages. Or include an instruction that the order of rows can be changed.	Re-order the rows more logically or state the order can be changed.
Freeline Therapeutics	63	113	0,3	'Version' - Change 'Version' to 'Version Number and Date' for clarity - the version number alone is insufficient identification.	Change 'Version' to 'Version Number and Date'.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Freeline Therapeutics	63	113	0,3	'Amendment Number' and 'Amendment Scope' - For an original protocol there is no amendment yet so Amendment Number and Amendment Scope are not relevant - add a note to delete if not applicable. However, current Amendment Scope is too detailed for a front page anyway and is not information which is important for the daily management of the trial by the site - so all amendment details (list & scopes) should be in an appendix. Note that previous version numbers/dates should be described in an appendix and should not appear on title page.	Move all details of current and previous versions to an appendix. Retain only the version number and date on front page.
Freeline Therapeutics	63	113	0,3	'Sponsor Approval Date' - it is not possible to know the approval date (assuming this is the date of the last approval signature) when the protocol is being written. Therefore, for wet-ink signatures, this Sponsor Approval Date would need to be added after approval. However, we should not make changes of any sort to approved text. The Sponsor Approval Date can anyway be seen from the date on the signature pages if required but but does not need to be transcribed onto the title page (it is not needed for the identification of the version if a Version Number is used). Since it is acceptable to say 'The approval date is included with the electronic signatures located...' can we not say 'The approval date is shown on the Sponsor Agreement page' if wet-ink is used? Furthermore, for electronic signature, 1) is it not mandatory to include the copy of the electronic signature and certification with the protocol itself (eg insert the pages at the end of the protocol during publishing)? and 2) what 'location' is acceptable? Trial Master File? Note that if wet-ink is used the scanning often makes the page grainy (reduces quality) and so it is better to have signatures on a separate page to avoid making the synopsis itself grainy/poor quality. Consider including approvals as an appendix not relevant to the management of the trial, as with abbreviations, amendment history, references which are appendices	Allow 'The approval date is shown on the Sponsor Agreement page' if wet-ink is used. Consider if need to include electronic signature & certification with the protocol. Include signature block on a separate page to retain quality of synopsis post-scanning. Consider moving signature sections to an appendix.
Gilead Sciences	63	63	Title page	Suggest to add details needed for Protocol Full Title in the instructional text (eg, phase, high-level study design, study drug); Rationale: current instructions are too sparse	
TransCelerate BioPharma Inc.	63	63	0,3	As the title page is not part of a numbered section of the document, the title page should be identified as such to offset the start of the official template from the instructional section to ensure correct use.	Recommend inserting an identifier or header to indicate the end of the preface and start of the title page.
TransCelerate BioPharma Inc.	63	63	0,3	The sponsor confidentiality statement may work better in another location. The other protocol elements on the title page are key study details and should be prioritized. The sponsor confidentiality statement is often added as a footnote or smaller font on the bottom of the title page or elsewhere. The CPT does not mandate placement of this, allowing sponsors to add at their discretion.	Recommend that the "Sponsor Confidentiality Statement" is prioritized lower on the title page.
TransCelerate BioPharma Inc.	63	63	0,3	In order to maintain consistent terminology use, the option for “other” for trial phase should be avoided.	For Trial Phase, recommend that CDISC/NCI Standard Controlled Terminology options are used to define trial phase and eliminate "other." Ensure all options are available (e.g., Phase 0).
TransCelerate BioPharma Inc.	63	63	0,3	For Acronym, as there are no known regulatory restrictions on acronym/study name abbreviation, the details on allowance of numerals is not necessary.	For Acronym, suggest deleting sentence "The acronym may include numerals such as 1, 2 or I, II…"
Charité Research Organisation	63	63	Title page	Regulatory Agency Identifier Number(s) - EudraCT Number	Is the Eudra CT Number still applicable?
Charité Research Organisation	63	63	Title page	Regulatory Agency Identifier Number(s) - EU Trial Number	Please consider changing 'EU Trial Number' to 'EU CT Number'
EFPIA	64	64	0,4	Page 9 -- Suggest removing the "Acronym" row from the summary	Acronyms are often part of the Title. If the plan is to move them from the title and place here, this needs to be clearly indicated for the title entry.
EFPIA	64	64		Amendment Scope is not necessary if the sponsor includes country-specific requirements in the appendix of the global protocol instead of providing country-specific amendments.	Recommendation to make this section optional.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	64	64		Short Protocol Title and Acronym should follow the Full Protocol Title.	Recommendation to rearrange the title page so that the Short Protocol Title and Acronym follow the Full Protocol Title.
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	65	67		Sponsor Signatory: For most academic sponsored trials, the sponsor is not identical with the trial funder, therefore the name of the funder and a statement to the role of sponsor and funder should be added (see SPIRIT item 5c).	
EFPIA	65	67		Please remove the wet signature from this document. By implying that wet signatures are acceptable, it creates significant difficulties for sponsors that cannot provide them because they work in electronic documentation systems.	Recommendation to delete these lines from the document.
EFPIA	65	65	0,4	Recommendation to remove the wet signature option from the template as this is an eDOC. Sponsors can identify alternative means for signing if necessary, such as signing with an accompanying form or delegating e-signature.	Recommendation to remove the wet signature option from the template as this is an eDOC.
EFPIA	65	67		Context: Sponsor Signatory We suggest including instructions when there are multiple signatories (sponsor, investigator).	
EFPIA	67	74	0,5	Out of concern of the safety and privacy of associates we stopped putting actual names in the protocol. Instead we have a separate document for the trial site that contains these names. Could this concern be considered?	
Interpharma, Association of Switzerland's research-based pharmaceutical industry	67	74	0,5	Out of concern of the safety and privacy of associates we stopped putting actual names in the protocol. Instead we have a separate document for the trial site that contains these names. Could this concern be considered?	
CSL Behring	72	73		It is not clear to us as Sponsor how the signature block may be replaced "with appropriate description of the electronic/digital approval and the location of relevant information for traceability" after the protocol has been approved and further changes can no longer be made. Please clarify.	n/a
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	74	80		Since a clinical trial is a scientific project, which requires a sound methodological planning, the name and signature of the biometrician responsible for study planning should be mandatory. In addition, according to SPIRIT item 5a, we miss a list of "Names, affiliations, and roles of protocol contributors". According to SPIRIT item 5d "Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable" should be listed. In the current version of the ICH M11 protocol template this is foreseen in the trial synopsis, but in our opinion it should be moved to this section.	
EFPIA	74	74		The terminology 'Medical Monitor' is unclear. Please change to 'Sponsor's medical expert' to align with ICH E6(R2) 6.1.4, if this is what is meant.	
Freeline Therapeutics	74	80	0,3	'Medical Monitor' - Suggest this would be more appropriate in a separate Emergency Contact section rather than as part of the title page.	Move Medical Monitor section to Emergency Contact section
EFPIA	77	80		SAE reporting options are email and fax. Reporting SAEs via the EDC system is common across large pharmaceutical Sponsor companies. Fax exchange is rare	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	77	79	title page	the term Email is inconsistently used; hyphenated vs. closed	strive for consistency
SÚKL CZ	81	81	Amendments details	Information about amendment if it is substantial or non-substantial is needed	Information about amendment if it is substantial or non-substantial should be added to this chapter
CSL Behring	81	82		The instructional text notes that this entire section should be deleted for an original protocol. We propose for consideration that the header "Amendment Details" (at least) should be retained in the original protocol, as a reminder to the authoring team to populate this section in case of a future protocol amendment.	n/a
CSL Behring	81	82		It is not clear if this section is intended to include both substantial and non-substantial/administrative amendments, or just substantial amendments. The reasons in the table following at Line Number 84 all appear to be related to substantial amendments only. Please clarify this point.	n/a
EFPIA	81	81		Consider making a bookmark so the 'Amendment details' section shows up in the Table of Contents.	
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 data models across sponors? Please clarify what is meant here.	
PTC Therapeutics, Inc.	81	81	0,4	For many studies, this amendment section could be extremely long and deflect/affect clarity and readability.	PTC recommends the whole amendment details section is moved to the end of the protocol/appendix 2 to avoid a very long section upfront.
Agios	81	113	N/A	Please consider including the majority of the 'history of amendment' information as an Appendix, and retain only the summary of substantial changes in this section. While acknowledging that having the entirety of amendment history information upfront is useful to regulatory authorities, the end users (sites/investigators) might find this distracting and cumbersome within the body of the prtocol.	
Freeline Therapeutics	81	113	0,3	'Amendment Details' - details of current and previous amendments are better placed in an appendix rather than as part of the title page or a numbered section of the protocol, eg Section 13.4, as this is supplementary information not needed during the routine use of the protocol document.	Delete this section from title page and add instruction to include all amendment details (current and previous) as an appendix.
Gilead Sciences	81	98	Amendment Details	Suggest that Current Amendment and Summary of Changes tables come before the Amendment History table; Rationale: former tables are of more important interest	
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	81	113	0.3	The first information should refer to the nature of the amendment: "Substantial" or "Non-substantial". Amendments to the trial are regarded as "substantial" where they are likely to have a significant impact on: the safety or physical or mental integrity of the subjects, or the scientific value of the trial, or the conduct or management of the trial, or the quality or safety of any IMP used in the trial	insert a question on the nature of the amendment: "Substantial" or "Non-substantial"
Quotient Sciences	83	84	Amendment Details, History of Amendments	'History of Amendments' and text immediately below: The template should specify that the amendment history relates to amendments to the protocol, not amendments to the trial as a whole. The current text implies that all amendments to the trial should be listed, including, for example, any amendments to information for participants, or to the investigator's brochure.	Edit the title: 'History of Protocol Amendments' Change '{#/A total of #} prior {global} amendments have occurred, as shown in the table below:' to '{#} prior {global} amendments have been made to this protocol, as shown in the table below:'

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	83	84	0,4	Clarify introductory statement to the table with "The original protocol dated dd Month yyyy has been amended and reissued as shown in the table below." Add a reminder to insert Amendment and number in the page header and on the title page (eg, Protocol with Amendment x).	Add a reminder to insert Amendment and number in the page header and on the title page (eg, Protocol with Amendment x).
Agios	83	95	N/A	While acknowledging that this information is optional, inclusion of the number of subjects enrolled globally or locally in a protocol amendment does not add clarity as to the conduct and analysis of the clinical trial. This will also be operationally complex and potentially misleading as subjects are enrolled in studies at different times even under the same global amendment and these numbers may be very innacurate by the time a global protocol amendment is submitted in a specific country, for example. To ensure protocols are streamlined, suggest that this information be deleted altogether from the template.	Delete column of approximate number and percentage of subjects enrolled and associated text.
Quotient Sciences	84	85	Amendment Details, History of Amendments	Amendment history table: The third column (Approximate #/% enrolled) is helpful for large, late phase trials but is not useful for a multi-part/multi-cohort phase 1 clinical trial in healthy volunteers. It should be clarified that, for phase 1 clinical trials, the third column (Approximate {(#/%)} Enrolled) can be adapted to indicate to which parts, cohorts or participants the amendment applies. For example, one amendment might apply to cohorts 3-8 of a single ascending dose part and to cohorts 1-4 of a multiple ascending dose part, whereas another amendment might apply only to a food-effect part.	Please add clarification that, for phase 1 clinical trials, the third column (Approximate {(#/%)} Enrolled) can be adapted to indicate to which parts, cohorts or participants the amendment applies.
CSL Behring	84			The table appearing directly below Line 84 captures the history amendments to the protocol. A fair number of subjects can already be enrolled under the original protocol before an amendment is put in place, thus we suggest using the same placeholder as above and not to assign '0'; e.g., if the amendment occurs late in the study conduct, then the majority of patients will already have been enrolled under the original protocol.	{(#/%)} {globally/locally}~~0~~
EFPIA	84	85	0,4	We recommend deleting requirements to provide numbers and percentages of participants enrolled.	Delete requirements to provide numbers and percentages of participants enrolled.
EFPIA	84	84		Please clarify whether 'global' above the table should be 'global/local'.	
EFPIA	84	84	Table	Shouldn't 'Original Protocol' be black text (mandatory) and be surrounded by [square brackets]? Please be consistent in the use of the template conventions.	
EFPIA	84	84		propose to remove the sentence since it is redundant with the information in the table	~~A total of X prior amendments have occurred, as shown in the table below:~~
EFPIA	84	84		Consider adding a sentence referring to Section 13.4 for details of prior protocol amendments. Consider moving the history of amendments table to Section 13.4.	Details of prior amendments are presented in Section 13.4.
Freeline Therapeutics	84	97	0,3	Do not include enrollment numbers in the tables - it is irrelevant and prone to errors.	Delete enrollment numbers from the tables.
SÚKL CZ	89	89	Amendments details	Do not agree with " Inclusion of regional-, country-, and site-specific amendments in the table is optional.". This should be mandatory because it could clarified numbering of versions and why some version was skipped and not submitted to member state. Any regional/countryúsite specific amendments should be mandatory for transparency and clarity.	Proposal " " Inclusion of regional-, country-, and site-specific amendments in the table is necessary for better understaning of live-cykle of protocol."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Quotient Sciences	92	95	Amendment Details, History of Amendments	Please clarify that these bullets apply to international trials (see also comment above).	Please add text shown in bold: • For global amendments to international clinical trials, list approximate global enrollment total or percentage at the time of the amendment and select “globally”. • For country/region amendments to international clinical trials, list the approximate local enrollment total or percentage at the time of the amendment and select “locally”.
EFPIA	92	95		If the optional text on enrollment numbers is kept in: Add clarification for including enrollment numbers in a consolidated protocol amendment (as described in Section 13.3). This would be applied to a global amendment but for country-region requirements.	Add a new second bullet "For global amendments providing only country/region-specific requirments, list approximate local enrollment total or percentage at the time of the amendment and select "locally" for the affected country/region only."
EFPIA	92	95		There is an inconsistency in wording in these lines under 'History of Amendments: "at the time of the amendment" and similar wording in the 'Current Amendment' section which states "at the time of the Sponsor approved the amendment". Please make the wording consistent.	Use consistent wording "at the time of the Sponsor approved the amendment".
TransCelerate BioPharma Inc.	92	97	0,3	TransCelerate members have not been asked to document enrollment numbers in the protocol previously; since this is not a regulatory requirement, this should be removed to avoid the interpretation that this should be present for most studies.	Recommend removing approximate enrollment at time of amendment.
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	96	113		Table "Current Amendment" and Table "Summary of Changes in the Current Amendment": This should be done outside the protocol. In case of many changes this might be confusing. History of Amendments (lines 83 to 84) should remain.	
EFPIA	96	104	n/a	For the Table shown at Line #103, is the intention to have each change listed in numerical order, by Section? Extensive changes in any current amendment would restul in a long tabular list of these many changes and seems counter to the desire to streamline and simplify protocol documents wherever possible.	Suggest grouping changes by Raionale and using the Section # and Name column to contain a list of the affected sections (in numerical order). This would greatly reduce the number of rows needed for the table of changes made.
EFPIA	96		1,1	The instructional text says that not all protocols will have a complete estimand. ICH E9(R1) doesn’t define or anticipate incomplete estimands. What is an incomplete estimand, and in what situation(s) does M11 anticipate an incomplete estimand?	
EFPIA	96		1,1	Does M11 anticipate protocols with no estimands at all? The instructional text is silent on this.	
PTC Therapeutics, Inc.	96	96	0,4	For clarity, it is more informative for readers to have the most recent amendment details presented first.	PTC recommends to have the history of amendments appear after the current amendment details to ensure correct (reverse) chronological order appears in the document.
Quotient Sciences	97	98	Amendment Details, Current Amendment	2nd row of table: Approximate {%/#} Enrolled: Approximate #/% enrolled is helpful for large, late phase trials but is not useful for a multi-part/multi-cohort phase 1 clinical trial in healthy volunteers. It should be clarified that, for phase 1 clinical trials, the third column (Approximate {(#/%)} Enrolled) can be adapted to indicate to which parts, cohorts or participants the amendment applies. See also comment relating to lines 84-85 above.	2nd row of table: Approximate {%/#} Enrolled: Clarify that 'Approximate {%/#} Enrolled:' can be adapted to specify part, cohort or participants affected by amendment.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Quotient Sciences	97	98	Amendment Details, Current Amendment	3rd row of table: Reason(s) for Amendment The row name should clarify that this table relates to a protocol amendment. Please include additional categories in row 3 to cover common reasons for amendments to phase 1 trials: exploration of dose levels predicted to exceed the exposure limit; logistics/feasibility; to improve quality of data. Please clarify what is meant by 'Manufacturing change'. Is it a change to a device manufacturer? A change to an IMP manufacturer or manufacturing process would not normally be captured in a protocol.	Edit 3rd row of table: 'Reason(s) for Protocol Amendment:' Please add to the bulleted list: exploration of dose levels predicted to exceed the exposure limit; logistics/feasibility; to improve quality of data
Quotient Sciences	97	98	Amendment Details, Current Amendment	4th row of table: Summary of the Amendment: The row name should clarify that this table relates to a protocol amendment. Please change 'Specify on the primary reason' to 'Explain the primary reason' as the former is grammatically incorrect.	Edit 4th row of table: 'Summary of the Protocol Amendment:' Change 'Specify on the primary reason' to 'Explain the primary reason'
Takeda	97		Summary	Reasons for amendment: To avoid confusion, we recommend aligning the list of reasons for amendment with an existing list and citing that source in the document.	For example, the list maintained by the Center for Medicines Research (CMR).
Takeda	97		Summary	Substantiality statement: The overarching substantiality rationale is correct. However, the EU CTR has a more robust list of substantial vs nonsubstantial protocol amendments. Should there be a better alignment with EU Clinical Trial Regulation (EU-CTR)? (Regulation (EU) No 536/2014 Questions & Answers version 6.4, Annex IV, February 2023). This is in the template. We recommend making expectation clear in the initial instructions that users need to consult the current version of the template when amending a protocol.	
CSL Behring	97			Suggest rewording of the language regarding estimated % or # enrolled (refer to the proposal below).	Enter the approximate number or percentage of participants expected to be enrolled as a percentage of the expected total.
CSL Behring	97			Within the ‘Reason(s) for Amendment’ field, reference is made to ‘Adaptive clinical trial: IMP addition’. We propose a revision to refer to trial intervention.	Adaptive clinical trial: ~~IMP addition~~ trial intervention
CSL Behring	97			Within ‘Summary of the Amendment’, reference is made to ‘Incidental changes’ which are included in the amendment. Please clarify if incidental changes relate to the reason for amendment described under ‘Other: [Describe]’ within the preceding row of the table. We suggest using consistent terminology between sections if this should be the case.	n/a
CSL Behring	97			Regarding the table outlining the current amendment to the study protocol, the question is asked “Is this amendment likely to have a substantial impact on…”, and the instructional text associated with this refers to “significant impact”. Please consider the consistency of terminology within this section of the template and use either substantial or significant (but not both).	n/a
EFPIA	97	97		In Reason for Amendment section, adaptive clinical trial IMP addition is listed. However, there are other common adaptive trial changes, like increase or decrease in dose, changing dose frequency, inclusion of additional subpopulation. Consider these examples also be included.	
EFPIA	97	97	1	Section 1/1, protocol synopsis...will this be confused with the new EUCTR (EU Clinical Trial Rule) requirement for the EUCTR Synopsis?	
EFPIA	97	97	0,4	Suggest adding a field "Clarification" to the list of "reasons for amendment'.	Suggest adding a field "Clarification" to the list of "reasons for amendment'.
EFPIA	97	97	Table	Shouldn't 'Amendment Number' in column 2 be black text? The use of the various template conventions is unclear and inconsistent.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	97	97		As a general rule, there should be only 1 primary reason listed for an amendment. Listing more than one primary reason should be the exception. Can this please be clarified?	Primary: [Primary Reason for Amendment]* Select from the following (~~multiple selections allowed,~~ The default should be to select only one. Multiple reasons should only be selected if reasons are truly equally important):
EFPIA	97	113		Please clarify that the 'Summary of the Amendment' and the 'Summary of Changes in the Current Amendment' should not provide duplicate information. It is currently unclear what the difference is between these two sections and what (level of detail) needs to be described where, eg, on rationale (without duplicating info).	
EFPIA	97	98	title page	Reasons for amendment: In the table reasons for amendment are listed as "Primary" and "Other", but in the explanatory text below the table, they are described as "primary" and "secondary". Terminology should be consistent	Choose either "other" or "second" and use terminology both for table and explanatory text
EFPIA	97	98	title page	Impact on safety/rights of patients: not clear if this is supposed to be only a "Yes/No" field or should explanation be added? If answer is "Yes" I would expect a brief summary of the impact with a reference to a chapter in the protocol with more explanation, no?	Make the explanatory text more clear whether to provide information about impact in the table or not; if no information is to be provided in the table, it should be provided later on in the protocol with a clickable reference to the chapter in the table
PTC Therapeutics, Inc.	97	97	0,4	PTC would like clarification on how/if the reasons for amendment are expected to correlate with the Annex II Substantial Amendment form's amendment categories/reasons.	PTC proposes that additional guidance around if alignment with Annex II Substantial Amendment Notification form is necessary.
Agios	97	98	N/A	The final bullet, "on the reliability and robustness of the data generated in the clinical trial" please provide more guiding/instructional text on whether an elaboration for why is also requested in addition to "Yes/No"	
Agios	97	97	N/A	While acknowledging that this information is optional, inclusion of the number of subjects enrolled globally or locally in a protocol amendment does not add clarity as to the conduct and analysis of the clinical trial. This will also be operationally complex and potentially misleading as subjects are enrolled in studies at different times even under the same global amendment and these numbers may be very innacurate by the time a global protocol amendment is submitted in a specific country, for example. To ensure protocols are streamlined, suggest that this information be deleted altogether from the template.	Delete placeholder for "Estimated % or # Enrolled] enrolled [Globally/Locally]
Charité Research Organisation	97	97	Title page	Amendment table: Other Reason for Amendment:	Is a change of the investigator (for single center studies) covered by "site feedback"?
EFPIA	98	98		The table indicates "primary" and "other," not "primary" and "secondary" reasons. Please ensure consistency.	
EFPIA	99	99		It is unclear what "key measures" refers to. Only key endpoints (confirmatory)? What about changes to estimands for confirmatory objectives or related estimation? Please clarify.	
EFPIA/EFSPI Estimand Implementation Working Group	99	100	0	Unclear what “key measures” refers to. Do you mean only key endpoints? Change to the primary and key secondary estimands for “confirmatory” objectives, and/or the aligned estimation methods would also be a change in strategy?	Clarification required. Potential change to: Changes to the primary and key secondary objectives, their related estimand(s) and/or estimation methods would be listed as a change in strategy.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Quotient Sciences	103	104	Amendment Details, Summary of Changes in the Current Amendment	Please clarify that it is not the intention that every edit, including typographic errors, be detailed in this table. A tracked changes copy of the protocol is submitted with the amendment so every edit is transparent to regulators/ethics committees, but it is not helpful to list each individual change. Instead, each key change should be described (eg increase in exposure limit; additional safety monitoring tests and timepoints; addition of new groups of participants) alongside all the section numbers and names affected by that change. It would also be helpful to indicate whether each key change is substantial (ie affects participants' safety or rights, or affects data integrity) and thus whether it requires approval before implementation. Often, when a protocol is amended, non-substantial changes are made in parallel with substantial changes. It is useful for regulators for us to specify which changes are considered substantial.	Please add guidance to clarify that the table should summarise the amendment by listing key changes and the affected locations. Please add a column to indicate whether each change listed in the summary is substantial. In 1st column, change 'Location of Change' to 'Location(s) of Change' as a key change might affect multiple sections.
EFPIA	103	103	Table	Presumably at least one row in the table should be black (mandatory). Please align use of template conventions.	
EFPIA	103	103		We recommend that this table list the key changes and provide guidance on what key changes would typically be (eg, changes to endpoints, eligibility criteria, schedule of assessments).	Recommendation to modify text to recommend that only key changes be listed in the table.
Freeline Therapeutics	103	113	0,3	'Summary of Changes in Current Amendment'. Delete 'Brief Rationale for Change' column as rationale will be described for all key changes in the preceding table. To list the rationale against every item in a table of this format will be unsightly as the column width mean the table will extend potentially to pages. Delete the requirement to include the name of the section (for the same reason as above) - the section number is sufficient.	Delete 'Brief Rationale for Change' column. Delete the requirement to include the name of the section.
EUCROF - EU CRO Federation	107	107	Instructions Under Summary of Changes	Section referring to previous amendment has different names, either “History of previous amendments”, “History of amendments” or “Prior protocol amendments”- 13.4. Consistency is necessary to avoid confusions.	Use only one term to reach consistency
EFPIA	114	114		key changes would typically be (eg, changes to endpoints, eligibility criteria, schedule of	key changes be listed in the table.
EFPIA	116	119	1	Protocol synopsis	Header 1 and 1.1 - should be swapped. Header 1 should be Called protocol synopsis - and encompass three sections -study design summary, followed by study schema, and separately schedule of activities - which is a useful part of the synopsis for the Ops for feasibility - this also helps having 1 synopsis, with sections serving different purpose and being developed at different stages of protocol development.
PTC Therapeutics, Inc.	127	127	4.1.1	PTC requests clarification on whether this applies to selection of endpoints generally (for example disease-specific QOL endpoints, etc) or just this specific study.	PTC proposes additional guidance is provided for this section detailing specific requirements.
EFPIA	132	132	TOC	Toc: chapter 4.3 "Access to Trial Intervention After End of Trial" fits better into chapter 6 than in chapter 4	Move information about access to trial intervention to chapter about trial intervention
PTC Therapeutics, Inc.	132	132	4,3	PTC considers, as stated, this section title and content is ambiguous. PTC requests clarification on if this applies to trial participants years after participation is complete or just straight after trial.	PTC considers inclusion of the word "continued" in the section title would assist with clarify.
EFPIA	136	136		Original Text: “5.2 Rationale for Trial Population ..... 29” Rationale for trial population section should be deleted. This is not necessary and is likely to be covered in the purpose section of the document. By adding multiple rationale sections to the TOC, the document will become unnecessarily long.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	147	147		Original Text: "6.2 Rationale for Trial Intervention..... 31" Rationale for trial intervention section should be deleted. This is not necessary and is likely to be covered in the purpose section of the document. By adding multiple rationale sections to the TOC, the document will become unnecessarily long	
EFPIA	148	152		From a site perspective, it seems that preparation of study intervention (6.5.1) should come before dosing and administration (6.3).	Proposal to combine 6.3 with 6.5.1 and remove 6.5.1 from 6.5
EFPIA	150	154		Consider moving 'Section 6.4 Treatment of Overdose' to after the current 'Section 6.5 Preparation, Handling, Storage and Accountability'.	6.4 ~~Treatment of Overdose~~ Preparation, Handling, Storage and Accountability 6.5 ~~Preparation, Handling, Storage and Accountability~~ Treatment of Overdose
EFPIA	177	202	0	Suggest moving all safety topics to AFTER line 207 (that is, after MRU and HE sections) - the rationale is that safety data will be presented last in the Clinical Trial Report - so this will maintain consistency in the order of presentation	
EFPIA	197	197	TOC	ToC: chapter 8.6 Medical Device Product Complaints for Drug/Device Combination Products: calling it "complaints" limits the information provided here. Using terminology like "Medical Device Events" seems to be a more holistic description	change wording to include events with medical devices that are not complaints
EFPIA	210	216		[Minor] Original Text: "9.2 Analyses Supporting Primary Objective(s) ..... 45 9.2.1 Statistical Model, Hypothesis, and Method of Analysis .....45 9.2.2 Handling of Intercurrent Events of Primary Estimand(s) .....45 9.2.3 Handling of Missing Data ..... 46 9.2.4 Sensitivity Analysis .....46 9.2.5 Supplementary Analysis .....46 9.3 Analysis Supporting Secondary Objective(s) ..... 46" Many sponsors put analysis methods for all primary and secondary objectives in a single table in a single section of the protocol. Splitting the analysis methods for the primary and secondary objectives across different sections will create unnecessary redundancy.	Recommendation to consolidate the sections for analyses of primary and secondary objectives into one section.
EFPIA	217	217		[Major] Original Text: "9.4 Analysis of Exploratory Objective(s) ..... 46" Analyses of exploratory objectives should not be included in the protocol. These are exploratory because they are not part of the main objectives of the study. The analysis methods for these objectives should be in the SAP and not in the main protocol.	Recommendation to delete the analyses of exploratory objectives section.
Agios	253	254	1	The protocol summary is often extracted for translations/submitted separately. Please consider adding under 1. Protocol summary key administrative fields as proposed, to ensure accurate representation of the study, should this section be extracted as a separate document.	Add the followingfields under Section 1 Protocol Summary to allow for easy extraction for translations/submissions globally: Sponsor, Investigational Product, Study title, Phase of Development
EFPIA	254	254	1	This instructional text should be deleted as text is required in Section 1.	objectives section
EUCROF - EU CRO Federation	255	255	Protocol Synopsis	No statistical, rationale, or inclusion/exclusion information appears in the synopsis.	Consider adding these items which are very important for a brief review of the study.
EUCROF - EU CRO Federation	255	255	Protocol Synopsis	Including the end of clinical trial definition in the synopsis and in the trial design sections of the protocol is very useful for prompt identification of this key milestone.	Consider adding this item in both places.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
SÚKL CZ	255	255	Synopsis	General comment: the synopsis as such must be based on the information contained in the protocol itself. The body of the protocol cannot refer to the information given only in the synopsis	Provide general statement that the synopsis as such must be based on the information contained in the protocol itself. The body of the protocol cannot refer to the information given only in the synopsis
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	255	361	1.1.	Regarding the protocol synopsis, there are discrepancies between the requirements of CTR (e.g., limitation to a max. of 2 pages, no details such as trials committees) and the ICH M11 protocol template. Please see also our previous comment in line 17, that it should be added in the description at the beginning of this template that country or region-specific requirements for protocol contents, such as EU Regulation 536/2014 (Annex 1), are not included and must be additionally taken into account.	
EFPIA	255	346	1,1	In order to comply with regulatory requirements in all ICH member countries, please clarify whether trial numbers, the full trial title, rationale, interventions, and ethical considerations should be included in the synopsis as per the EU CTR Q&A question 5.8 on content of the synopsis.	
EFPIA	255	346	1,1	If the synopsis is not a stand-alone document, can there be an optionality to cross-refer to the main body of the protocol? This will help avoid redundancy and the risk of inconsistency between the synopsis and protocol main body.	
Agios	255	255	1,1	*Regulation (EU) No 536/2014 Questions & Answers September 2022* states that benefit-risk should be discussed in protocol synopses. Please consider amending the template to reflect this.	
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	255	370	4.1	Statistical methodology/plan is not mentioned in the synopsis, rationale, or inclusion/exclusion information appears in the synopsis.	Add Statistical methodology/plan in the synopsis
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	255	370	4.1	Inclusion/exclusion criteria do not appear in the synopsis.	Inclusion/exclusion criteria in the synopsis
TransCelerate BioPharma Inc.	255	255	1,1	Protocol Title and Health Authority Identifier are required in the synopsis per EU CTR and are included in the CPT.	Recommend including Protocol Title and Health Authority Identifier to the protocol synopsis.
EFPIA	256	256	Section 1.1	Identifier such as protocol title and HA number are missing in the synopsis	Insert these items

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	256	257	1,1	The title of the protocol should be included here for completeness.	
Interpharma, Association of Switzerland's research-based pharmaceutical industry	256	257	1,1	The title of the protocol should be included here for completeness.	
EFPIA	258	258	1,1	If estimand is defined in protocol, it should also be mentioned in the synopsis.	Suggest using the same title as section 3 of protocol
EFPIA	258	259		In case estimands have been defined, primary and any key secondary estimands should be defined. This will be the backbone of the trial. Please also update heading to add estimands, line 258.	
EFPIA/EFSPI Estimand Implementation Working Group	258	258	1.1	If defined, primary and any other important estimands should also be included in the Protocol synopsis	Add "{and Estimands}" to heading. Add to the instructional text (below point)
Estimand Review team	258	258	1,1	Endpoints can be seen as part of an estimand. Also, estimands should have a more prominent role in the title.	Change heading to "Primary and Secondary Objectives and Estimands (incl. Endpoints)"
TransCelerate BioPharma Inc.	258	261	1,1	If estimands are present, they should be included in the synopsis as equal importance to the objectives and endpoints, because the estimand is a core element of the study.	Recommend that the header "Primary and Secondary Objectives and Endpoints" also include Estimands, and clarify expectation to provide primary and secondary estimand in the synopsis.
Interpharma, Association of Switzerland's research-based pharmaceutical industry	258	258	1,1	If estimand is defined in protocol, it should also be mentioned in the synopsis.	Suggest using the same title as section 3 of protocol
Estimand Review team	259	259	1,1	As estimands are crucial for the understanding and planning of the trial, we propose to include them into a table. It would make sense not to include the full estimand description in the synopsis, but rather a high-level summary which is less detailed as the tables that will follow in section 3. Also, in order not to create a too lengthy synopsis, we propose to include only the primary estimand(s) and important secondary ones. "Important" secondary estimands could be ones related to objectives that are part of a confirmatory analysis strategy	Change to "Include a copy of the Objectives/Endpoints/Estimands Tables including primary and important secondary endpoints ..."
EFPIA	259	261	1,1	Is the intention to include all secondary objectives or just "key" secondary objectives? Please clarify.	
Estimand Review team	260	261	1,1	The sentence "Not all trials will have a complete estimand" may be true in some exceptional cases, but it gives a wrong impression to the reader. This could be better clarified in section 3, if needed.	Delete the sentence. One could add a statement that here in the synopsis not all details of all attributes might be requirted and that the full specification will be in Section 3.
EFPIA	260	261	Section 1.1	As per the current instructions, presumably a description of estimands in the protocol synopsis is not expected ("Not all trials will have a complete estimand." - The meaning of this sentence is not quite clear.). We agree that providing the full elaborate definition of estimands with all details in the synopsis will often not be appropriate. Instead, protocol authors may be encouraged to provide more specific trial objectives (describing the clinical question(s) of interest) in plain/layman language to ensure clarity and transparency.	Propose encouraging protocol authors to provide a short description of the clinical question or use more detailed clinical objectives, see Bell, J, Hamilton, A, Sailer, O, Voss, F. The detailed clinical objectives approach to designing clinical trials and choosing estimands. Pharmaceutical Statistics. 2021; 20(6): 1112– 1124. https://doi.org/10.1002/pst.2129
EFPIA	260	260		Please clarify what is meant by 'Not all trials will have a complete estimand', i.e. are there incomplete estimands? Do you mean 'not all trials will have estimands'?	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA/EFSPI Estimand Implementation Working Group	260	261	1.1	Unclear what you mean by "Not all trials will have a complete estimand.". Do all trials at least have “incomplete estimands” and what will that be? As per above point, it is best practice to encourage inclusion of estimands in the synopsis (though detailed breakdown into attributes and full rationale of strategy choices is not necessary in synopsis).	Suggest deleting: “Not all trials will have a complete estimand”. Suggest adding “include primary and key secondary estimands, if applicable; it Is not necessary to spell out each attribute but rather a concise form in a description is acceptable”
Estimand Review team	262	262	1,1	Endpoints can be seen as part of an estimand. Also, estimands should have a more prominent role in the title.	Change heading to "Primary and Secondary Objectives and Estimands (incl. Endpoints)"
EFPIA	262	262	1,1	For completeness, we suggest adding here a high level summary of the statistical methods (on primary endpoint and key secondary endpoints). This section could be reused in the CSR synopsis and CSR body.	We suggest adding here a high level summary of the statistical methods (on primary endpoint and key secondary endpoints)
EFPIA	262	262	1,1	It may be preferable that data is entered by each objectives/endpoints to enable content reuse.	Primary Objective [Objective X] Primary Endpoint [Endpoint X] Secondary Objective [Objective X] Secondary Endpoint [Endpoint X]
Quotient Sciences	264	264	1,1	Overall Design The word 'Several' at the start of the sentence is unnecessary.	Delete 'Several' and start the sentence with 'Key aspects'.
CSL Behring	264			Within the table that appears immediately after Line 264, it is not clear what information is expected to be provided regarding the ‘active comparator’. For example, is the intention that the sponsor should provide a generic name, international non-proprietary name (INN), brand name or all these details. Please clarify the requirement.	n/a
CSL Behring	264			Within the table that appears immediately after Line 264, we suggest that the table should include the study/test product and not only the control and/or active comparator.	Include a section for Study/test product in the table.
EFPIA	264	264	1,1	Please consider adding sex/gender as mandatory for Clinicaltrials.gov, jRCT (Japan Registory of Clinical Trials), and other clinical registration	{Sex/Gender}: [Sex/Gender]
EFPIA	264	264	1,1	We suggest adding a row for study phase (to have a summary of a comprehensive view of the study in this table).	We suggest adding a row for study phase (to have a summary of a comprehensive view of the study in this table).
EFPIA	264	265	1,1	Please clarify what is expected for the active comparator field; the name of the intervention, or something else? This field seems like a duplicate of the 'control' mentioned above.	Please clarify what is expected for the active comparator field.
Gilead Sciences	264	264		Suggest to present table as 1 column, as there is no side-by-side comparison or mapping needed	
TransCelerate BioPharma Inc.	264	264	1,1	Most protocols include a narrative summary of the study design in the synopsis, so users may be looking for this in addition to the structured table provided. The table does not include the overall/high-level purpose of the trial which the sponsor may want to include in the synopsis (which may be higher level than the objectives/endpoints/estimands).	Recommend including an optional section/variable field in the synopsis under overall design where narrative text can be entered to summarize the study design.
TransCelerate BioPharma Inc.	264	264	1,1	Available terms for this table should be restricted to standardized terms, which will maintain the use of consistent terminology that is globally accepted and support digitization efforts.	When defining the options for the fields in the overall design table, recommend following CDISC/NCI Standard Controlled Terminology options.
TransCelerate BioPharma Inc.	264	264	1,1	There is not a field for “trial population” in the overall design table. In the experience of TransCelerate member companies, CTCG has asked to add a bullet for main eligibility criteria; a field for trial population would address this request and provide key information to the user.	Recommend that the Overall Design table include a field for "Trial Population".

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	265	284	1,1	Per CTCG, please add instruction to provide a brief statement for the main exclusion criteria.	
Quotient Sciences	266	267	1,1	Overall Design, - intervention method A single intervention model cannot be used to describe a complex, multi-part phase 1 trial. Many first in human trials comprise multiple parts. For example, they may include a single-ascending dose part (which may be parallel-group, crossover or partial crossover), a crossover food effect part, age-effect and sex/ethnicity parallel-group comparisons, and a parallel-group multiple ascending dose part.	Allow specification of more than one intervention model, eg: Part 1: partial crossover Part 2: crossover Parts 3 & 4: parallel-group
EUCROF - EU CRO Federation	268	270	Protocol Synopsis	There should be more flexibility in protocol synopsis and body text of the protocol, by allowing the comparator to be identified by active substance or ATC code for registered products in a region, or in case of multiple regions, by different trade names.	Please add relevant instructional text in this respect
ICON PLC	268	270	1,1	Suggest including statement that both control and active comparator will fall under the definition of IMP and as such will follow safety oversight.	Suggest including some instructional text that control and active comparator fall under the definition of IMP.
EFPIA	269	269	1,1	Consider using sham comparator instead of sham procedure	
Quotient Sciences	271	273	1,1	Overall Design - trial intervention assignment method In ADME studies, a small group of healthy volunteers are all given a dose of radiolabelled IMP. There is no control. What should be entered here for those studies?	Please provide guidance for ADME trials.
EFPIA	272	273	1,1	Please explain why it is important to specify in this table the timing of randomization in relation to screening. We suggest deleting this instruction.	We suggest deleting instruction to specify timing of randomization in relation to screening.
Agios	273	273	1,1	The more relevant specification is the allowed window for when intervention will take place after randomization rather than when randomization will take place compared to screening (as it will typically be after eligibility has been confirmed)	Change to "If assignment to intervention is by randomisation, describe the allowed window for when intervention will take place after randomization"
CSL Behring	274	275		The sentence commencing on Line 264 provides some examples of trial population types. Trial populations could fulfill several such categories, e.g., healthy and adult, and it may also be important to know if either only males or only females are included, because this information does not figure elsewhere in the table. We recommend this section of the template is expanded upon to include further examples of population types, to account for the many eventualities that could arise. We also propose an administrative edit to remove the word 'trial' from the point in question, as it is obvious to the reader that the template is referring to a clinical trial.	Trial p Population type…
Agios	273	273	1,1	The more relevant specification is the allowed window for when intervention will take place after randomization rather than when randomization will take place compared to screening (as it will typically be after eligibility has been confirmed)	Change to "If assignment to intervention is by randomisation, describe the allowed window for when intervention will take place after randomization"
EFPIA	274	275	1,1	Does this description pertain to inclusion criteria only or should main exclusion criteria also be listed? Always or voluntarily?	Population description should include instruction around exclusioncriteria
Quotient Sciences	278	282	1,11	Overall design - Population age range For phase 1 trials that include an age comparison part, the majority of the trial would be done in young adults (eg 18-45 years) and only one group of older volunteers (eg 65-80) would be included. Would it not be more helpful to present age range by trial part?	For multi-part phase 1 trials, specify that age range should be specified per trial part.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
CSL Behring	281			Proposed amendment to the wording of the last sentence for clarity.	…, with an additional comment for the individual age ranges or for any excluded age ranges.
EFPIA	283	284	1,1	The tech specifications document instructs to include the country ID from the ISO country code list. If that is the case then it should be indicated here.	To align with the tech specification guidance, please instructs to include the country ID from the ISO country code list.
TransCelerate BioPharma Inc.	283	284	1,1	There could be variability in how the "site distribution" field is interpreted/used. Also, this information may not be known at the time of protocol finalization.	Recommend making "site distribution" a variable field (optional). Also, suggest clarifying exact meaning of this field; "site distribution" may be ambiguous, and could be interpreted as geographic scope (e.g. North America vs EU vs global) or single vs. multi-center.
Estimand Review team	284	284	1,1	Add a bullet point to explain that estimands need to be included. See also our comment on line 259.	"Include primary and other important estimand(s) that are relevant for decision-making (Please provide a high-level summary of each estimand, including the endpoint, summary measure, intercurrent events and estimand strategies to handle the intercurrent events)"
EFPIA	284	285	Section 1.1	Site distribution may not be known by the time of protocol finalization.	Suggest to make this a variable item.
EUCROF - EU CRO Federation	285	285	Protocol Synopsis	Could the Number of Arms section be integrated into the Arms and Duration section (Line 308)?	
Quotient Sciences	285	288	1,11	Overall design - Number of arms In a multi-part phase 1 healthy volunteer study, the maximum number of arms per part is not useful information. A typical multi-part first in human trial might have, for example, 6 planned single dose levels plus placebo, with one fed treatment, 4 planned multiple dose levels plus placebo, and examination of one dose level in different phenotypes, eg women, older volunteers, Japanese volunteers. Please can this be either not applicable for phase 1 exploratory trials or include a breakdown per part.	For multi-part phase 1 trials, specify that number of arms should be specified per trial part or allow an entry such as 'Varies with trial part' for multi-part trials.
EFPIA	285	285		Please consider providing a definition of 'arm'. In addition, please clarify how the number of arms should be determined, e.g. in platform trials/master protocols.	
EFPIA	285	288	1,1	Please consider allowing more flexibility when drafting this description and not restricting it to a specific number of arms.	Please revise to allow more flexibility when drafting this description and not restricting it to a specific number of arms.
EFPIA	285	346	1,1	Please consider including 'Number of Arms', 'Blinding' 'Number of Participants', 'Arms and Duration', and 'Commitees' also in the tabular format described in line 264.	
Agios	285	300	1,1	Please consider providing the option to include the number of arms/blinding scheme in each period rather than populating this field based on the period of the study with the gratest number of arms/blinding to avoid confusion.	
Charité Research Organisation	285	285	1,1	Number of Arms: The word "arm" is not frequently used in single and multiple ascending dose studies and studies with cross-over designs with e.g. two sequences.	Please consider to add other options
EFPIA	286	288	1,1	For trials with a different number of arms in different periods, listing only the period with the greatest number of arms might be misleading. Consider instructing to provide the number of arms for all periods.	
SÚKL CZ	287	288	Number of Arms	Sentense "populate this field based on the period with the greatest number of arms. "This approach will provide misleading information - arms for all periods should be stated.	Proposa sentense : "Arms for all periods should be listed"

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Freeline Therapeutics	289	344	1,1	It should be allowed to omit sections which are not relevant eg blinding, committees, especially if stated elsewhere e.g., 'open-label' is stated in study design/title. Including such sections only serves to lengthen the protocol unecessarily.	Add note to allow ommission of sections which are not relevant eg blinding, committees.
EFPIA	290	290		Note that the outcomes assessor can be a role at the sponsor.	
EFPIA	291	291	1,1	Please clarify that multiple roles may be selected if applicable.	
EFPIA	291	296	1,1	Please consider adding adjudicators as a category.	Please consider adding adjudicators as a category.
EFPIA	291	296	1,1	List of blinded roles is not complete. For example, Sponsors are not included. Does this imply that the sponsor is not considered blinded? Also, in some trials the pharmacist may be also blinded.	Please add "Sponsor" and "Other"
TransCelerate BioPharma Inc.	291	296	1,1	The current list of blinded roles may be limiting, and trials may include other blinded roles such as adjudicators or committees.	Recommend including adjudicators as an option for blinded roles and consider if a committee should be added as an option. A committee may be more applicable or widely understood than "outcomes assessor." Also consider if "other" should be an option here.
Charité Research Organisation	291	296	1,1	Blinding: Please consider adding "Sponsor" in this list.	
Interpharma, Association of Switzerland's research-based pharmaceutical industry	291	296	1,1	List of blinded roles is not complete. For example, Sponsors are not included. Does this imply that the sponsor is not considered blinded? Also, in some trials the pharmacist may be also blinded.	Please add "Sponsor" and "Other"
SÚKL CZ	293	293	masking	It should be clarified who a care provider is.	
EFPIA	293	293	1,1	Please define what "care provider" means. For example it could mean the clinical trial pharmacy, treating physician, nurse, or home care provider.	Please define what "care provider" means.
SÚKL CZ	297	298	masking	Sentense : "answer according to the portion of the trial in which the greatest blinding occurs" This approach will provide misleading information - summary for all the periods must be stated here.	propose to delete sentense "answer according to the portion of the trial in which the greatest blinding occurs"
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	298	298	5.1	To describe if there are some population restrictions in terms of ethnicity	
EFPIA	299	300		According to the template conventions this is instructional text not protocol text. However the protocol should also address blinding of sponsor. Consider changing to optional blue text, or adding a blue protocol text addressing blinding of sponsor roles for the sake of transparency.	
EFPIA	301	301	1,1	Suggest to change to red text as this statement appears to be guidance text. Or remove this sentence completely and add "indicates an open-label trial" in the text for the bullet on line 296	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Quotient Sciences	302	307	1,11	Overall design - Number of Participants In some phase 1 healthy volunteer trials, eg bioequivalence, ADME, it is planned to enrol N participants, with the aim of achieving n evaluable datasets. Those trials would fit well into the proposed structure. However, in complex multi-part phase 1 trials, the total number of planned participants is not very informative - it is much more useful to know how many are planned in each part, eg 64 planned in the single ascending dose part (6 per active dose level); 48 planned in the multiple ascending dose part (9 per active dose level). This section would be more informative if it allowed flexibility for multi-part phase 1 trials.	For multi-part phase 1 trials, specify that the planned number of participants should be specified per trial part.
CSL Behring	303			Suggest deleting "randomly" and invert "assigned" and "enrolled", as enrollment precedes treatment assignment, and assigned isn't always random.	Number {~~randomly assigned~~ enrolled to trial intervention/assigned ~~enrolled~~} …
EFPIA	303	305	1,1	A specific number of patients is sometimes difficult to achieve in clinical trials.	Please change to "State the approximate expected number of patients..."
TransCelerate BioPharma Inc.	303	304	1,1	The current statement may be limiting for some studies, so allowing more variability/flexibility to add text here may be necessary for some study types.	Recommend allowing flexibility to this statement or provide additional guidance on use for complex trials or trials with multiple phases (e.g., phase 2/3) or multiple parts (e.g., double-blind followed by open label part).
Interpharma, Association of Switzerland's research-based pharmaceutical industry	303	305	1,1	A specific number of patients is sometimes difficult to achieve in clinical trials.	Please change to "State the approximate expected number of patients..."
EFPIA	305	307	1,1	Please provide additional guidance on how studies with several phases (eg phase 2/phase 3) or several parts (eg double-blind part followed by open-label part) should be managed.	
EUCROF - EU CRO Federation	308	308	Protocol Synopsis	Is "Arms and Duration" suggested text (shown in blue) or is it a required subheading (shown in black), like for "Number of Participants"?	
Quotient Sciences	308	322	1,11	Overall design - Arms and Duration In complex multi-part phase 1 trials, the duration of intervention will vary depending on the part - eg single dose (for parallel group single ascending doses) versus 2 single doses (for food effect comparison) versus repeated doses for N days. Similarly, the duration of participation will vary depending on part.	For multi-part phase 1 trials, specify that duration should be specified per trial part.
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	308	334	1.1.	Arms and Duration: It needs to be clarified if duration is to be indicated separately for each arm. If it is not required, the section should be called "Duration" instead of "Arms and Duration".	
EFPIA	308	334		Please consider rewording the title. The instructions focus on the duration of participation and details regarding the study treatment (e.g., dosing regimen, route of administration). The synopsis should provide information that is analogous to that in the main body of the protocol, and vice versa.	There should be two separate titles in the synopsis: "Study Treatment" (analogous to Section 6, Line 587) and "Duration of Participation." The main body of the protocol should also include a section that covers duration of participation, by adding Section 4.5, entitled "Duration of Participation."
SÚKL CZ	309	309	Arms and Duration	Total "expected" duration is preferred	Total "expected" duration is preferred
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	309	310	1.1.	For duration of the trial, year(s), month(s) and day(s) are indicated. In some rare cases hours and minutes are also applicable.	The description should be adapted to: "Total duration of trial intervention for each participant: [Approximately] [x] Year(s)/[x] Month(s)/[x] Day(s)/[x] Hour(s)/[x] Minute(s)"

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	309	309	1,1	Please clarify what is considered duration of trial intervention. Eg, does it include the period during which drug is washed out (eg, after single dosing or after the last dose for multiple dosing). Please also clarify what to use when there are several single doses given in same individual but with several weeks in between (eg, in cross-over design or in dose escalation studies).	
EFPIA	310	310	1,1	total duration of trial intervention for each participant: do we have the option to enter e.g 4 days as 4 single doses in 4 separate periods?	flex to add more that only number of days of months
CSL Behring	312			Propose an amendment to the subheading for the purpose of clarity/readability.	Duration will vary because of/depending on…
SÚKL CZ	313	313	Arms and Duration	Total "expected" duration is preferred	Total "expected" duration is preferred
CSL Behring	316			Propose an amendment to the subheading for the purpose of clarity/readability.	Duration will vary because of/depending on…
EFPIA	323	335	1,1	We recommend adding a definition for End of Study here. It is a specific requirement by Competent Authorities for trial registries and must be defined in the protocol.	We recommend adding a definition for End of Study here.
CSL Behring	327			It is unclear what the difference between the two terms "period" and "stage" is as they are used in the template. For example: is period intended to be the broader term, and there can be several stages (i.e., phases) within a period? If there is no difference intended, we suggest that the reference to "stage" be deleted.	Dose regimens in each trial period ~~and stage~~ (if applicable) …
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	327	327	6.1	To specify if the drugs is under orphan drug designation	
EFPIA	330	332	1,1	This section can be very extensive (eg dose adjustments may vary according to types of AEs and number of reasons leading to discontinuation can be large), further instructions would help.	
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	336	346	1.1.	Committees: This section should be moved to the administrative section at the beginning of the document.	
EFPIA	336	346	1,1	Please provide instruction to clarify that committees should be listed only in the 2 content fields 'Independent committees' and 'Other committees'. This would impact the technical specifications document.	Further clarity on how committees should be pressented is needed.
EUCROF - EU CRO Federation	342	342	Protocol Synopsis	Incorrect section name and number.	Change section name and number from "10.3 Committees Structure" to "10.2 Committees".
EFPIA	342	342		Reference to Section 10.3 should be 10.2	
LFB Biotechnologies	342	342		Error in the referenced section, Commitees structure is in 10.2 instead of 10.3	described in section 10.2 Commitees structure

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
TransCelerate BioPharma Inc.	349	349	1,2	There is some inconsistency in the use of terminology regarding trials arms and trial interventions vs. treatment groups. This also applies in Section 6 Study Intervention and throughout document where applicable.	Recommend ensuring clear and consistent use of terminology in this section and elsewhere in the document.
CSL Behring	350			Please clarify if the reference to “epochs” is intended to have the same meaning as “stage” referenced earlier in the template (ref: Line 327). We recommend using one term throughout the template, if possible, for consistency.	n/a
CSL Behring	352			Propose an amendment to refer to end of study and post-treatment follow-up as examples of progression of trial periods.	…(such as screening, washout/run-in, intervention, and key milestones [for example, randomisation, cross-over, end of treatment, end of study, post-treatment follow-up]).
EUCROF - EU CRO Federation	355	355	Section 1.3	Suggest adding an example Schedule of Activities table.	
EFPIA	355	355		Recommend adding any text to specify, when applicable, include a separate PK sampling schedule table.	
EFPIA	355	361	1,3	Please clarify whether the Schedule of Activities has to be in text format or whether tabular format is also acceptable.	
EFPIA	356	359		Please clarify whether the Schedule of Activities can be a high-level summary of procedures, including elements such as 'laboratory assessments' or whether more detail on e.g. individual lab assessments is expected.	
EFPIA	356	359		Suggest to also to specify whether it is home, clinic or off-site activities/visit	
ICON PLC	356	359	1,3	Suggest verbiage for the schedule of activities captured includes collections/assessments completed/could be completed by remote methods. Possible wording: "....intervention discontinuation, whether completed in person or through remote methods."	Current wording includes varied contact with the participant to be captured but not specify varied types of activities. Suggest clarity of meaning with increased 1)decentralized trials and 2) need for adaption throughout trials.
EFPIA	357	357	1,3	With the instructional text below, the term Study Rationale seems more precise	
EUCROF - EU CRO Federation	359	359	Section 1.3	The term “medicinal product” is used in different sections of Protocol template and in the guideline, while the term “trial intervention” in section 1.3 and section 6 (header) of Protocol template.	
Quotient Sciences	359	359	1,3	Allowable windows should also be specified for trial procedure timepoints. In phase 1 trials, which have a very intensive schedule of procedures, multiple procedures are often scheduled at the same timepoint (eg vital signs, PK blood sampling, ECG, AE questioning, PD measures) so protocols specify time windows for those procedures. It's typical, for example, to allow all pre-dose procedures to be done within 1 h before dosing, and for PK samples to be taken within 5 min of the scheduled time for, say, the first hour after dosing, and within 15 min until 24 h after dosing, and within 1 h after 24 h post dose. In addition, most first in man protocols include flexibility in timepoints (eg timepoints may be added, changed or removed to improve the quality of the emerging data). This section is the best place to include that information. Note that there will be multiple schedules in multi-part phase 1 trials.	Please add: 'Allowable windows should be stated for all visits and timepoints. Any flexibility in the schedule of activities, such as scope to add, change or remove timepoints should be described.'
CSL Behring	360			Please clarify if there is a reason why no example Schedule of Activities table is included in the template. Such a template would provide a suggested format/layout and standardize the wording around at least some of the activities. The accompanying guideline states that this template is developed with the investigator/study site in mind, and this is usually a central piece of information. We find it odd that an example would not be proposed for inclusion.	n/a
EUCROF - EU CRO Federation	362	362	Section 2	Background section is not available in the M11 template. This section was useful for the medical writer to include a summary of findings from non-clinical studies that potentially had clinical significance and from other clinical trials that were relevant to the clinical trial. It is not clear from the template where this information should be included (2.1)?	Please consider adding Background section and instructions where summary of findings from non-clinical studies that potentially have clinical significance are to be specified. Suggestion is made on the basis of ICH E6(R2) (among others, for example CTR protocol requirement 17(c)).

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUCROF - EU CRO Federation	362	362	Section 2	Plus Lines 388, 396, 472, 399 Is it necessary to have the rationale included for each segment? This adds to the length of the protocol and the different rationale sections are likely to overlap. Duplications should be avoided.	Consider combining all rationale sections (Rationale for Trial Design, Rationale for Trial Population, Rationale for Trial Intervention) and possibly the Purpose of the Trial section into a single subsection of the Introduction. Give instruction for which topics a rationale should be given.
CSL Behring	362			It is unclear where in Section 2 Introduction the details of the investigational medicinal product (IMP) and its mechanism of action should be introduced. Whilst we assume that the summary of benefits and risks are related to the IMP in addition to the clinical trial itself, clarification is sought around this issue.	n/a
SÚKL CZ	363	363	Introduction	A subsection for a summary of available clinical data regarding the study intervention is missing and should be amended (this is also in line with ICH GCP E6R2 point 6.2.2 - summary from nonclinical and clinical trials that are relevant to the trial). Such an information is not sufficiently covered by the list of benefit/risk summary and also might not always be sufficiently described in IBs/SmPCs of the study drugs, for example in case when a new combination of drugs is to be investigated For new drug combinations rationale for the combination must also be stated, including the potential for drug-drug interactions (between the study interventions) based on available clinical/nonclinical data etc. Since this is not covered by any of the prespecified sections, section for a summary of available clinical/nonclinical (when relevant) data must be amendned. Also, the protocols often contain more up-to-date data compared to IB, therefore this should be amended	Add chapter summary from nonclinical and clinical trials that are relevant to the trial
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	364	369	2.1.	Purpose of Trial: A clinical trial is a scientific project. As such it needs a sound rationale, stating the research question as well as a discussion of available evidence in favour of the trial. We suggest changing the heading to "Rationale of the Trial", and extend the instructions accordingly (see SPIRIT item 6a).	We suggest to change the heading to "Rationale of the Trial". Add the following text: "Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention"
EFPIA	364	364		The Introduction starts off directly into why the trial is needed and why the research questions being asked are important. Suggest adding that there should be at least some small quick background into the compound being investigated.	
Agios	364	369	2,1	With the goal of reducing redundancies within a protocol, a section of "Purpose of trial" may be deemed redundant with other Sections in the template including Section 3 (trial objectives), Section 4.2 (Rationale for trial design) and Section 5.2 (Rationale for Trial Population) . Alternatively consider rewording this Section 2.1 as "Study Rationale"	Delete section or retitle as "Study Rationale".
Quotient Sciences	365	366	2,1	We are instructed not to restate the IB. However, a summary of key data from the IB is useful to put the trial into context for members of the investigator's team and the ethics committee who do not review the IB. For example, in a first in man protocol, a summary of the NOAEL data and explamation of the most relevant species is invaluable background information to aid review of the chosen starting dose and exposure limit. Effects in animals above the NOAEL exposure is also necessary background information for the later discussion of risk-benefit.	Please allow a brief summary of key information from the IB.
CSL Behring	365	366		The instructional text notes "do not restate the IB". Please clarify if, in context, "restate" means to include too much detail from the IB, or to "use different wording than in the IB". For example, if there is a succinct, internally approved paragraph on the purpose of the trial(s) contained in the IB, is it acceptable for such content to be included in this section? We suggest that the existing instruction is made more precise, such that the expectations are clearer.	n/a
EFPIA	365	365		What is meant by research question here? This is apparently not the same as the clinical question that is being introduced in section 3, i.e., basically the estimand. Suggest specifying that this is not a repetition of the objective.	
EFPIA	365	366	2,1	Suggest adding instructions to cross-reference the IB as appropriate.	No re-statement of IB content should be done in the protocol.
EFPIA	365	365	Section 2	The introduction lacks a subsection on (clinical) background.	Suggest to insert such item

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	365	365	Section 2.1	The subsection "Purpose of Trial" in the beginning of the introduction is welcomed. However, before explaining why the research questions are important, it may be helpful to explicitly state the research questions.	Consider providing instruction that the actual "research questions being asked" should be provided (along with a rationale) either here or refer to the respective CSP section (current Section 3?), if applicable.
EFPIA/EFSPI Estimand Implementation Working Group	365	365	2.1	We support the need to justify the purpose of the trial; however: 1) It is unclear what is meant by "research question" and how that differs from the clinical question of interest [Section 3, ICH E9(R1)] 2) Given this section should introduce the clinical background, suggest instead this refers to unmet medical need and purpose of the intervention itself.	Clarification and/or alignment with "clinical question of interest" terminology in other sections (Section 3 etc) Consider removing or rewording "research question" from here and rewording to: Explain the unmet medical need in the clinical setting and thus, purpose of the intervention itself and why the trial is needed.
TransCelerate BioPharma Inc.	365	365	2	Typically titled "Background" or similar, nonclinical and/or clinical background information is content that is commonly included by sponsors to provide a brief overview of the study intervention to the user. Therefore, it would be helpful to indicate placement for this in the template. This is also an expected section in the CSR, so for content reuse and continuity it should be included in the protocol.	Recommend including a separate level 2 heading within the Introduction section for a brief summary of relevant clinical and nonclinical data.
EFPIA	367	369	Section 2.1	The description of this section suggests that "rationale" is asked for here, rather than "purpose" (which may be viewed as identical to "objective").	1. Specify exactly what is expected in this section. 2. Provide a clear definition of all terms used that may not be universally self understood.
Boehringer Ingelheim	368	368	2,1	Remove the word "the" in, "Refer to the Section 1.2, Trial Schema, and Section 1.3, Schedule of Activities, for"	"Refer to Section 1.2, Trial Schema, and Section 1.3, Schedule of Activities, for"
Freeline Therapeutics	368	369	2,1	This section does not discuss trial design so there is no need to include a reference to 1.2 & 1.3	Delete reference to 1.2 & 1.3
TransCelerate BioPharma Inc.	368	368	2,1	It is important not to confuse this section, "Purpose of Trial," with the objective of the study as that is not the content that is intended here.	For the section heading "Purpose of Trial," it is recommended to ensure clarity in terminology. "Rationale" may be a better selection to differentiate from the trial objectives, and it better corresponds to the requirements of the CSR. The term "research question" may also be difficult to distinguish from clinical question of interest/estimand.
ACRO (Association of Clinical Research Organizations)	370	405	2,2	The EMA Recommendation Paper on decentralised elements in clinical trials, December 2022, makes reference to including a specific and documented risk benefit assessment. The Recommendation Paper states that "This risk benefit assessment as well as any risk mitigation action taken should be clearly described in the clinical trial protocol or other protocol related document as part of the clinical trial application to the MS." ACRO suggest including provision for this within section 2.2 of the Protocol Template and the associated section of the Technical Specification.	Line 398. Add "Include risk benefit assessment and any risk mitigation for decentralised clinical trial (DCT) elements proposed for use in the study."
EFPIA	370	370	2	Please consider adding a new Section 2.2 (after Section 2.1 'Purpose of Trial and before the current Section 2.2 'Summary of Benefits and Risks') to include 'Key Background Information' as a section to include key information on the relevant clinical/preclinical background information (eg, stage of development, key clinical information) for the study (without restating the IB). This could reference the rationale sections and vice versa, to put the relevant information in the most appropriate section and support the benefit-risk assessment for investigators to clearly understand the context of the study.	Add a new section (Section 2.2) heading 'Key Background Information' (or similar) with guidance on keeping this limited to relevant key background information only, to support the benefit-risk assessments and study rationale, with brief examples.
CSL Behring	371			We propose a simple amendment to language used to refer to identified and potential risks.	Include an assessment of known benefits and identified and potential risks, …
CSL Behring	373			The template states that the "Benefit Summary" should be "written from the perspective of an individual participant…" whereas the protocol template section relating to overall benefit: risk conclusion (ref: Line 400) appears to be focused on the benefit for the overall trial i.e., cumulative safety data, protocol procedures etc. In our opinion this appears to be a disconnect between the two sub-sections of 2.2.	n/a
Freeline Therapeutics	373	373	2,1	Would benefit from being a Level3 heading	Make this is Level 3 heading

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
TransCelerate BioPharma Inc.	373	373	2,2	It should be clarified in the start of this section that this is in regard to trial participation for an individual trial subject.	Suggest including this reference to the individual subject and trial participation in the instructions immediately following 2.2, and then it does not need to be repeated in the below sections.
EFPIA	374	374	Section 2.2	It should be spelled out that B/R for trial participants is the topic here.	Add "for trial participants" after "…and potential risks…"
EFPIA	374	377	Section 2.2	The participant's perspective should be taken for both, benefits and risks. No need to spell this out twice.	Delete "should be written from the perspective of an individual participant , and"
CSL Behring	375			Reference is made to "other potential benefits", whereas Line 371 refers to "known benefits". Please review terminology used for consistency across the section of the template.	n/a
Quotient Sciences	378	380	2,2	Benefit summary The template instructs the author to describe all potential benefits (not only medical benefits). Ethics committees have previously objected to any acknowledgement of any non-medical benefits (eg social, altruism) in healthy volunteer studies.	
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	381	381	2.2.	It is indicated that benefits to society in general may also be included but should be discussed separately. It needs to be indicated in which section this information should be included.	
EFPIA	383	387	2,2	We suggest adding guidance text to indicate that this section can only be updated/entered if a "first-in-human" study has been conducted or a "proof-of-Concept" study has been done, to ensure prior knowledge of any possible anticipated risks. Otherwise, risks would be unknown until the trial with the new IMP has been carried out. Not all risks are known at study start, especially for a novel compound or first-in-class compound. Also, including a mitigation strategy would imply anticipation of all potential risks, which may not be applicable.	We suggest adding guidance text to indicate that this section can only be updated/entered if a "first-in-human" study has been conducted or a "proof-of-Concept" study has been done
EFPIA	383	387	2,2	Propose to allow/state that the presentation of risk summary and corresponding mitigation strategy can be presented in a tabular format.	
Freeline Therapeutics	383	383	2,1	Would benefit from being a Level3 heading especially as unnumbered sub-headings follow	Make this is Level 3 heading
Charité Research Organisation	383	383	2,2	Please consider to insert a table for risk mitigation including the potential risks, summary of the rationale of the risk and mitigation strategy	
CSL Behring	384			Please clarify the difference between "trial intervention" and "treatments". In this context, does "treatments" also include concomitant therapies such as rescue medication, etc.	n/a
EFPIA	384	384	2,2	Trial intervention is not only the investigational compound but also placebo and active comparator. Consider adding to the instruction that risks related to the use of active comparator should be discussed separately from those of the investigational product.	
SÚKL CZ	385	385	Risk Summary and Mitigation Strategy	"Only" should be removed. Broader risk information and mitigation should not be discouraged.	"Only" should be removed. Broader risk information and mitigation should not be discouraged.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	385	387	2.2	Section 2.2 has instructions indicating that sponsors can cross-reference a protocol section that covers risks and risk mitigation strategies, but there is no such section in the template. Some sponsors have protocols that devote 30+ pages to describing risks and risk mitigation strategies, including comprehensive guidelines for managing patients who experience adverse events considered identified risks (e.g., by interrupting, resuming [rechallenge], or permanently discontinuing study intervention or by reducing the dose). The M11 template doesn't have a separate section for describing this type of information, and it is too lengthy to include in Section 2.2.	Add a subsection (8.4.XX) entitled "Safety Plan: Management of Adverse Events" with instructions stating that the section should describe identified risks and risk mitigation measures, including guidelines for managing patients who experience adverse events considered identified risks. Management could include initiation of medications, reducing the dose, or interrupting, resuming (rechallenge), or permanently discontinuing study intervention.
EFPIA	386	387	2,2	The instruction includes " ...or provide a cross-reference to the relevant protocol section." However, the only protocol section that also talks about "risks" is 8.3.5 Suicidal Ideation and Behaviour Risk Monitoring. (Section 11 is about "quality" risks). Is it the intent that for specific other risks where risk mitigation is put in place sections are added? Please clarify.	
CSL Behring	390			Propose a revision to the existing language to refer to mitigation of risk.	….and any measures to control or mitigate the risks.
EFPIA	394	394	2,2	Suggest to delete, since this is already stated in line 391-392.	
EFPIA	395	395	2,2	Suggest that cross-reference be made to the IB instead of another section of the protocol (or at least that the IB is suggested as a document to cross-reference	
EUCROF - EU CRO Federation	397	398	Section 2.2		Add in-vitro diagnostic devices, as a separate category of companion products in a clinical trial. Add also instructional text whether or not the IVD is approved for the intended purpose in the respective region where CT is conducted.
Quotient Sciences	397	398	2,2	Trial-specific Discussion of Procedure Risks and Mitigations Exposure to ionising radiation should be included in the list of other risks.	Please add to the list of other items: 'exposure to ionising radiation'.
EFPIA	397	397		Comparators are by definition part of the trial intervention, and would be addressed above. Please delete here or else clarify the intention.	
EFPIA	397	399		[Minor] Original Text: "Other – Consider risks associated with other items (for example, comparators, challenge agents, imaging agents, medical devices). Insert a line for each, as needed." The examples listed in Other Risks and Mitigations can fall in either interventions or procedures. Having this section is confusing to authors and creates opportunity for redundancy.	Recommendation to delete other risks and mitigations section and consolidate with interventions and procedures.
Eva Degraeuwe, Ghent University, BPCRN	398	398	0	Medical devices are included, but looking ahead MedTech trials will be used for (longitudinal) use. It would be good to include or plan a section.	
Freeline Therapeutics	400	400	2,1	Would benefit from being a Level3 heading	Make this is Level 3 heading
CSL Behring	403	404		It is our understanding that the statement 'Risks need to be assessed against the benefits for the individual participant at least once a year' presumably refers to the annual review of the Investigators' Brochure (IB). If so, we propose a revision to omit reference to individual participants because the risk/benefit for each specific participant is out of scope of the or IB and is based upon the clinical judgment of the investigator. Furthermore, it is not clear from the instructional text if this section needs to be reviewed and updated every year, or is it referring solely to the IB. Please clarify the intent of this guidance.	Risks need to be assessed against the benefits ~~for the individual participant~~ at least once a year.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	403	404	2,2	Please clarify when the clock starts when referring to yearly risk assessment: is it counted as of protocol finalisation, as of first patient in? Or is it related to the international birthdate (ie, aligned with DSUR reporting)?	Pls clarify or remove "Risks need to be assessed against the benefits for the individual participant at least once a year." as it might create confusion on the need to yearly update the protocol risk-benefit section.
EFPIA	403	404		Unclear what is meant by 'Risk needs to be assessed against the benefits for the individual participant at least once a year." This seems to be an odd statement, since risk for the individual participant should be evaluated continuously. If it refers to evaluation of the benefit-risk of the drug, this is part of the yearly update of the IB. The statement is unclear and could be interpreted as an extra scheduled activity to be documented, which brings no additional value. Please clarify or omit this sentence.	
EFPIA	404	405	3	Include additional level 2 headers under Section 3 Trial Objectives, Endpoints, and Estimands as needed.	Include additional level 2 headers under Section 3 Trial Objectives, Endpoints, and Estimands as needed.
EFPIA	407	415		Section 3 has Level 2 subheadings (e.g., Section 3.1) for different categories of objectives, but many sponsors present objectives and endpoints in a single table, with no need for any Level 2 subheadings in this section (especially if estimands do not come into play, which is often the case for Phase I studies).	To make it clear that the Level 2 subheadings can be omitted, the entire Section 3.1 heading should be formatted in a blue font. Sponsors that present objectives and endpoints in a single table will have a sentence that introduces (precedes) the table and will include a title for the table (e.g., Table XX: Objectives and Endpoints).
EFPIA/EFSPI Regulatory ESIG	407	422	3	The template tries to incorporate the estimand framework as defined in ICH E9(R1). However, the result is a hybrid version between the old paradign (objective --> endpoint) and the new one (objective --> estimand). As a matter of fact, in the estimand framework the "endpoint" is one of the five attribute of an estimand, hence we do not see the need to call it out in this section. The "endpoint", along with the other attributes, should be described with the estimand. We would therefore recommend removing any reference to "endpoint" in this section (see an example on the right). If the intent is to allow some flexibility for studies not designed using the estimand framework, please add a clarification note.	"TRIAL OBJECTIVES, ENDPOINTS AND ESTIMANDS"
TransCelerate BioPharma Inc.	407	407	3	To clarify why the estimand justifies the study objectives, there should be a requirement to include justification of choice of estimand(s).	Recommend including a rationale for estimand selection in Section 3, with instructions to specify the rationale below (each) estimand.
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	408	409	3	It is indicated that each clinical question of interest should be defined by stating each trial objective and specifying the endpoint(s) and estimand(s) that correspond to each objective. However, there can be objectives such as "Does intervention X lead to a reduction in blood parameter Y" that are legitimate to understand mechanisms even if they are not considered clinical per se. We suggest deleting the word "clinical" in this sentence.	The description should be adapted to: "In this section, precisely define each question of interest by stating each trial objective and specifying the endpoint(s) and estimand(s) that correspond to each objective."
Takeda	408	421	3,1	We suggest updating the text to be inclusive of studies that do not require estimands.	
EFPIA	408	410	3	Please clarify if is it expected to use the estimand framework for all types of objectives or is it primarily expected for efficacy objectives. For example, consider whether an estimand framework should be used for a safety objective in a trial where the primary objective is to demonstrate efficacy.	Please clarify if is it expected to use the estimand framework for all types of objectives or is it primarily expected for efficacy objectives.
EFPIA	408	408		Clinical question of interest is not the same as the combination of objectives, estimands and endpoints. Suggest rewording, e.g. "In this section, precisely define each objective, associated endpoint(s) and, where applicable, associated estimands."	Suggest rewording, e.g. "In this section, precisely define each objective, associated endpoint(s) and, where applicable, associated estimands."
EFPIA/EFSPI Estimand Implementation Working Group	408	409	3	We disagree that the clinical question of interest is the combination of estimands, endpoints and objective. The wording here seems to mandate the use of estimands, is this intended? Estimands are most often not appropriate for exploratory objectives, which are often (deliberately) vague.	Update to: "In this section, precisely define the aims of the trial by stating all objectives, their corresponding endpoints and, where applicable, their estimands. Estimands for exploratory objectives are not required."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
TransCelerate BioPharma Inc.	408	412	3	The current wording suggests that estimands are required in all protocols, but this is not the case. Also, the use of “clinical question of interest” may not be interpreted consistently. The clinical question of interest should address the same attributes as the estimand except perhaps the population-level summary, so should essentially be the estimand worded as a question.	Include statement that estimand is not required for all protocols. Recommend rephrasing the instructional text for this section to ensure clarity on what is meant by "clinical question of interest." as this is not totally equivalent to the sum of trial objective/endpoint/estimand.
Estimand Review team	409	409	3	Endpoints are part of an estimand, so no need to mention them explicitly.	Delete "endpoint(s) and"
Estimand Review team	409	409	3	Add more details for clarity	Change sentence to "...specifying estimand(s) (i.e. the research question(s) of interest being addressed with the clinical trial) that correspond to each objective."
EFPIA	411	412	3	Please clarify how additional 2-level headers may be used. It is not clear in which cases additional level 2 headers are expected. It may be helpful to insert some additional common 2 level headers and keep them optional.	Please clarify how additional 2-level headers may be used.
Estimand Review team	414	415	3,1	Endpoints can be seen as part of an estimand and not vice versa. Also, estimands should have a more prominent role in the title.	Change Section 3 heading to "Trial Objectives and estimands (incl. endpoints)"
Estimand Review team	414	415	3,1	See above, in line with explanation for section 3 heading	Change to {Primary/Secondary/Exploratoty} Objective + Associated Estimand {and Endpoint}
Quotient Sciences	414	422	3,1	Estimands are not applicable to exploratory phase 1 healthy volunteer trials, such as first in man trials, where effficacy is not an objective. Phase 1 protocols do, however, define evaluable participants and circumstances under which data will be excluded from the analysis. They may also specify whether any data may be imputed for interim or final analysis. Please clarify whether estimands would be required for pivotal bioequivance trials or QTc trials in healthy volunteers.	Please specify that estimands are required where efficacy is the primary objective, but not for exploratory trials, and clarify whether they are needed for pivotal bioequivance trials or QTc trials in healthy volunteers.
EFPIA	414	422	3,1	In studies with multiple estimands, the first two attributes (treatment condition and target population) will almost always be the same for all estimands. Additionally, the intercurrent events and population summary attributes may be the same for multiple estimands. This will create a lot of redundancies if all attributes are provided for all estimands.	Permit common estimand attributes to be specified a single time.
EFPIA	414	422	3,1	It seems that the intent regarding intercurrent events in this section is to merely name the IEs. To be consistent with E9(R1), the *strategy for addressing the IEs* should also be provided.	Include a requirement to indicate the strategy for addressing intercurrent events.
EFPIA	414	414		Shouldn't the section number 3.1 be black (mandatory)?	
EFPIA	414	414	3	Please adjust title to allow for multiple objectives and endpoints: Objective(s)/Endpoint(s)	Objective(s)/Endpoint(s)
EFPIA	414	415	3,1	Please clarify if each objective needs to have its own level 2 header or if multiple objectives can be included in the same table, using multiple rows. For example, are all Secondary Objectives supposed to be specified in Section 3.2?	
EFPIA	414	416		The existing options for endpoints include "Primary/Secondary/Exploratory", but we suggest considering an "Other” option if the intent is not to only capture one of the three existing options.	
EFPIA	414	421	3,1	The endpoint is an attribute of the estimand. If this template would like to embrace the estimand framework, then the table should exhibit all 5 attributes of the defined estimands. If estimands are not defined for some objectives (such as for the exploratory objectives) then the table can display the endpoints only.	
EFPIA	414	414		Should be "Endpoint(s)" for primary and "Endpoints" for secondary and exploratory endpoints	
EFPIA	414	415	3,1	The proposed flexible section header is not clear. It seems that a section header could, eg, read "Primary Objective + Associated Endpoint and Estimand". Is this intended?	Suggest clarifying the use to the header, avoiding "+" and "and". An alternative could be "{Primary/Secondary/Exploratory} Objective, Associated Endpoint(s) {and Estimand(s)}"

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	414	422	3,1	It´s unclear how the estimand attributes should be provided, eg below table or within table	Use a single table for objectives and estimands. This provides a line of sight between them. To facilitate tools that electronically extract endpoints for public registers, each endpoint is separated from the other 4 estimand attributes and from other endpoints for an objective. For example:
EFPIA/EFSPI Estimand Implementation Working Group	414	415	3	The structure of the section is unclear, and the title should not include a "+" sign. Suggest including "Estimands" in the title and not only as optional even though estimands are not always required	Suggest splitting Section 3.1 Primary Objective(s), Endpoint(s) and Estimands Section 3.2 Secondary Objectives, Endpoints and Estimands Section 3.3 Exploratory Objectives, Endpoints and Estimands Add instructional text: "Estimands should be used for primary and key secondary objectives in confirmatory trials, but otherwise optional."
Agios	414	416	3,1	Estimand for exploratory endpoints should be optional	Consistent with line 415, please make "Estimand" in line 416 blue text
Freeline Therapeutics	414	415	3	Rename heading simply to 'Objectives and Endpoints'.	Rename heading 'Objectives and Endpoints'.
Estimand Review team	415	416	3,1	We cannot have a table where the caption says "estimand" and the two columns are on Objectives and Endpoints only. We suggest to replace the "Endpoint" column with "Estimand" (which will include endpoints). This table will probably have to be further revised to be more granular in the estimand column and to reflect the other ingredients of a complete estimand definition.	Revise the table and reflect Estimands in it and not only Endpoints.
Quotient Sciences	415	416	3,1	The table of objectives and endpoints should include an instruction to indicate the relevant part(s)/cohort(s) of a multi-part trial. For example, an objective to determine time to steady state would apply only to the multiple dose part of a multi-part first in man trial and an objective to determine the effect of food on PK would apply only to the food-effect part.	Please add an instruction to indicate the relevant part(s)/cohort(s) of a multi-part trial.
SÚKL CZ	415	415	endpoins	It should be indicated that each endpoint should correspond to the respective objective.	It should be indicated that each endpoint should correspond to the respective objective.
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	415	415	3.1.	{Primary/Secondary/Exploratory} Endpoint Please add an explanatory text regarding endpoints. Endpoints have to be operationally defined. It has to be completely clear how they are derived from the data for every single patient. See SPIRIT item 12 "including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome."	
EFPIA	415	416	3	We prefer to present the objective(s) and endpoint(s) in 1 single table with the primary, secondary and exploratory sections clearly identified.	
EFPIA	415	415	Table	Suggest adding an optional column for estimand labels, so objectives and estimands are linked.	
EFPIA	415	415	Table	Please use "[Endpoint(s)]" for primary and "[Endpoints]" for secondary and exploratory endpoints.	
EFPIA/EFSPI Estimand Implementation Working Group	415	416	3.1	The table(s) should be able to accommodate multiple endpoints per objective	Change the "Endpoint" field to "Endpoint(s)"
EFPIA/EFSPI Estimand Implementation Working Group	415	416	3.1	Linking of objectives and estimands is important.	Suggest either to add cross-reference to Estimand labels/sections in the "Endpoint" column ([Endpoint] [See Estimand label]) or add an optional third column with the link.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
TransCelerate BioPharma Inc.	415	415	3	It is common for a single objective to have multiple endpoints (such as an objective of safety with several safety-related measurements as endpoints); therefore, this option should be clearly allowed in the template. Multiple endpoints are allowed per the technical specification.	Suggest making the objectives/endpoints table clear that each objective could have more than one endpoint – i.e., change "endpoint" to "endpoint(s)"
Estimand Review team	416	416	3,1	While the estimand framework is useful for any estimand (primary/secondary/exploratory), it might be sensible stating that exploratory endpoints can be included optionally.	
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	416	421	3.1.	{Primary/Secondary/Exploratory} Estimand For each objective there is a) the endpoint, i.e. what is measured in a single patient, b) a population estimand, i.e. that characterizes the endpoint in a single population c) a difference estimand that is used to characterize the contrast between the comparators. Example: Compare overall survival between arms a) Time to death or last observation with vital status indicator. b) Survival curve and 5 year rates (or median or..) c) Hazard ratio (assuming proportional hazards) Additional information should be moved to the section 9.	
EFPIA	416	416		Shouldn't this be blue text since "{and Estimand}" in the level 2 heading is blue?	
EFPIA	416	416	3,1	We suggest providing more guidance and instructional text based on ICH E9 R1 about estimands that can be defined, to clarify which estimands are mandatory or recommended among primary, key secondary, other secondary and exploratory, as well as some examples.	We suggest providing more guidance and instructional text based on ICH E9 R1 about estimands that can be defined
Freeline Therapeutics	416	421	3	Include additional Level 2 heading 'Estimands' for this information (perhaps with Level 3 heading for 'Primary Estimand' and 'Secondary Estimands'	Include additional Level 2 heading 'Estimands' with Level 3 headings for 'Primary Estimand' and 'Secondary Estimands'
Charité Research Organisation	416	416	3,1	Should be an optional heading	
EFPIA	417	420	3,1	It is important to state the justification of the selected estimand, and clinical rationale of the selected strategies for accounting intercurrent events.	Suggest adding references to Section 4.2 and Section 9.2.2 where the template provides the rationale of endpoint selection, estimand and clinical rationale of intercurrent event handling strategies
EFPIA	417	418		A clinical/regulatory justification of the estimand(s) is required in the protocol. It has not been mentioned explicitly anywhere, but justification of some of the attributes are scattered around the protocol. Suggest including the rationale for the primary and key secondary estimand in the level two sections in section 3.	
EFPIA	417	418		Describe the attributes that construct the estimand: the treatment condition of interest, the population of patients/individuals targetd by the clinical question of interest …	
EFPIA	417	418	3,1	For most of the studies, the "population of participants targeted by the clinical question of interest" will be the same for all objectives. How should this be managed to avoid repeating the same information many times? The same question applies for the "treatment condition of interest" that can be the same for all the objectives.	
EFPIA	417	420	3,1	Template text or format for each estimand attribute and the overall estimand definition could be useful for consistency across protocols. Including the estimand attributes in the table would address this issue.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	417	420	3,1	"ICH E9(R1) states “Precise specifications of treatment, population and variable are likely to address many of the intercurrent events considered in sponsor and regulator discussions of the clinical question of interest”. Therefore, the order of the attributes should be rearranged, with some adaption to the wording. It might be helpful to state where all of the intercurrent events are to be identified, if the estimand definition itself is only addressing other intercurrent events. It might be difficult to identify intercurrent events that are addressed via the treatment, population or variable attributes. See also line 753 where it says ""... must align with the intercurrent events introduced in Section 3..."". This implies that Section 3 lists all intercurrent events explicitly. The population is referring to the target population. Therefore, please replace ""participants"" by ""patients/individuals"". Regulators seem to expect a rationale for key estimand(s). For some of the estimand attributes rationales are to be provided in other sections of the protocol. A rationale for the strategies for handling intercurrent events, or preferably, the estimand(s), should be provided as well."	Proposed alternative wording: “Define the estimand(s) providing the treatment condition(s) of interest, the population of patients targeted by the clinical question of interest, the variable(s) [or endpoint(s), specified in the table above], the population-level summary and intercurrent events (including those captured by the other attributes) together with (the clinical principles) of their respective handling strategies. Consider providing a label or name for each estimand for later reference.” Add instructions for providing a rationale for estimand(s), as applicable, possibly referring to other sections but discussing a rationale for the strategies chosen to handle intercurrent events here.
EFPIA/EFSPI Estimand Implementation Working Group	417	421	3.1	We question whether the instructional text provided by M11 needs to be this prescriptive or whether leaving it to be more flexible with a reference to ICH E9(R1) would be a better approach. If it is decided to be prescriptive then the instructional text needs to be updated: 1) It is important to be able to easily refer to a specific estimand, so we suggest adding instructional text that recommends use of estimand labels 2) Replace “participants” by patients because this is about the target population (versus the set of trial participants) 3) A clinical/regulatory justification should be given for the key estimand(s). Currently, the rationale for some of the individual attributes is provided separately: a. Endpoints in Section 4.2, b. Trial (not target) population is covered in Section 5.2. c. Is a rationale for the “treatment condition(s)” expected in Section 6.2? If yes, state this explicitly d. Choice of strategies for the intercurrent events seems to be expected in Section 9.2.2 (“This section should describe with more detail the rationale”). Is this intended? We recommend providing the rationale of the estimand in Section 3 4) Suggest rearranging the order of the attributes stating first those 3 attributes that might already capture some of the intercurrent events (ICH E9(R1): “Precise specifications of treatment, population and variable are likely to address many of the intercurrent events considered in sponsor and regulator discussions of the clinical question of interest.”) 5) To list “other intercurrent events” is not sufficient. All intercurrent events including those incorporated into other attributes should be listed together with the strategies chosen to handle them for transparency. In Section 7, line 753, you write “This section must align with the intercurrent events introduced in Section 3, Trial Objectives […]” and to enable this, a clear list of all intercurrent events is needed in the protocol.	Update instructional text to: “Define the estimand in line with ICH E9(R1).” Or if it is desirable to be more prescriptive in M11 then: “Define the estimand(s) (the clinical question of interest) by providing the five attributes: the treatment condition(s) of interest, the population of patients targeted by the clinical question of interest, the variable (or endpoint) (specified in the table above), the population-level summary and all intercurrent events together with their handling strategies. It is recommended to provide a label (number and/or name) for each estimand for later reference in the protocol, analysis plan, report, publications, etc.”
Interpharma, Association of Switzerland’s research-based pharmaceutical industry	417	420	3,1	It is important to state the justification of the selected estimand, and clinical rationale of the selected strategies for accounting intercurrent events.	Suggest adding references to Section 4.2 and Section 9.2.2 where the template provides the rationale of endpoint selection, estimand and clinical rationale of intercurrent event handling strategies
Interpharma, Association of Switzerland’s research-based pharmaceutical industry	417	420	3,1	CTGOV requires a timeframe to be disclosed for each primary and secondary endpoint. Therefore, it would be ideal to provide the timeframe adjacent to the endpoint. The protocol synopsis as required by the EU CTR for CTIS also solicits the timeframe for each primary and secondary endpoint.	Please modify the sentence with the below suggestion, "Describe the attributes that construct the estimand: the treatment condition of interest, the population of participants targeted by the clinical question of interest, other intercurrent events (if applicable), a population level summary, and the endpoint (or variable) specified in the table above, and 'the time point(s) at which the endpoint will be measured.'"
Estimand Review team	418	418	3,1	"other" intercurrent events implies that additional information is available. Please replace with "all", this is the place where all intercurrent events need to be specified.	Delete "other" and replace with "all"
CSL Behring	418	419		Proposed amendment to the language used to describe intercurrent events.	…other intercurrent events ~~(if applicable)~~ and the strategy for handling them

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	418	418	3,1	Please clarify whether it is expected to define both the clinical population of interest, and analysis population.	
EFPIA	418	418	3,1	"other intercurrent events": consider replacing by "Intercurrent events strategy"	Add instructions for providing a rationale for estimand(s), as applicable, possibly referring to other sections but discussing a rationale for the strategies chosen to handle intercurrent events here.
EFPIA	418	418		An overview of all intercurrent events is needed, so it is not sufficient only to list those intercurrent events not captured by one of the other attributes. Rather all intercurrent events should be clearly listed. Also, the strategies chosen to handle them should be clear	
TransCelerate BioPharma Inc.	418	418	3	This instruction is referring to the general patient population that the trial is targeting rather than an analysis population, so this should be clarified.	Recommend updating this line to refer to the population of “patients” targeted by the clinical question of interest rather than “participants.”
Estimand Review team	419	419	3,1	A full specification of the estimand framework also includes strategies.	Change to "... events (if applicable) and strategies, a population..."
EFPIA	421	421	3,1	Estimands could be presented in a table to help standardize content across protocols and organizations. If so, an example table could be added to guide sponsors.	
Charité Research Organisation	421	421	3,1	Attributes of an Estimand should be describes, e.g. general population, endpoint, intercurrent events, difference of endpoint between groups	
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	423	425	4	The introductory statement of this section is unclear. In this section the trial design should be described and the choices made are to be justified.	
EFPIA/EFSPI Estimand Implementation Working Group	424	428	4	The protocol writers should be reminded to align with the objectives/estimand(s) defined in Section 3, where applicable.	Add instructional text: “The trial design must align with objectives/estimand(s) described in Section 3.”
TransCelerate BioPharma Inc.	424	427	4	The study design must align with the estimand, so this should be addressed in the instructions for this section.	Recommend including a reminder to align with the estimand(s) in Section 3 in the instructional text for this section.
EFPIA	426	427		Please insert a reminder to align the design with the estimand(s), where applicable.	
Quotient Sciences	429	467	4,1	Description of Trial Design For a multi-part phase 1 trial, the section should contain a heading for each part and, under each heading, the authors should include information about the intervention model, trial duration and method of assignment to trial intervention. Rules for transitioning between different parts of a phase 1 healthy volunteer study should be described in the relevant part, eg the section about the multiple dosing part should say when multiple dosing can start in relation to the single-dose part of the trial and how the starting dose in the multiple dose part will be determined based on the data available from the single-dose part. Dose escalation should be summarised for dose-escalating parts (eg there should be a statement that the dose will be escalated only if the previous dose is safe and well tolerated and if plasma concentrations are predicted not to exceed the exposure limit) but dose escalation criteria should be in a clearly labelled separate section.	Provide instructions for multi-part trials.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Quotient Sciences	429	471	4,1	Description of Trial Design Include an optional subheading 4.1.2 Criteria for Dose Escalation, to be included in phase 1 dose escalation trials. This section should include dose escalation rules for all dose-escalating parts of the trial, with suitable subheadings for applicable parts of the trial. It is essential that all dose escalation criteria be in one place in the protocol for ease of reference. Dose decisions in phase 1 healthy volunteer trials typically have to be made and reviewed rapidly so, to reduce the risk of non-compliance, the rules need to be very clear, in one place, and easy to find. Dose escalation rules must specify the minimum dataset to be reviewed, who will review the data and decide the dose, and the criteria applied to the data (eg exposure limit).	Add an optional subheading '4.1.2 Criteria for Dose Escalation' for use in phase 1 dose-escalating trials.
EFPIA	429	437	4,1	It would be helpful to have the study design diagram here as well.	Please add the schematic of trial design or reference to where it's located within Section 1.
Interpharma, Association of Switzerland's research-based pharmaceutical industry	429	437	4,1	It would be helpful to have the study design diagram here as well.	Please add the schematic of trial design or reference to where it's located within Section 1.
EFPIA	432	432	4,1	All doses should be mentioned and not only the low dose.	Add "range of doses" instead of "low dose".
Interpharma, Association of Switzerland's research-based pharmaceutical industry	432	432	4,1	All doses should be mentioned and not only the low dose.	Add "range of doses" instead of "low dose".
EFPIA	434	434		According to ICH E8(R1), type of trial refers to Human pharmacology, exploratory, confirmatory or post-approval. Suggest writing "aim of the trial" not to confuse it with other ICH terminology.	
TransCelerate BioPharma Inc.	434	434	4	ICH E8(R1) refers to "type of studies" as human pharmacology, exploratory, confirmatory, and post-approval, so "type of trial" may be misleading terminology in this context.	Recommend changing "type of trial" to "aim of trial"
SÚKL CZ	436	436	design	This Protocol does not seem to be suitable for some complex/platform trials where a master protocol + subprotocols are needed, both containing specificities for such a design. For CCT Identification of master protocol is needed.	For CCT Identification of master protocol is needed.
EFPIA	436	437	4,1	Consider noting that if the protocol is a Master Protocol this is to be summarized as well.	Umbrella, Basket, Platform designs should be considered as applicable.
SÚKL CZ	438	446	design	Seems that these twou headlines "Description of Intervention Model" and " Description of Trial Duration" are mixed	Correct headliners
SÚKL CZ	439	439	design	reference to Section 1.2 - Full information must be provided also in this section, reference to section 1.2 only for some informations is not sufficient since it is a synopsis. No information should be included only in the synopsis and missing in the Protocol itself.	delete reference to Section 1.2
EFPIA	443	445	4,1	Consider adding to the instruction that a crossreference to Section 10.2 should be included in text, similar to what is done in lines 461-462.	If dose modification decisions are dependent upon review by a committee, include details in Section 10.2, Committees Structure and refer to that section.'
EFPIA	446	454	4,1	Consider adding guidance on what to include for studies such as oncology studies where it is difficult to ascertain trial duration. In many cases patients are treated to "independently verified" disease progression.	Please add guidance on what to include for studies such as oncology studies where it is difficult to ascertain trial duration.
SÚKL CZ	447	448	design	Statification, where included, should be described here. And randomization ratio and criteria should be described	Description of methods of straticication/radndomisation is needed.
EFPIA	447	450	4,1	Section 6.6 (line 681) is a dedicated section for randomization and blinding, but it is mentioned in Section 4.1 also. Instructions in section 4.1 should point out what needs to be described in Section 4.1 and refer to Section 6.6 for details to avoid repetition.	Add instructions to describe what needs to be described in Section 4.1 and refer details in Section 6.6.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	447	455		Original Text: "Describe the method of assignment to trial intervention (for example, stratified randomisation). If assignment to trial intervention is by randomisation, describe when randomisation occurs relative to screening. Describe the level and method of blinding; for example, single-blind, double-blind, [including Sponsor unblinded], matching placebo, double-dummy, or open-label). Include mention of measures taken to minimise bias on the part of participants, investigators, and analysts. If applicable, describe within-trial transition rules, for example, transitions involving cohorts or trial parts. Dose escalation or dose-ranging details should also be described." Treatment assignment and blinding details are provided in Section 6.6. Including these details here will create unnecessary redundancy.	Recommendation to delete the section beginning on line 447.
Agios	447	455	4,1	Randomisation ratio should be described if assignment to trial intervention is by randomisation. And stratification factors if stratified randomisation	Propose to amend wording to: "If assignment to trial intervention is by randomisation, describe randomization ratio, when randomisation occurs relative to screening, and stratification factors (if stratified randomisation)"
Agios	447	449	4,1	The more relevant specification is the allowed window for when intervention will take place after randomization rather than when randomization will take place compared to screening (as it will typically be after eligibility has been confirmed)	Change to "If assignment to intervention is by randomisation, describe the allowed window for when intervention will take place after randomization"
Interpharma, Association of Switzerland's research-based pharmaceutical industry	447	450	4,1	Section 6.6 (line 681) is a dedicated section for randomization and blinding, but it is mentioned in Section 4.1 also. Instructions in section 4.1 should point out what needs to be described in Section 4.1 and refer to Section 6.6 for details to avoid repetition.	Add instructions to describe what needs to be described in Section 4.1 and refer details in Section 6.6.
SÚKL CZ	452	452	design	sentense "measures taken to minimise bias" - It should be added whether the person administering IMP is blinded - this is often unfeasible (e.g. due to different color of IMP and placebo) and treatment therefore must be prepared and/or administered by an unblinded person, This information should be provided here.	
CSL Behring	455			We propose amending the header at Line 455 to refer to blinding.	Method of Assignment to Trial Intervention and Blinding
EFPIA	456	466	4,1	Consider adding a bullet for "Post-Trial Access" .	Consider adding a bullet for "Post-Trial Access"
Quotient Sciences	458	459	4,1	Geographical scope would be better placed in the subsection Description of Interventional Model.	Please move geographical scope to the Description of Interventional Model (lines 438-445).
EFPIA	460	460	4,1	It is important to highlight the impact of decentralized procedures on trial estimand, design, conduct, data integrity and results interpretation. For example, they could have an impact on the trial population leading to an undesirable patient selection, on the primary variable or on the occurrence of intercurrent events.	Propose to add the following phrase to the bullet point about decentralized procedure "and their impact on trial estimand, design, conduct, data integrity and results interpretation". It is recommended also to clarify if the decentralized procedures are optional and who maintains the oversight of the procedures.
Interpharma, Association of Switzerland's research-based pharmaceutical industry	460	460	4,1	It is important to highlight the impact of decentralized procedures on trial estimand, design, conduct, data integrity and results interpretation. For example, they could have an impact on the trial population leading to an undesirable patient selection, on the primary variable or on the occurrence of intercurrent events.	Propose to add the following phrase to the bullet point about decentralized procedure "and their impact on trial estimand, design, conduct, data integrity and results interpretation". It is recommended also to clarify if the decentralized procedures are optional and who maintains the oversight of the procedures.
EUCROF - EU CRO Federation	465	466			Add instructional text to clearly address Declaration of Helsinki 2013, No. 22 "In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Takeda	468	470	4.1.1	Some studies (e.g., phase 1 pharmacokinetic studies in healthy subjects) do not require participant input. We recommend making this an optional subsection that can be deleted if not relevant. The EU CTR Annex 1 D 17(e) states that a "protocol shall at least provide: where patients were involved in the design of the clinical trial, a description of their involvement. " This suggests that protocol writers would describe patient involvement in the design, but not the absence of patient involvement.	
CSL Behring	468	470		The header title and instructional text is confusing. It is not clear if this refers only to enrolled subjects (either before or after they are enrolled in the study), or more broadly to any pre-study consultations with patient interest/advocacy groups that the Sponsor may engage with. If the latter, we recommend this section be updated to include an example or examples around what is expected, because the term “participant” as currently used suggests that feedback only from subjects that have already been enrolled in the study is Expected here. It is also not clear whether input from key opinion leaders (KOLs) from the participant’s viewpoint is out of scope. Furthermore, the term “if applicable” is used within the section and it is not clear to us when this might be applicable. Please clarify, in the context of the template, when participant input into design is applicable and consider expanding the instructional text to include examples of expectations.	n/a
EFPIA	468	468	4.1.1	Should this section "Participant Input Into Design" be in Blue text or is it a mandatory section? If the section is mandatory to include, then in cases of no participant input (phase 1, for example), it would be helpful to have an optional statement to use.	
EFPIA	468	468		Section 4.1.1 is entitled "Participant Input into Design," but it is not accurate to refer to "Participant Input." The study will be designed before any participants are enrolled, and it is likely that people from a certain patient community or patient advocacy group will have provided input into the study design, rather than the study participants themselves.	Section 4.1.1 should be entitled "Patient Input into Study Design."
EFPIA	468	469	4.1.1	Is it the "participant" input or "patient" input that is obtained when preparing a trial protocol?	Consider replacing "participant" by "patient".
EFPIA	468	470	4.1.1	Rarely do participants provide feedback to protocols. This is rather achieved through interactions with patient groups or foundations dedicated to the specific disease.	Change "Participant" to "Patients" or "Patient groups"
EFPIA	468	470	4.1.1	Consider providing additional guidance here. Per CTCG, this section should also include a justification if there is no engagement of patients.	
EFPIA	468	471	4.1.1	it might be more logical to have a section towards the end of the protocol describing the input into the entire protocol (not only the design) by potential participants, community groups, etc.	
Agios	468	470	4.1.1	Is this intended to include trial design input from the relevant patient population who may not end up participating in the trial, not just trial participants, if so please clarify/correct	suggest to amend "participant" to "patient population"
TransCelerate BioPharma Inc.	468	470	4.1.1	CTCG requests that a justification be included if there is no patient input into trial design. If this is something that regulators expect to see, there should be guidance to include it.	Recommend regulatory members of M11 consider if this content is expected; if so, include instructional text to include a justification if there is no input into trial design.
Interpharma, Association of Switzerland’s research-based pharmaceutical industry	468	470	4.1.1	Rarely do participants provide feedback to protocols. This is rather achieved through interactions with patient groups or foundations dedicated to the specific disease.	Change "Participant" to "Patients" or "Patient groups"
LFB Biotechnologies	469	470	4.1.1	according to ICH E8 R1 stakeholders, including patients/patient organisations and healthcare providers can be involved in the study design	proposition to change the title of this section 'Stakeholders input into design' and to specify that patients/patient organisations and healthcare providers can be involved
Estimand Review team	472	486	4,2	General comment on section 4.2: Please include a subsection on rational for estimands	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	472	472	4,2	Consider changing this heading to 'Rationale for Trial Design Elements' and include all subsequent rationale sections under this heading (ie, rationale for trial intervention, rationale for trial population etc), which would then enable referencing from the benefit-risk assessment and keep all key rationale sections together. These sections could be referenced from the relevant sections where they are now, which would consolidate the key information for clarity.	Consolidate all rationale elements into a single section to ensure clarity. Change this heading title to 'Rationale for Trial Design Elements'.
EFPIA	472	499	4,2	Some rationales that need to be included in Section 4.2 have their own numbered subsection and some have not, which makes them more difficult to trace in the Table of Contents. Propose to make consistent.	
EFPIA	472	500	4,2	Selection of trial population (5.1), rational for trial population (5.2) and rationale for trial intervention (6.2) are also part of rationale for trial design (4.2). Preference would be to describe this information in a subsection of 4.2 and remove them from Sections 5 and 6.	Move section 5.1, 5.2 and 6.2 to be subsections in Section 4.2 Rationale for Trial Design.
Charité Research Organisation	472	472	4,2	There should be a separate section for the rationale of the starting dose; this might be deleted for later phases, however it is most essential for phase 1 and should be easy to find	
EFPIA	473	485	4,2	Some of the requested rationales for different aspects of the trial design (here but also in Section 5.2) may be redundant to what would be needed when writing a rationale for the defined estimand(s), if desired.	Clarify if the requested rationales for different aspects of the trial overlap with a rationale that might be requested for the estimand(s) and clarify expectation for a possibly needed rationale for estimands while avoiding repetition across different sections of the protocol.
EFPIA	475	502	4,2	Not clear why some topics deserve a dedicated Level-3 headings (e.g. choice of comparator), others not (e.g. intervention model)..	Consistently apply headings to all relevant topics.
CSL Behring	476	486		In its current state, Section 4.2 Rationale for Trial Design is not consistently formatted when the first sub-heading commences with 4.2.1 Rationale for Comparator whilst rationale for intervention model, rationale for duration, rationale for endpoints, and interim analysis are not presented as such. We recommend that the template be revised to start sub-heading 4.2.1 with Rationale for Intervention Model.	n/a
TransCelerate BioPharma Inc.	476	486	4,2	The use of variable text, non-numbered headings in this section may be confusing as to whether these elements are required or not. Some of these elements are required by the CSR, so it may need to be clearer that these are to be included. This applies throughout the document but is very apparent in this section where the rationale sub-headings are listed but not numbered.	Recommend using numbered level 3 headings where this content is expected, and clarify when a level 3 headings should be used versus a bold, non-numbered heading.
EFPIA	477	477		Perhaps 'show a reliable and relevant effect' should be changed to 'enable a reliable and relevant evaluation/analysis'. This would avoid confusion in trials not designed to measure efficacy/effectiveness.	
Estimand Review team	480	486	4,2	Please add a subsection where the rationale for the estimands can be described. This new part of section 4.2 should be cross-referenced with section 9.2	Please add in red: "Provide a rationale for the estimands. This includes the choice of a suitable strategy, intercurrent events and attributes. It needs to be aligned with section 9.2." Please add in blue: [Rationale for estimands]
Eva Degraeuwe, Ghent University, BPCRN	480	480	8.5.1	There is a different section around pregnancy during the trial, which always makes me wonder why not the following: - from an analysis perspective:there is not a standard children, adolescence maturation consideration as well as geriatric population e.g. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1884408/ - from a reconsent perspective: reconsenting in regards to a changing population: turning 18y, in case of dementia, trials longer than 2 years etc. Perhaps this is included in another guideline, but can be easily overlooked in protocol development and needs to be included in the design. - other	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Estimand Review team	483	486	4,2	suggest to move Interim analyses (not singular) after the rationale for the trial duration as these two issues are closely linked	
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	483	485	4.2.	Rationale for Endpoints: We suggest moving this subsection to 3.1.	
Takeda	487	492	4.2.1	In these lines and elsewhere in the document, the terms "control" and "comparator" are used somewhat interchangeably. We recommend choosing one term or explaining the distinction.	
CSL Behring	487			Sub-section 4.2.1 Rationale for Comparator discusses the type of control selected for the trial (if applicable). The placement of this section (within the template) appears illogical as we would expect that the protocol should first present the investigational medicinal product (IMP) before presenting details of the comparator. Furthermore, the introduction to Section 4 Trial Design (ref: Line 423) does not contain any detail on IMP. Please clarify and consider the placement of sub-sections in this part of the template.	n/a
EFPIA	487	492	4.2.1	Please clarify whether this rationale is also to discuss the risks associated with the active comparator. Consider adding an instruction to crossrefer to the risk section in Section 2.2 (in line with comment on line 384).	
EFPIA	487	492	4.2.1	Some trials are run on background therapy.	Add option for "Rationale for choice of background therapy"
EFPIA	487	487		Rationale for comparator is included in Section 4.2, but the rationale for the dose of the drug under study is not included in this section. Move section 6.2 up to Rationale section 4.2.	
EAHP	487	492	4.2.1	In case of clinical trials with a comparator that is already on the market, it would be necessary that these drugs would need to be managed as experimental drugs that need to be provided by the sponsor.	
Agios	487	494	4,2	For simplicity please consider deleting "Rationale for" from the subsections 4.2.1 and 4.2.2 titles as these are subsections of a section that is already titled "Rationale for Trial Design"	Delete "Rationale for" from Header for Sections 4.2.1 and 4.2.2
Freeline Therapeutics	487	487	4.2.1	Include statement that this section can be deleted if not applicable	Include statement that this section can be deleted if not applicable
Interpharma, Association of Switzerland's research-based pharmaceutical industry	487	492	4.2.1	Some trials are run on background therapy.	Add option for "Rationale for choice of background therapy"
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	491	492	4.2.1.	To avoid misunderstanding, clarification is suggested for the following sentence: "Describe prior trials that support the dose and/or dose regimen." We suggest adding "of the comparator".	The description should be adapted to: "Describe prior trials that support the dose and/or dose regimen of the comparator."
EFPIA	494	494		Rationale for adaptive or novel trial design is included in Section 4, but often adaptive changes are related to dose of the study intervention. However, in the current layout, the initial dose has not yet been described and explained. Move section 6.2 up to Rationale section 4.2.	
Freeline Therapeutics	494	494	4.2.2	Include statement that this section can be deleted if not applicable	Include statement that this section can be deleted if not applicable

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	495	495	4.2.2.	Trial design needs to be justified. We therefore suggest changing the wording: "If applicable, provide a rationale for the use of an adaptive or novel design." to "If applicable, justify the choice of an adaptive or novel trial design."	The description should be adapted to: "If applicable, justify the choice of an adaptive or novel trial design."
Quotient Sciences	497	499	4.2.3	Please consider adding in section 4.2.3 'The rationale for the choice of trial population is in Section 5.2'.	Add in section 4.2.3 'The rationale for the choice of trial population is in Section 5.2.'
EFPIA	497	499		Recommend a "Rationale for Exploratory Biomarkers" section to allow for scientific rationale to be presented as part of the trial design (rather than including scientific rationale in Section 8: Trial Assessments and Procedures)	
Freeline Therapeutics	497	497	4.2.3	Include statement that this section can be deleted if not applicable	Include statement that this section can be deleted if not applicable
Freeline Therapeutics	500	500	4,3	Include statement that this section can be deleted if not applicable eg for gene therapy trials	Include statement that this section can be deleted if not applicable
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	500	505	4.3/4.4	Follow the study history to set the sequence of paragraphs.	Inverting of the paragraph "Access to Trial Intervention After End of Trial" and "Start of Trial and End of Trial"
SÚKL CZ	503	503	4.3Access to Study Intervention After End of Study	Clearly explain if extension is planned within this CT or within CT under separate study protocol	Clearly explain if extension is planned within this CT or within CT under separate study protocol
Quotient Sciences	505	512	4,4	The instructions say that sponsor and investigator decision rights to close a site or end the trial should be delineated, criteria for early site closure should be provided, and responsibilities of sponsor and investigator after termination or suspension of the trial should be listed. However, that information is to be provided in Section 10.5, so shoud not be repeated here. Instead, the reader should be referred to Section 10.5.	Remove the following instructions from section 4.4: 'Delineate sponsor and investigator decision rights to close a site or end the trial, including criteria for early closure of a site. List responsibilities of the sponsor and investigator following termination or suspension of the trial.'
EFPIA	505	507		Please clarify whether 'timepoints' e.g. 'start date' refer to defining the milestone (i.e. what is meant by 'start date'), and not the actual start date of the trial, which is unknown. If so, please consider changing 'timepoints' to 'milestones,' and 'start date' to 'start of trial' to emphasise this.	If so, please consider changing 'timepoints' to 'milestones,' and 'start date' to 'start of trial' to emphasise this.
EFPIA	505	507	4,4	Is it the intent to give the actual date of the start of the study? This date is not known at the time of protocol wording, and hence will be difficult to include. If it is the intent to give a definition rather than an actual date, please consider rewording to:	~~Define~~ Include definitions for key timepoints in the trial, such as the start date.....'
EFPIA	505	511	4,4	This section does not have explicit instruction asking authors to define "end-of-study" or "end-of trial". It talks about site closure, which is not the same.	Please include instructions to define "end-of study"/"end-of-trial"
EFPIA	505	512	4,4	It is difficult to assess, with great accuracy, when the trial will begin and end. What are the expectations for this, as these dates would be approximate, barring any unforeseen delays in approvals, participant recruitment, etc. and there is a risk of inaccuracy.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	505	512	4.4	consider to completely re-write this paragraph. What is the relevance of site closure here or the sponsor/investigator rights of closing a site. This is regulated in the individual site contracts and bears a risk of contradiction. Study start is as defined as first patient signed an ICF. Do we allow for other (individual) definitions?	Here we need to define the regular end of the study in relation to answering the primary/.... objectives. Also it needs to explain that based on the outcome of various analyses (futility, interim, primary) the sponsor will decide on shortening/terminating the study (details to be described elsewhere) or altering of specific study parts (e.g. OS observation period). Allow for sponsor decision to shorten/terminate the study at any time under prerequisite of ensuring treatment for ongoing patients where ethically required.
Charité Research Organisation	505	505	4,4	This heading should be changed into 'planned' start data and 'planned' end date of the trial, in order to avoid amendements due to delays	
EFPIA	506	507	4,4	We suggest not including a description of "end of study" and "site closure" in the same section. These are different concepts and "site closure" is not reflected in the title of the section.	We suggest not including a description of "end of study" and "site closure" in the same section.
PTC Therapeutics, Inc.	506	507	4,4	PTC considers that it is important for specific definitions for start/stop date of the trial should be provided.	For consistency and reference purposes, PTC suggests that definitions could be aligned with the clinicaltrial.gov glossary of terms or another standard glossary.
Gilead Sciences	506	511	4,4	Suggest to include primary completion in instructional text; Rationale: reporting requirements for primary analysis	
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	507	509	4.4.	"Delineate sponsor and investigator decision rights to close a site or end the trial, including criteria for early closure of a site." It is not clear what information is expected here. One of the objectives of the template is to avoid redundancies, but criteria for early closure of sites should be included here and again in section 10.5 according to the template. We suggest that this information should be only given in one specific part of the protocol.	
EFPIA	507	510	4,4	instructions for text to be added on sponsor and investigator decision rights seem a duplication of text to be included in Section 10.5. Consider only including only a reference to Section 10.5 and removing the details.	...These definitions should consider local regulatory requirements. Delineate sponsor and investigator decision rights to close a site or end the trial, including criteria for early closure of a site. List responsibilities of the sponsor and investigator following termination or suspension of the trial. Provide a cross-reference to Section 10.5, Early Site Closure or Trial Termination for criteria and responsibilities related to early site closure or trial termination.'
EFPIA	507	511	4,4	Both Section 4.4 and Section 10.5 include instructions to list 1) sponsor and investigator decision rights to close a site or end the trial, and 2) responsibilities of the sponsor and investigator following termination of the trial.	Suggest including these instructions only in Section 10.5 Early Site Closure or Trial Termination to avoid repetition within the protocol.
Freeline Therapeutics	507	512	4,4	It is only necessary to define the start and end of the trial here. All information about the early ermination should be included in Section 10.5 otherwise it's duplication.	Delete 'Delineate sponsor…' to end of section 4.4.
EUCROF - EU CRO Federation	508	511	Section 4.4 Section 10.5	Plus Line 1149 What is the difference to section 10.5? what information should be provided here, what in section 10.5?	Change 4.4 to "Planned Start of Trial and End of Trial" and 10.5 to "Early Termination of Site or Trial".
EFPIA	509	510		Please clarify what is meant by 'List responsibilities of the sponsor and investigator following termination..', i.e. is it only responsibilities directly related to early termination? Otherwise it could appear to be a very extensive list of all post-trial responsibilities, including site closures, regulatory reporting, data analysis and submission, data retention, etc.	
EFPIA	514	585	5	There could be a subsection for additional inclusion criteria pertinent to sub-studies in the trial.	Please add guidance on tools for sub-studies

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Interpharma, Association of Switzerland's research-based pharmaceutical industry	514	585	5	There could be a subsection for additional inclusion criteria pertinent to sub-studies in the trial.	Please add guidance on tools for sub-studies
EFPIA	518	519	5	In phase1 trials in healthy volunteers a significant amount of in- and exclusion criteria are not easily answered with yes/no (discretion of the investigator).	Ensure that each criterion can be easily assessed definitively and strive to have them answered with yes/no responses.'
EFPIA	520	520		Unclear what meant here. Please clarify or consider including examples of what is intended.	
EFPIA	527	527		In trial population section, instructional text should be added to refer to the appendix where country specific changes in the inclusion/exclusion criteria, if appropriate.	
EFPIA	527	533	5,1	Considering the new omnibus legislation requires FDA to issue guidance documents on clinical trial diversity, should a mention be made here of seeking to include a diverse population in the trial?	Describe the population selected (for example, healthy volunteers, adult participants, paediatric participants) and how the enrollment criteria reflect the diveristy of the populations that are likely to use the drug if approved.
Agios	527	543	5	Sections 5.1 and 5.2 would best be integrated into the considerations associated with the rationale for the trial. The protocol should make it easier for "like" information to be found together rather than interspersed throughout the protocol. Considerations associated with the "why" of the trial and its elements would best be placed in a single section upfront in the protocol.	Move the content in Section 5.1 and 5.2 to Section 2.1 which per prior comment could best be relabeled as "Study Rationale".
EFPIA	528	528	5,1	Please replace "volunteers" with "participants" (also in other locations in the document) - everyone is a clinical trial is a volunteer	
Gilead Sciences	528	533	5,1	Suggest including instructions and example text for measures taken for increasing diversity in study population	
Estimand review team	529	529	5,1	A note could be included that the trial population should be aligned with the population attribute of the estimand.	
EFPIA	529	529		Care should be taken that this section does not overlap with the inclusion/exclusion criteria.	
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	530	532	5.1.	It is described here: "Specify the population age range (for example, ≤3 months, ≥18 to ≤80 years old) and any key diagnostic criteria for the population (for example, "acute lung injury", or a specific biomarker profile)." These factors are also part of the Inclusion/Exclusion criteria, listing them again in this section creates redundancy that may be prone to errors. We suggest deleting this request for specification in this section.	
Takeda	532	533	5.1 Selection of Trial Population	"If applicable, describe similar conditions or diseases and their differential diagnosis." This would likely be overly detailed and clinical for this document. We recommend requesting a succinct description of how the disease of disorder or interest can be distinguished clinically from other similar disorder.	If applicable, describe how the condition or disease is distinguished from similar disorders.
EFPIA	534	534		Enrollment criteria' can be misunderstood; please use 'eligibility criteria' as in line 516.	
EUCROF - EU CRO Federation	535	535	Section 5.2	The instructional text should also state here: "if a specific gender or age group is excluded from or underrepresented in the clinical trials, an explanation of the reasons and justification for these exclusion criteria"	Add instructional text as per comment.
EFPIA	535	543	5,2	Given formation of the E21 IWG, the M11 experts should consider adding "pregnant patients" to the list of possible populations where justification (or lack thereof) is included in the rationale for the trial population.	Given formation of the E21 IWG, the M11 experts should consider adding "pregnant patients" to the list of possible populations where justification (or lack thereof) is included in the rationale for the trial population.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	535	541	5,2	Consider moving this section to a subsection of Section 4.2. In this way, all rationales for trial design can be found in the same subsections. This will make it easier to retrieve the rationales, instead of having them mixed up with protocol assessements.	
EAHP	535	540	5,2	For the trial population, a quote for women and geriatric patients or patients with comorbidities should be established.	
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	535	543	5.2	A separate section/subsection including the Rationale for involving special populations (e.g., paediatric patients) might be added	"Rationale for special population" section or subsection to be added
Interpharma, Association of Switzerland's research-based pharmaceutical industry	535	543	5,2	Given formation of the E21 IWG, the M11 experts should consider adding "pregnant patients" to the list of possible populations where justification (or lack thereof) is included in the rationale for the trial population.	Given formation of the E21 IWG, the M11 experts should consider adding "pregnant patients" to the list of possible populations where justification (or lack thereof) is included in the rationale for the trial population.
CSL Behring	537			It is not clear from the template what "clinically recognisable" is intended to mean in context. Please clarify.	n/a
EFPIA	537	537	5,2	As per ICH E11, the population "children" is a distinct subset (ages 2-11 years) of the larger "pediatric" population (ages birth - 18 years). The language in the M11 protocol template should revise this statement to use the phrase "pediatric patients".	Change "children" to "pediatric patients"
Interpharma, Association of Switzerland's research-based pharmaceutical industry	537	537	5,2	As per ICH E11, the population "children" is a distinct subset (ages 2-11 years) of the larger "pediatric" population (ages birth - 18 years). The language in the M11 protocol template should revise this statement to use the phrase "pediatric patients".	Change "children" to "pediatric patients"
Takeda	541	546	5.1 Selection of Trial Population Description of Trial Design - Rationale for Trial Population	The blue text in the subheading in line 541 is the same as the heading in line 535. The approach here, and throughout the template, is distracting and duplicative. We recommend streamlining the document by removing duplicative text.	
Takeda	542	543	5.1 Selection of Trial Population Description of Trial Design - Rationale for Trial Population	This statement on protocol waivers or exemptions is out of place. We suggest making a new subeading (eg, eligibility waivers) and moving it below the inclusion or exclusion criteria.	
CSL Behring	542	543		We suggest rewording the sentence to avoid the use of double-negatives and to aid readability.	Individuals who do not meet criteria for trial eligibility must not be enrolled via protocol waivers or exemptions. Enrolment of screen failures via waivers or exemptions is not permitted/prohibited.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	542	543	5,2	The sentence "Individuals who do not meet criteria for trial eligibility must not be enrolled via protocol waivers or exemptions." e.g. protocol waivers/exemptions does not belong under 'rationale for population'.	
TransCelerate BioPharma Inc.	542	543	5,2	Placement of the statement regarding protocol waivers/exemptions seems incorrect. The prohibiting of protocol waivers is more applicable to the eligibility criteria and requirements, not so much applicable to the rationale behind the requirements.	Recommend to place this under the Section 5.0 heading so that it applies to the entire section.
EFPIA	544	559	5,3	Please include instructions on how to handle multiple cohorts/populations with different criteria.	
EFPIA	548	559	5,3	Please consider including subcategories here, similar to those in the TransCelerate template, and guidance on what to include in each subcategory. This could be helpful for example, to ensure we have contraception included as inclusion criteria.	Please consider including subcategories here, similar to those in the TransCelerate template
EFPIA	548	550	5,3	Is the intention to have Inclusion critieria grouped in "categories" as in the TransCelerate Common Protocol Template? These categories are difficult to clearly delineate so the preference would be not to insert categories.	
TransCelerate BioPharma Inc.	548	550	5,3	There may be benefit to introducing structure to the eligibility criteria, such as using a table instead of numbered narrative text. This further facilitates digital extraction for other uses.	Recommend having the inclusion and exclusion criteria structured, such as in a table format.
TransCelerate BioPharma Inc.	556	558	5,4	There may be benefit to introducing structure to the eligibility criteria, such as using a table instead of numbered narrative text. This further facilitates digital extraction for other uses.	Recommend having the inclusion and exclusion criteria structured, such as in a table format.
SÚKL CZ	559	559	5.4Exclusion Criteria	Study drugs contraindications must always be taken into account in the eligibility criteria. Contraception requirements must be always mentioned in the eligibility criteria as well. Pregnancy/breastfeeding should be addressed. It is recommended to provide here some basic recommendation what is generally expected to be covered by the eligibility criteria regardless of study type.	Study drugs contraindications must always be taken into account in the eligibility criteria. Contraception requirements must be always mentioned in the eligibility criteria as well. Pregnancy/breastfeeding should be addressed. It is recommended to provide here some basic recommendation what is generally expected to be covered by the eligibility criteria regardless of study type.
Quotient Sciences	560	580	5,5	It's not clear why contraception requirements are in Appendix 13 and not in Section 5.5 (Lifestyle Considerations) - they would be best placed in Section 5.5.	Please move Section 13.1 headings and text to Section 5.5.
EFPIA	560	564	5,5	Some guidance would be great to avoid redundancy with exclusion criteria.	
Agios	560	580	5,5	Restrictions associated with the clinical trial would either be captured in eligibility criteria or in the Section associated with trial assessments or procedures as some of these restrictions speak to whether or not a patient will be eligible and others are not a characteristic of the trial population but rather a description of assessments that will be performed or how assessments will be performed	Delete Section 5.5 and move contents as notes for consideration to Sections 5.3 and 5.4 for Inc/Exc criteria and to Section 8 as appropriate.
Freeline Therapeutics	560	580	5,5	It should be stated that is allowed to amend sub-sections as appropriate for the trial.	Add general note that is allowed to amend sub-sections from Level 2 onwards as appropriate for the trial. Perhaps one overarching comment at the start of the protocol is sufficient rather than stating it piecemeal in some but not all sections.
EFPIA	561	580	5,5	Consider removing the level 3 subheadings and put all under Section 5.5 Lifestyle Considerations.	
EFPIA	561	564		It is not clear what should be written here. Is it general "introduction" text for the subsections, or is it something specific for Lifestyle? In case of the latter, what is then considered as a Lifestyle item (which is not part of what is already mentioned - diet, tobacco, physical activity etc.). If the text box is only intended for cases where no restrictions are required, suggest to write the relevant sentence with blue text.	
Agios	565	572	5.5.1	Caffeine and Alcohol are more appropriate in Section 5.5.1 as they are part of Meals and Dietary Restrictions	Move Caffeine and Alcohol under section 5.5.1 instead of 5.5.2
EFPIA	569	569		Consider to add e few examples of what this could be, as done for 5.5.4 Other Activity.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Quotient Sciences	578	578	5.5.4	Sperm donation is a common restriction - please add it to the examples given in line 578.	Please add: '(for exampe, blood, sperm, or tissue donation)'
EUCROF - EU CRO Federation	581	581	Section 5.6		Consider adding instructions to indicate if re-consenting is to be required in case of rescreening.
EUCROF - EU CRO Federation	581	581	Section 5.6	There should be a section to describe "procedures for replacement of subjects" in case a subject is enrolled and then subsequently withdraws from the study. Note that there is a similar requirement in ICH E6(R2) document (see item 6.5.3(c)).	Add instructions as noted in comments.
CSL Behring	581			As lifestyle restrictions are usually applied during clinical studies, we suggest it is appropriate to relocate section 5.6 Screen Failures to appear before Section 5.5 Lifestyle Considerations in the protocol template.	n/a
EFPIA	581	581		Recommend to remove the "s" - Screen Failure. Could potentially also be screening failure.	
EFPIA	581	581		Section 5.6 is entitled "Screen Failures" but there is a possibility for individuals to be enrolled in the study after they are re-screened (which means they would not have failed screening). In addition, some sponsors try to avoid referring to potential study participants as "failures." Some sponsors also avoid stating that participants have "failed" study treatment.	Change the Section 5.6 heading from "Screen Failures" to "Re-Screening."
EFPIA	585	585		Consider to add that a minimum set of data should be reported in the CRF for screen failures (e.g. informed consent date, demography, reason for screen failure etc.)..	
EFPIA	586	586		Please also include a place to address Run-in criteria, randomisation criteria and dosing day criteria.	
EFPIA	586	586	5,6	Consider adding an optional section after 5.6: Section 5.7.Criteria for Temporarily Delaying [Enrollment] [Randomization] [Administration of Study Intervention]	Section 5.7. Criteria for Temporarily Delaying [Enrollment] [Randomization] [Administration of Study Intervention]
EFPIA	587	591	6	Please clarify whether trial intervention(s) includes both IMP and AxMP.	Please clarify whether trial intervention(s) includes both IMP and AxMP.
EFPIA	587	587		It is not clear where to add information on other trial supplies (non-medicinal products) like needles, blood glucose meters and injections kits. It could be relevant in several subsections e.g. potential storage conditions and the need for accountability.	
EFPIA	587	605		It is problematic for "trial intervention" to refer to challenge agents, rescue medications, and diagnostic agents, as described in the instructions for Section 6.1. Sponsors need a term that describes the assigned study treatment (including assigned background therapy), without also referencing challenge agents, rescue medications, diagnostic agents, required standard-of-care therapy (e.g., asthma medications), etc. For example, sponsors need to be able to require discontinuation of all assigned study treatment, without having to call out the name of each specific drug each time ("discontinue XX, YY, ZZ"); this is especially important in oncology studies where assigned study treatment can consist of 4-5 agents. With the current terminology, "discontinue trial intervention" would also unintentionally lead to discontinuation of rescue medications, diagnostic agents, required standard-of-care therapy, etc. Sponsors should be allowed to use the term "study treatment" to refer to all assigned study treatments, including the investigational drug, comparator, and background therapy (such as chemotherapy).	To enable "study treatment" to be distinguished from challenge agents, rescue medications, diagnostic agents, etc., Section 6 should be entitled "Study Treatment, Other Treatments Relevant to the Study Design, and Concomitant Therapy" and Section 6.1 should be entitled "Description of Study Treatment and Other Treatments Relevant to the Study Design."
EFPIA	587	587	6	This heading could be confusing if non-therapeutic agents are included in the study (eg, challenge agents, PET tracers, diagnostic agents, which are not therapeutic). Would add the option of adding 'Other Agents' or similar in this heading or in the 'Concomitant Therapy' and/or 'Other Therapy' sections.	Add option to extend the title of Secction 6 (and/or Section 6.8/Section 6.8.4) to include 'Other Agents' (or similar) to clarify use of eg, challenge agents or PET tracers which are not therapies.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	587	587	6	It Could be useful to have an overview of all IMP and no-IMP in a list.	A complete list of all investigational medicinal products, all auxiliary medicinal products, all concomitant medicinal products and all rescue medication should be added;
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	587	587	6	It is missing a description of whether the investigational medicinal products and auxiliary medicinal products used in the clinical trial are authorised; if authorised, whether they are to be used in the clinical trial in accordance with the terms of their marketing authorisations, and, if not authorised, a justification for the use of non-authorised auxiliary medicinal products in the clinical trial;	"a description of whether the investigational medicinal products and auxiliary medicinal products used in the clinical trial are authorised; if authorised, whether they are to be used in the clinical trial in accordance with the terms of their marketing authorisations, and, if not authorised, a justification for the use of non-authorised auxiliary medicinal products in the clinical trial;"
Estimand Review team	588	592	6	Trial intervention and concomitant thereapy should be aligned with the estimand attribute on treatment conditions.	Cross reference to sections 3.1, 4.2, 9.2
EFPIA	588	588	6	The sentence may be interpreted as if the control product is not considered 'trial intervention'. However, lines 40-42 states that trial interventions include the control. Please make consistent and consider repeating the definition of 'trial intervention' in the instructions of Section 6.	Trial intervention refers to any therapeutic, prophylactic, or diagnostic agent including pharmaceuticals, biologics, vaccines, cell or gene therapy products (when applicable), and drug-device combination products when registered as a drug. Trial interventions include the agent being tested or used as a control (for example, placebo or active comparator). Procedures conducted to manage participants or to collect data are excluded from the usage of this term. In this section, describe the trial intervention being tested and any control product being used.'
EUCROF - EU CRO Federation	594	594	Section 6.1	The instructional text in this section should say that the author should include, "a statement of whether the investigational medicinal products and auxiliary medicinal products used in the clinical trial are authorised; if authorised, whether they are to be used in the clinical trial in accordance with the terms of their marketing authorisations, and, if not authorised, a justification for the use of non-authorised auxiliary medicinal products in the clinical trial".	Add suggested instructional text.
EFPIA	594	601	6,1	We ask to add the international code of Trial Interventions so that this code will be able to be reuse for a clinical trial notification.	Description of Trial Intervention [Table of Trial Interventions]
EFPIA	594	601	6,1	Intervention information: information about the study drug (dose unit, route of administration, etc.) will be displayed in the data according to CDISC controlled terminology. For alignment and consistency it would be advisable to encourage the usage of controlled terminology for these terms. E.g. dose units: if the protocol states a unit of ug/mL for the study drug, the unit will be displayed in the data as mg/L, as ug/mL is a synonym for mg/L and mg/L is the submission value for the SDTM datasets. To avoid confusion it should be encouraged to use the same wording in the protocol that will be later displayed in the data	Encourage the usage of controlled terminology according to CDISC wherever possible in the explanatory text

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Freeline Therapeutics	596	596	6,1	Delete 'storage conditions' as this is covered in Section 6.5.2	Delete 'storage conditions'
CSL Behring	597			Section 6.1 Description of Trial Interventions covers many topics within the section. As such, we suggest amendment to include optional Level 3 subheadings for study product, comparator product, and drug/device combination product. Whilst this information will of course be very individual to each clinical study, the inclusion of only a Level 2 heading here is in our opinion too broad.	n/a
EFPIA	597	597	6,1	Please use consistent terminology. 'sham comparator' vs 'sham procdure'	strive for consistency
CSL Behring	598	605		Rescue Therapy and challenge agents are also to be described in Section 6.8 Concomitant Therapy, Subsections 6.8.3 Rescue Therapy and 6.8.4 Other Therapy. It is not clear from the instructional text if redundant information should be provided in both Sections 6.1 and 6.8? Or are non-investigational medicinal products according to EudraLex Volume 10 to be described in Section 6.1, and other products that do not fall into this category described in Section 6.8? It is not clear if this is dependent upon who provides the additional product (e.g., rescue therapy provided by Sponsor to be described in 6.1, and rescue therapy prescribed by a study site described in 6.8)? Please clarify the intent of the instructional text.	n/a
EFPIA	598	599		According to the definition of 'trial intervention' given on page 5, trial intervention only covers 'agent being tested or used as a control'. This would seem to exclude NIMP/AxMP being used as background medications. Please clarify.	
EFPIA	598	599	Section 6.1	There is no guidance for cases where the designation as IMP or NIMP/AxMP varies across countries targeted for participation.	Consider adding such guidance
Gilead Sciences	598	605	6,1	Suggest including details on what constitutes IMP vs NIMP/AxMP, as it is unclear where the additional products (background intervention, challenge agent, rescue medication, diagnostic, etc) fall.	
TransCelerate BioPharma Inc.	598	599	6,1	It is important to ensure the right designation for IMP/NIMP/AxMP is followed throughout the protocol; while it is understood the template is not a place to tell the user how to define IMP or NIMP, it is preferable to refer the user to the correct source to determine this, particularly in cases where there may be regional variance in the status of an intervention.	Suggest including in this section instruction to refer to the applicable regulatory guidance for determination of whether the intervention is considered IMP or NIMP.
TransCelerate BioPharma Inc.	601	601	6,1	This placeholder indicates a table is expected, but the instructional text makes it sound suggested/optional. A table with prespecified fields will better facilitate data exchange.	Recommend including the table as part of the template with appropriate prespecified fields.
EFPIA	602	602		Suggest to add to indicate by whom 'additional products' will be supplied	
EFPIA	602	602		The description of 'additional products' given in parentheses (background intervention, challenge agent, etc.) are encompassed by the terms NIMP/AxMP which is mentioned in the paragraph above. Please align the terminology being used throughout the document.	
EFPIA	602	605		Rescue therapy, challenge agents, etc. are considered to be trial interventions (described in Section 6.1, "Description of Trial Intervention") and are also considered to be concomitant therapy (described in Section 6.8.3, "Rescue Therapy," and Section 6.8.4, "Other Therapy"). Any agents that are required as part of the protocol (e.g., rescue therapy, challenge agents) should be described in Section 6.1, whereas any agents that are permitted but not required should be described in Section 6.8.2 ("Permitted Concomitant Therapy").	Given that rescue therapy, challenge agents, etc. are to be described in Section 6.1, the heading should be changed to "Description of Study Treatments and Other Treatments Relevant to the Study Design." Section 6.1 can then include three subsections: 6.1.1 ("Description of Study Treatment"), 6.1.2 ("Rescue Therapy"), and 6.1.3 ("Other Therapy").
EFPIA	603	603		Note that rescue medication is also addressed above under trial intervention (where AxMP is mentioned) and in section 6.8.3 under Concomitant therapy. It needs to be very clear whether rescue therapy is considered as trial intervention, AxMP or concomitant therapy.	
EFPIA	606	607	6,1	Consider creating a subsection 6.1.1 for drug/device combination information. In this way all relevant info can be placed in this section, which will be easily retrievable from the Table of Contents.	
EFPIA	606	607	6,1	This statement may be more relevant for device studies or vaccine studies. Please clarify the intention of this statement: For drug/device combination products, include details on the configuration and use of the device and device manufacturer. The device user manual may be referenced in this section.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	606	607	6,1	Medical Devices should have an individual sub-chapter in chapter 6	Add sub-chapter for medical devices
Quotient Sciences	609	619	6,2	For dose-escalating phase 1 trials in healthy volunteers, it is essential that dose escalation criteria be described in a clearly labelled section (see request above that an optional section 4.1.2. be added). In Section 6.2 of protocols for phase 1 dose-escalating trials, that section should be cross-referenced.	Instruct the author to cross refer to a section containing rules and procedures for dose escalation.
EFPIA	609	619	6,2	Consider moving this section to a subsection of Section 4.2. In this way, all rationales for trial design can be found in the same subsections. This will make it easier to retrieve the rationales, instead of having them mixed up with protocol assessements. Also, the section heading is a bit misleading. Please consider rewording to 'Rationale for Trial Intervention Regimen' as it is not the choice of trial intervention that is being defended in this section, but rather doses and regimen.	Rationale for Trial Intervention Regimen'. Move section 6.2 up to Rationale section 4.2.
Agios	609	619	6,2	Please clarify the how the purpose of Section 4.2 differs from Section 6.2, which currently both suggest including rationale for intervention/control products and seem redundant. Please streamline into a single section	Combine 4.2 and 6.2
Agios	609	619	6,2	Consider moving rationale for dose to the section 4.2 to complement rationales of other aspects of the study. Having the info in one section provides a more comprehensive understanding of the study and its design elements.	Combine 4.2 and 6.2
EFPIA	610	612		Instructions for Section 6.2 ("Rationale for Trial Intervention") state that a rationale should be provided for the dose, route of administration, and dosing regimen for any control product. A control product will often be placebo or an approved active comparator. There will be no dose for placebo, and the route of administration and dosing regimen for placebo will be the same as those for the active drug (i.e., no rationale needed). There is no need for a protocol to provide a rationale for the dose, dosing regimen, and route of administration for an approved comparator. Nevertheless, Section 4.2.1 ("Rationale for Comparator") already provides a rationale of use of a comparator, with no need to repeat any of that information in Section 6.2. Section 6.2 should be focusing on a rationale for the dose, dosing regimen, and route of administration for the sponsor investigational medicinal products. The heading "Rationale for Trial Intevention" is not specific enough because it could be taken to mean a rationale for administering this study drug in this population as part of a clinical trial.	A better heading for Section 6.2 would be "Rationale for Dose, Dosing Regimen, and Route of Administration for Sponsor Investigational Medicinal Products." The heading could also be simplified as "Rationale for Dosing Plan for Sponsor Investigational Medicinal Products."
EFPIA	610	618	6,2	Please include guidance to provide a rationale for the AxMP as well.	Please include guidance to provide a rationale for the AxMP as well.
EFPIA	614	615	6,2	Because of study population diversity, consider that there may be PK and/or PD differences in metabolism.	Include any information about age, race, or sex-based pharmacokinetic and/or pharmacodynamic differences known from previous trials.
EFPIA	614	614		Suggest to change to 'known demographic pharmacokinetic or pharmacodynamic differences..' to also cover e.g. race, ethnicity.	
EFPIA	615	615		Recommend to include a statement/information about dosing in special populations, ie renal, hepatic impairment, if applicable.	
Gilead Sciences	617	618	6,2	"Rationale for Prospective Dose Adjustments" refer to IA results, which will be CCI. Suggest to move under Section 6.3 "Dosing and Administration" in order to keep the dose modification information in the same section.	
SÚKL CZ	620	620	6.3Dosing and Administration	It must be added that detailed instructions are required especially for drugs with subcutaneous/intravascular or similar administration (and for any route in early phase studies/FiH) - how long must the subject stay in the trial center for the safety monitoring, the infusion rate, vital signs monitoring during and after infusions etc. This is often only in Pharmacy Manuals or similar documents which is not sufficient since it is an important safety information to be covered by the Protocols	Add information how long has to participant observed in study centre after the drug administration
EFPIA	620	620		Please insert a reminder to align with the estimand(s), where applicable.	
EFPIA	620	620		Section 6.3 ("Dosing and Administration") falls under Section 6 ("Trial Intervention and Concomitant Therapy"). Because concomitant therapy is mentioned in the heading for Section 6, the heading for Section 6.3 must make it clear that "Dosing and Administration" does not apply to concomitant therapy.	Section 6.3 should be entitled "Study Treatment Dosing and Administration." Or separate concomitant therapy as a title level 1
EFPIA	621	622	6,3	The wording 'trial intervention and control product' reads as if the control product is not regarded as 'trial intervention. This is in contradiction with the statements in line 40-42. Please ensure consistency.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA/EFSPI Estimand Implementation Working Group	621	633	6.3	Add a reminder to protocol writers that this section must align with the intercurrent events and their handling strategies.	Add text: "This section must align with the intercurrent events and their handling strategies introduced in Section 3."
CSL Behring	622			Within Section 6.1 it appears that "Trial Intervention" is the highest-level term that includes both the test/study product and controls/comparators. If this is the case, consider deleting reference to "control product" as it is not necessary for comprehension.	Describe the detailed procedures for administration of each participant's dose of trial intervention ~~and control product~~.
EFPIA	625	625		Include the device used in the administration of the trial intervention.	
SÚKL CZ	626	627	Dosing and Administration	Add that it should be clarified whether treatment is to be administered in the trial center by medical personnel/in the inpatient or outpatient setting/by the subject alone at home etc.	Add that it should be clarified whether treatment is to be administered in the trial center by medical personnel/in the inpatient or outpatient setting/by the subject alone at home etc.
EFPIA	626	626		Please state that a Direction for Use (instruction for use) can be handed out to participant and that it must be documented by the investigator that it has been provided	
CSL Behring	628	631		Consider relocating the paragraph of guidance text from the current location to Subsection 6.3.1 Trial Intervention Dose Modification where it is most appropriate.	n/a
EFPIA	628	631		Enrollment criteria' can be misunderstood; please use 'eligibility criteria' as in line 516.	Please consider if this text should be covered in section 6.3.1, since this section specifically concerns dose modification.
EFPIA	628	631		Instructions indicate that dose modifications should be described in Section 6.3, but dose modifications are also described under Section 6.3.1 (entitled "Trial Intervention Dose Modification"). There is no need for instructions to be repeated in both places.	Add the following to Line 631: Dose modifications can be described in a separate subsection (see Section 6.3.1).
EFPIA	628	639	6,3	Both Section 6.3 (Dosing and Administration) and Section 6.3.1 (Trial Intervention Dose Modification) contain instructions to describe dose modifications allowed for the individual participant. It is difficult to determine which dose modifications should be described in each section.	Suggest clarifying instructions for dose modifications under both Section 6.3 and Section 6.3.1 to avoid duplication of content.
Quotient Sciences	632	633	6,3	Dosing and Administration The following text could be more precise: 'Discussion of dose escalation of cohort expansion as part of the overall design should be covered in Section 4.2 (Rationale for Trial Design)', as Section 4.2 specifically describes the rationale for the design.	Please edit to: 'Discussion of the rationale for inclusion of dose escalation or cohort expansion as part of the overall design should be covered in Section 4.2 (Rationale for Trial Design)'
EFPIA	632	633	6,3	Consider whether a description of the dose escalation or cohort expansion would fit better in "section 4.1 description of trial design".	Consider whether a description of the dose escalation or cohort expansion would fit better in "section 4.1 description of trial design".
TransCelerate BioPharma Inc.	632	633	6,3	Section 4.1, Description of Trial Design, is a more appropriate place to describe these elements of trial design.	Suggest changing the correct place for discussion of dose escalation or cohort expansion as part of overall design to Section 4.1
Quotient Sciences	635	635	6.3.1	To improve clarity, please can 'for Individual Participants' be included in the heading.	Please edit to: 'Trial Intervention Dose Modification for Individual Participants'
SÚKL CZ	635	635	6.3.1 Study Intervention Dose Modification	A subsection for toxicity management must be added (could be optional to be filled in) - for any drugs with known/expected toxicities, these must be adressed in the Protocol - list of known/expected toxicities + how should these toxicities be managed/treated/diagnosed/followed-up and whether study medication is to be modified/discontinued when these occur.	A subsection for toxicity management must be added (could be optional to be filled in) - for any drugs with known/expected toxicities, these must be adressed in the Protocol - list of known/expected toxicities + how should these toxicities be managed/treated/diagnosed/followed-up and whether study medication is to be modified/discontinued when these occur.
EFPIA	635	635		Dose modifications secondary to toxicities are sometimes better presented in a tabular format alongside the dose stopping criteria. Sometimes the severity of an individual toxicity will determine whether the dose will be decreased, paused, stopped, restarted. It simplifies the action required for the investigator to have this information co-located.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	639	641	6.3.1.	In the section "Trial Intervention Dose Modification" it is described: "Do not include information on stopping trial intervention for individual participants due to safety/other reasons as this is detailed in Section 7, Discontinuation of Trial Intervention and Participant Discontinuation/Withdrawal from the Trial." However, subsequent dose modifications after reoccurring toxicities may lead to treatment interruption and/or treatment stop. It would be very confusing for site staff to find the instructions on how to deal with toxicities in two different chapters, depending on whether the dose is reduced or interrupted/stopped. The requirement here is massively error-prone, and may even endanger patients.	
EFPIA	639	641	6.3.1	Rather than suggesting not to include information on stopping trial intervention etc as this is included in Section 7, consider adding an instruction to reference Section 7 from here.	Reference Section 7
EUCROF - EU CRO Federation	641	642	Section 6.3.1 and Section 6.8.3	Plus Lines 743-744 Incorrect Section name	Delete second “Discontinuation” and “the” in section name from “Discontinuation of Trial Intervention and Participant Discontinuation/ Withdrawal from the Trial”.
CSL Behring	641			It is not clear in the template what the difference between the terms ‘Discontinuation/Withdrawal’ is for the participant. If there is no difference intended, we propose to use a single term and suggest “Withdrawal” to distinguish from “trial intervention discontinuation”.	Discontinuation/Withdrawal
SÚKL CZ	643	643	6.4Treatment of Overdose	Add that any overdose must be properly recorded in the CRF.	Add that any overdose must be properly recorded in the CRF.
EFPIA	643	643		Section 6.4 ("Treatment of Overdose") falls under Section 6 ("Trial Intervention and Concomitant Therapy"). Because concomitant therapy is mentioned in the heading for Section 6, the heading for Section 6.4 must make it clear that "Treatment of Overdose" does not apply to concomitant therapy.	Section 6.4 should be entitled "Treatment of Overdose of Study Treatment." *Section may not be needed here, it should be part of AE management*
Quotient Sciences	646	648	6,4	It's important to include clear and complete instructions in the the protocol for dealing with overdose, rather than cross-referring to the IB. Investigators seeking guidance in the protocol in the event of an overdose should not have to refer to another document.	Please delete from line 647 'and avoid unnecessary duplication with'
Quotient Sciences	651	680	6,5	This section contains more detail than we are used to seeing in phase 1 protocols. Much of this information may be provided in the IMPD or a pharmacy manual, so it is useful that a cross reference may be provided. Note that, owing to tight timelines, some fine details of IMP preparation for phase 1 healthy volunteer trials may not be finalised until after protocol submission.	Edit line 659-661: For phase 1 trials or if the instructions are lengthy or complicated, it is acceptable to reference the label (if applicable) or include them as a separate document(s) provided to the site (for example, a pharmacy manual).
EFPIA	651	651		Section 6.5 ("Preparation, Handling, Storage and Accountability") falls under Section 6 ("Trial Intervention and Concomitant Therapy"). Because concomitant therapy is mentioned in the heading for Section 6, the heading for Section 6.5 must make it clear that "Preparation, Handling, Storage and Accountability" does not apply to concomitant therapy.	Section 6.5 should be entitled "Study Treatment Preparation, Handling, Storage, and Accountability."
EFPIA	654	654		Control product' is a subset of 'trial intervention', according to the definition of 'trial intervention'. Please delete 'and control product' throughout the document, or else clarify what is meant.	
SÚKL CZ	661	662	6.5.1 Preparation of Study Intervention	If instructions are provided to the site as a separate document(s), this should be noted in here - note: This document must be then also provided within the clinical trial application	If instructions are provided to the site as a separate document(s), this should be noted in here - note: This document must be then also provided within the clinical trial application
Boehringer Ingelheim	662	662	6.5.1	Remove the word "in" from text, "should be noted in here"	"should be noted here"
SÚKL CZ	663	663	6.5.1Preparation of Study Intervention	Add also whether blinded or unblinded personnel is preparing the medication because of potential differences between study drug/placebo.	Add also whether blinded or unblinded personnel is preparing the medication because of potential differences between study drug/placebo.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
CSL Behring	664			It is not clear from the current template where handling and storage of standard of care (SOC) medicines should be placed if the trial Sponsor provides them as part of the study. SOC medicines are not an intervention, as typically a placebo group also received SOC medications. Please clarify this point.	n/a
EAHP	664	672	6.5.2	All the experimental drugs need to be sent with a system that is able to trace the temperature during the transport (e.g. datalogger). In general, it is important for toxic drugs to have a risk assessment on the toxicity in case the drug needs to be compounded.	
Agios	664	672	6.5.2	Please consider adding the instructions under 6.5.1 (lines 659 to 662) here as well - if handling/storage instructions are complicated, then use of a separate document (eg, pharmacy manual) might be warranted; instruction text should reflect this flexilibity.	Add the following text from Section 6.5.1 in Section 6.5.2 as well "If the instructions are lengthy or complicated, it is acceptable to reference the label (if applicable) or include them as a separate document(s) provided to the site (for example, a pharmacy manual). If instructions are provided to the site as a separate document(s), this should be noted in here. "
Gilead Sciences	665	672	6.5.2	Suggest to specify that this information may also be provided in the Pharmacy Manual	
EFPIA	668	668		Suggest to add information about control of temperature during transit, and secure storage.	
CSL Behring	669	672		Trial Intervention Storage and Handling would appear to be a distinct topic, that could benefit from being presented within a separate Level 3 subsection within the template. Consider creating such a subsection and placing within the template at the beginning of Section 6.5.1. Preparation of Trial Intervention.	n/a
EFPIA	669	669	6.5.2	Consider moving this field to below line 672. It sits between 2 parts of instructional text.	Move the field
EFPIA	670	670		Please add a description of allowed alternative dispensing methods e.g. delivery to home, set-up during pandemic if allowed by Health Authorities in a country	
EFPIA	670	670		Please delete 'control product' since this is part of trial intervention'.	
EFPIA	673	673		Suggest to add information about required retention of trial intervention samples in relation to bioequivalence and bioavailability studies	
EUCROF - EU CRO Federation	674	675	Section 6.5.3	Word missing. Text states “including trial intervention will be distributed and related details,”.	Add missed word, this should say, "including how trial intervention will be...".
CSL Behring	674			Proposed typographical amendment to aid readability of the template.	Describe the method by which the accountability will be achieved, including how trial intervention….
EFPIA	674	674	6.5.3	Minor typo.	…, including how trial intervention will...
EFPIA	674	674		A word is missing here, probably 'how'.	
EFPIA	674	675	6.5.3	Please delete the following text: ", including trial intervention, 675 will be distributed and related details" - it is repeated in the bullets	
Boehringer Ingelheim	674	675	6.5.3	Revise sentence for grammar and clarity, "Describe the method by which the accountability will be achieved, including trial intervention will be distributed and related details, including:"	"Describe the method by which accountability will be achieved, including:"
EFPIA	681	681		Consider adding language regarding the replacement of subjects who discontinued when applicable.	
EFPIA	681	681	6,6	In practice, protocol template typically includes a subsection on patient numbering.	Consider including a subsection "Patient/subject numbering"
EFPIA	681	681		Section 6.6 ("Participant Assignment, Randomisation, and Blinding") falls under Section 6 ("Trial Intervention and Concomitant Therapy"). Because concomitant therapy is mentioned in the heading for Section 6, the heading for Section 6.6 must make it clear that "Participant Assignment, Randomisation, and Blinding" does not apply to concomitant therapy. In addition, randomization is just one way of assigning a participant to treatment; it doesn't make sense for the heading to call out just that one way of assigning patients treatment. Blinding doesn't apply only to participants (also applies to the investigator), but the current heading implies that it does.	Section 6.6 should be entitled "Study Treatment Assignment and Blinding." Or separate concomitant therapy as a title level 1

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	681	716	6,6	Chapter 6.6 "Participant Assignment, Randomisation and Blinding" should include possibility for sub-chapter about criteria for temporal delay of enrollment/randomization	Add sub-chapter about temporal delay of enrollment/randomization
Interpharma, Association of Switzerland's research-based pharmaceutical industry	681	681	6,6	In practice, protocol template typically includes a subsection on patient numbering.	Consider including a subsection "Patient/subject numbering"
EFPIA	683	700	6.6.1	As the information to be included in Section 6.6.1, Participant Assignment and Section 6.6.2, Randomisation seem largely overlapping, consider combining into one section, for brevity and lean writing.	Section 6.6.1 Participant Assignment and Randomisation
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	693	699	6.6.2	Precise details of stratification variables (if applicable), including exact specification of any cut-offs or algorithms used must be detailed in this section.	
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	693	699	6.6.2	Who will have access to the randomisation codes throughout the study, and where the data on treatment codes will be stored must be detailed in this section.	
Quotient Sciences	698	699	6.6.2	The final sentence of this paragraph states that the use and validation of any computer systems or programs should be described. Presumably, it is the intention not to describe how the validation of computer systems or programs was achieved but simply to note their validation status.	Please replace: 'Describe the use and validation of any computer systems or programmes in randomisation, stratification, and unblinding' with 'Note the use of any computer systems or programs - and their validation status - in randomisation, stratification and unblinding'.
Quotient Sciences	701	716	6.6.3	Section 6.6.3 (Blinding and Unblinding) refers to planned and unplanned breaking of randomisation codes (line 704). The subsection 'Emergency Unblinding' refers to unblinding in the event of a medical emergency (which is a type of unplanned but intentional unblinding) and to unintentional unblinding (line 716). It would be clearer if Section 6.6.3 referred to planned and unintentional unblinding and the subsection 'Emergency Unblinding' referred only to unblinding in the event of an emergency.	Edit line 704: 'planned and unintentional'. Delete from line 716: 'and unintentional'.
SÚKL CZ	701	701	Blinding and Unblinding	Provide explanation if investigator is blinded to some results from any type of examination – if so, provide justification and evaluation on patient's health care and safety.	Provide explanation if investigator is blinded to some results from any type of examination – if so, provide justification and evaluation on patient's health care and safety.
EFPIA	702	702		Trial intervention' includes control products. This should be rephrased to e.g. 'test product(s) and control product(s)'.	
EFPIA	708	708		Suggest to add examples of other measure that can unblind, e.g. imaging.	
EFPIA	709	709		Consider including some guidance text about partial database lock, if the trial has interim analysis.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	710	710	6.6.3	"Blinding" and "unblinding" are separate concepts and should have separate data fields.	
SÚKL CZ	711	711	Emergency Unblinding	Please keep in mind that that the investigators are responsible for all trial-related medical decisions (ICH GCP 4.3.1). The investigator has to be able to unblind the investigation product immediately if he feels it is necessary without prior contact to the medical monitor or sponsor. However, the investigator should promptly document and explain to the sponsor any premature unblinding (ICH GCP 4.7).	Add note" It must be realized that the investigators are responsible for all trial-related medical decisions (ICH GCP 4.3.1). The investigator has to be able to unblind the investigation product immediately if he feels it is necessary without prior contact to the medical monitor or sponsor. However, the investigator should promptly document and explain to the sponsor any premature unblinding (ICH GCP 4.7).
CSL Behring	711			Consider making 'Emergency Unblinding' a numbered section of the template (i.e., section number 6.6.4) such that it shows up in the table of contents (TOC).	n/a
EFPIA	711	711		There is no heading number.	6.6.4 Emergency Unblinding
ICON PLC	714	714	6.6.3	Suggest updating "SAE" to "expedited safety reports" as SAEs specifically do not require unblinding.	Insert instructional text.
EFPIA	716	716		Please use consistent terminology regarding planned versus intentional (and unplanned versus unintentional) blinding.	
Quotient Sciences	718	723	6,7	Source data/records for phase 1 trials are typically documented in a source data agreement/identification list. Please allow cross reference to that document as an alternative to listing all source documents used to record compliance. Please also note that the vast majority of dosing in phase 1 trials is done in a single clinic by or under direct supervision of clinic staff who complete the source documents.	Add to the end of line 723: 'Alternatively, reference to a document defining source data and documents can be provided.'
CSL Behring	718	723		Propose that this section of the template be amended to include a clear definition of what "trial intervention" is intended to cover.	n/a
EFPIA	718	718		Please insert a reminder to align with the estimand(s), where applicable	
EFPIA/EFSPI Estimand Implementation Working Group	719	723	6.7	Add a reminder to protocol writers that this section must align with the intercurrent events and their handling strategies.	Add text: "This section must align with the intercurrent events and their handling strategies introduced in Section 3."
EUCROF - EU CRO Federation	725	725	Section 6.8	The subsections represent a repetition of what is said under section 6.8 Concomitant Therapy. Is text expected under 6.8 or only under the subsections? Please clarify.	
Quotient Sciences	725	731	6,8	The instructions under the heading for Section 6.8 (Concomitant Therapy) suggest that information should be provided here that is likely to be duplicated in the subsections 6.8.1 and 6.8.2. Should the instruction 'No text is intended here (header only)' be inserted under Section 6.8 (before Section 6.8.1)?	
SÚKL CZ	725	725	Concomitant Therapy	Information on potential drug interactions is to be also addressed here (i.e. resulting in prohibited concomitant treatment or treatment to be used with caution etc.) - this should be added here and also indicate that list of drugs with potential of interaction must be included in the Protocol.	Information on potential drug interactions is to be also addressed here (i.e. resulting in prohibited concomitant treatment or treatment to be used with caution etc.) - this should be added here and also indicate that list of drugs with potential of interaction must be included in the Protocol.
CSL Behring	725	728		The instructional text in Section 6.8 Concomitant Therapy appears to indicate that concomitant therapy does not cover standard of care medications. Please clarify if this is the case and consider revision of the instructional text as appropriate. Furthermore, we recommend that an additional instruction be included in the template to clearly distinguish between medications and non-pharmacological interventions.	n/a
EFPIA	725	725	6,8	Add 'and Other Agents' (optional, where relevant) to heading title (see changes to Line 587 above).	6.8 Concomitant Therapy 'and Other Agents' (as optional addition)
EFPIA	725	725		Please insert a reminder to align with the estimand(s), where applicable	
EFPIA	725	725	6,8	The section title should be "prior" and "concomitant " therapy.	Prior and concomitant therapy

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	726	727	6,8	Consider adding instruction to refer to the in- and exclusion criteria for medication restrictions, instead of repeating all information (to avoid duplication, which bears the inherent risk of inconsistencies).	
EFPIA/EFSPI Estimand Implementation Working Group	726	730	6.8	Add a reminder to protocol writers that this section must align with the intercurrent events and their handling strategies.	Add text: "This section must align with the intercurrent events and their handling strategies introduced in Section 3."
TransCelerate BioPharma Inc.	726	726	6,8	Excluded medication should be aligned with estimands when applicable, as this may be relevant to the population.	Recommend including a reminder in the instructional text to align with the estimand(s) defined in Section 3, if applicable.
EFPIA	729	729	6,8	"During the trial" is mentioned, but some medications are prohibited for a period prior to screening. Strictly speaking they are not "concomitant". Please clarify where these should be included.	
SÚKL CZ	732	732	Prohibited Concomitant Therapy	If there is no prohibited therapy, please provide this statement to the protocol. This chapter should not be omitted.	If there is no prohibited therapy, please provide this statement to the protocol. This chapter should not be omitted.
EFPIA	733	733		Consider to add also discontinuation criteria.	
SÚKL CZ	738	738	6.8.3 Rescue Therapy	If rescue treatment differs regionally, provide the information, that rescue therapy will be provided with accordance to local standard care.	If rescue treatment differs regionally, provide the information, that rescue therapy will be provided with accordance to local standard care.
EFPIA	738	744		Original Text: "6.8.3 Rescue Therapy List all medications, treatments, and/or procedures which may be provided during the trial for rescue therapy and provide relevant instructions about the administration of rescue medications. Describe the circumstances under which use of rescue therapy is permitted. If administration of rescue therapy leads to the temporary discontinuation of trial intervention or a participant's withdrawal from the trial, refer to Section 7, Discontinuation of Trial Intervention and Participant Discontinuation/Withdrawal from the Trial." With the EU CTR, rescue therapy falls under non-investigational therapy/AxMP. There is no category for rescue therapy. Having this section is confusing to authors and creates opportunity for redundancy.	Consider to delete the "Rescue Therapy" section or provide further clarification (see comment below)
TransCelerate BioPharma Inc.	738	738	6.8.3	Per EU Regulation 536/2014, rescue medication is considered auxiliary medicinal product (AxMP), therefore would fall under study intervention rather than concomitant medication.	Recommend that Section 6.8.3 Rescue Therapy be moved underneath Section 6.1 Description of Trial Intervention.
EFPIA	739	738	6.8.3	Please clarify what "may be provided" means. Does it mean provided by the sponsor?	We suggest rephrasing to " treatments/procedures which may be administered".
EFPIA	742	744	6.8.3	We recommend adding the possibility of "permanent IMP (or Trial Intervention?) discontinuation without withdrawing from the trial".	We recommend adding the possibility of "permanent IMP (or Trial Intervention?) discontinuation without withdrawing from the trial".
Quotient Sciences	746	749	6.8.4	The section title is 'Other Therapy'. Challenge agents are not always therapeutic - eg grass pollen used for allergen challenge, PET scan ligands. Please consider renaming this section 'Other Interventions'.	
SÚKL CZ	746	746	Other Therapy	If this is used according to SmPC, provide this SmPC as appendix to protocol.	If this is used according to SmPC, provide this SmPC as appendix to protocol.
EFPIA	746	746	6.8.4	Change heading title to 'Other Agents' (see changes to Line 587 above).	6.8.4 Other ~~Therapy~~ Agents
EFPIA	746	749	6.8.4	Auxiliary therapy is in 6.8.4 Other Therapy. Please consider making a separate subsection for Auxiliary Therapy.	
EFPIA	746	746		Please indicate where other trial supplies (e.g. needles, glucose meters) should be described.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	746	746		Original Text: “6.8.4 Other Therapy” The section for “Other Therapy” should be deleted since this information should already be in Section 6.1. If this section is retained, it should be renamed to “Non-Investigational / Auxiliary Therapy.” With the EU CTR, there is either investigational or non-investigational therapy. There is no category for “other therapy.” Having this section is confusing to authors and creates opportunity for redundancy.	Recommendation to delete the “Other Therapy” section.
Quotient Sciences	751	752	7	Please rename this section 'Stopping and Withdrawal Criteria'. It's very important that all stopping criteria - for individual participant withdrawal from dosing or the trial, for dose escalation, and for the trial as whole - are clear and easy to find in the protocol.	Rename Section 7 'Stopping and Withdrawal Criteria'
EFPIA	751	752		Please insert a reminder to align with the estimand(s), where applicable	
EFPIA	751	797	7	Please consider including a level 2 subsection on withdrawal from the use of research samples in Section 7. Participants may withdraw consent for [optional] research samples while they remain in the study. Also, if participants withdraw from the study, they may still allow use of collected samples according to the original informed consent.	Include a level 2 header "Withdrawal from the use of Research Samples".
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	751	798	7	There should be a section to describe "procedures for replacement of subjects" in case any subject is enrolled and then subsequently withdraws from the study.	
EFPIA	753	755	7	Guidance in this section is not sufficiently clear. More detail is needed to understand how section 7 must align with the intercurrent events specified in section 3.	Please provide clarifications.
EFPIA/EFSPI Estimand Implementation Working Group	753	755	7	Modify the reminder to protocol writers to reflect that this section must align with all intercurrent events and their handling strategies	Change to: “This section must align with the intercurrent events and their handling strategies introduced in Section 3 and the intervention described in Section 6.”
TransCelerate BioPharma Inc.	753	753	7	The instructional text includes guidance to align with the intercurrent events in Section 3, but this should also align with the handling strategies for the intercurrent events. Discontinuation criteria and the handling strategies should be aligned as they are closely related.	Recommend changing the instructions to "This section must align with the estimands…" instead of intercurrent events. Alternatively, the sentence should be expanded to "intercurrent events and their handling strategies."
EFPIA	754	754		Please clarify 'treatments', ie whether this includes concomitant therapy and other procedures.	
EUCROF - EU CRO Federation	757	759	Section 7.1	The explanatory text just gives a statement, but no instruction whether or not text is expected under section 7.1 in addition to text under the subsections. Please clarify.	
Quotient Sciences	757	757	7,1	Discontinuation of Trial Intervention Please clarify in the heading that this section refers to stopping criteria for individual participants.	Edit line 757: '7.1 Criteria for Stopping the Trial Intervention in Individual Participants'

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	757	759	7,1	The instructional text does not indicate if text is expected in section 7.1, or if the instructions there are just for information.	Please clarify instructions for this section.
EFPIA	757	759	7,4	Typically information for stopping rules is provided in the statistics section.	
Charité Research Organisation	757	757	7,1	Is should be considered to place sections on replacement policy, back-ups, and completers here	
Estimand Review team	758	759	7,1	This paragraph is important and the specification of whether data need (or not) to be collected after trial discontinuation should be aligned with the strategy chosen to deal with this intercurrent event. The same applies to temporary discontinuation in 7.1.2 if it is deemed as a relevant intercurrent event in the definition of the estimand.	Cross refenece to section estimand strategy/intercurrent events 9.2.2
EFPIA/EFSPI Estimand Implementation Working Group	758	759	7.1	It is important to capture reasons for such discontinuation. More text required to ensure these reasons will be captured.	Add instructional text: Detailed reasons for discontinuing intervention(s) should be collected.
Gilead Sciences	758	759	7,1	Suggest to include instructional text that "No text is intended here (header only)"; Rationale is consistency	
EFPIA	760	760	7.1.1	For consistency with Section heading 7.1.2, remove 'Criteria for'.	7.1.1 ~~Criteria for~~ Permanent Discontinuation of Trial Intervention
EFPIA	761	761		Participants withdraw and interventions are discontinued. Please rephrase to discontinuation of trial intervention by a participant.	
CSL Behring	767			Propose to add 'Criteria for' to the section heading 7.1.2 for consistency with other sections of the template	Criteria for Temporary Discontinuation or Interruption of Trial Intervention
EFPIA	767	772	7.1.2	The wording 'discontinuation' and 'interruption' is duplicative. Please consider removing 'or interruption' OR explaining how the two terms would differ.	7.1.2 Temporary Discontinuation ~~or Interruption~~ of Trial Intervention'
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	769	770	7.1.2.	In the section "Temporary Discontinuation or Interruption of Trial Intervention" the criteria for temporary discontinuation or interruption of trial intervention for an individual participant should be described. As stated above, subsequent dose modifications after reoccurring toxicities may lead to treatment interruption and/or treatment stop. It would be very confusing for site staff to find the instructions on how to deal with toxicities in two different chapters, depending on whether the dose is reduced or interrupted/stopped. The requirement here is massively error-prone, and may even endanger patients.	
EFPIA	773	773		If they will not continue in the trial then it is not temporary/interruption, hence, is this should not be relevant.	
EFPIA	773	773	7.1.2	Consider adding a crossreference to Section 7.2.	….whether they will continue in the trial (crossrefer to Section 7.2, Participant Withdrawal from the Trial), and…'
EFPIA	773	775	7.1.2	Please provide further clarifications concerning the expectations based on the guidance in this section. In particular, should the last 2 bullets be sub-bullets of the second bullet? If the participant stops the trial, the discontinuation of trial intervention is permanent (not temporary).	Please provide clarifications.
EFPIA	779	783	7.1.3	For this and other region, could a 'not applicaple' option be added here. E.g. In single-dose trials, this will not be relevant.	
EFPIA	783	783	7.1.3	If rechallenge is not allowed should Sponsor be directed to procedures for permanent discontinuation of treatment?	
Quotient Sciences	785	785	7,2	For improved clarity, please rename this section 'Criteria for Withdrawal of Participants'	Edit line 785: '7.2 Criteria for Withdrawal of Participants'
Estimand Review team	786	786	7,2	Withdrawl will lead to missing data. Hence, cross referencing to the section on missing data is essential becaue there it is described how missing data/assessments will be handled for the analysis.	Cross refenece to section in missing data 9.2.3

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	786	786	7,2	Please provide instructions to indicate whether participants who withdraw will be replaced.	
EFPIA	786	786		Consider addressing collection of reason for withdrawal and final assessments.	
Estimand Review team	788	788	7,3	The heading is too restrictive when "lost to"is included. The subsection not only deals with losses, but more generally with following up.	Delete "Lost to"
EFPIA/EFSPI Estimand Implementation Working Group	788	788	7.3	The instructional text of this section appears to refer to not just the definition of lost-to-follow-up, but also the measures that should be taken to follow participants up when they are still contactable e.g., when they miss a visit or discontinue treatment, which is important to have in a protocol. The section title does not therefore appear to align with the instructional text or the intent of the section.	Retitle the section, e.g., 'Measures to Reduce 'Lost to Follow-up'.
EUCROF - EU CRO Federation	793	797	Section 7.4	Difference between this section and section 10.5 not clear, what kind of information should be included here, what in section 10.5? Please clarify. Risk of Duplication of text.	
Estimand Review team	793	793	7,4	Section 7.4 used the term "stopping", but the term "termination" is also used in the templase, i.e. in section 10.5. What are the differences? If there are no differences, please align termionology.	
Quotient Sciences	793	793	7,4	Please provide the option to include dose escalation stopping criteria in this section.	Edit line 793: '7.4 {Dose Escalation and} Trial Stopping Rules' - the text 'Dose Escalation and' should be included for dose-escalating trials, and sponsors should be instructed to insert subsections as follows: '7.4.1 Dose Escalation Stopping Criteria' '7.4.2 Trial Stopping Criteria'
EFPIA	793	797	7,4	When a cohort or dose escalation is terminated, and/or when a given treatment arm is terminated, this does not necessarily equal stop of the study. Consider adapting the section heading to reflect that and consider adding level 3 headings to distinguish.	7.2 ~~Trial~~ Stopping Rules 7.2.1 Study Stopping Rules 7.2.2 Cohort/Treatment Arm Stopping Rules
EFPIA	793	797		Section 7.4 ("Trial Stopping Rules") does not logically belong in Section 7 ("Discontinuation of Trial Intervention and Participant Withdrawal from Trial") because Section 7.4 describes stopping of the entire study, whereas discontinution of trial intervention and withdrawal from the trial (elements in the Section 7 heading) are categories of things that happen only to an individual participant. Many studies do not have defined study stopping rules, so this topic does not warrant a Level 2 heading. For studies that do, the stopping rules are likely to be integral to the study design (e.g., for dose-escalation studies) and should be instead be described in Section 4.1, along with study-specific patient stopping rules (usually dose-limiting toxicities) and cohort stopping rules, both of which are also integral to the study design.	Remove Section 7.4. Add instructions to Section 4.1 indicating that study-specific stopping rules should be described in that section. *(or place the description in 7.1)*
Agios	793	797	7,4	Trial stopping rules for safety reasons or futility reasons should be defined in the context of safety or efficacy monitoring. These should be part of Section 9	Delete section (should be covered under Section 9)
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	793	797	7.4	It is unclear how to interpret this section. Should rules be specified for the stop for futility (Interim Analysis)? What kind of information should be included here?	
Estimand Review team	794	794	7,4	Trial stopping rules should be clarified in all protocols	Delete "If applicable,"
Gilead Sciences	794	796	7,4	Suggest to clarify subheadings for stopping rules for study, cohorts, and individual subjects based on treatment	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	796	796		Consider addressing by whom this decision will be made	
Quotient Sciences	798	798	7	Please add a subsection for temporary halts to the trial so that sponsors can explain the procedure for temporarily halting and restarting the trial and explain the criteria for pausing a trial without putting it on a formal temporary halt.	Add new section: '7.5 Temporary Halt of the Trial'
EUCROF - EU CRO Federation	799	818	Section 8	Section 8 is a description of assessments and procedures per endpoint. The information what activities and procedures will be performed at which time point/visit is only provided in the schedule of activities (SoA). From an auditor perspective, it can be said that the SoA is error prone and that a chronological description by time point/visit of the planned activities/procedures is usually more trustworthy than the SoA where fields are only ticked. Of course, time points/visits can be pooled in the description when exactly the same activities/procedures are scheduled.	Add a section which asks for the chronological description of activities and procedures per time point/visit.
Quotient Sciences	799	818	8	The bullets under the heading of Section 8 describe information that should be included in the subsections (8.1, 8.2 etc). Please clarify that no text is to be entered under the Section 8 heading.	Add 'No text is intended here (header only)' under Section 8.
EFPIA	799	799		suggest to add a section on eCRFs and data collection in general, including eCOA, CGM, or any other device used. This should include requirements on multiple signoffs by the primary investigator.	
EFPIA	799	800	8	There are many administrative procedures typically found in Seciton 8. There is/are no corresponding heading(s) for these items. Is this intended?	Consider how to include space for key administrative items.
PTC Therapeutics, Inc.	799	799	8	As the use of RWE/RWD as a comparator is increasing, it is notable that there are not proposed sections for PROs and QOL assessments.	PTC proposes consideration of this additional content.
Agios	799	818	8	Add a statement that the timing of the assessments listed in Section 8 can be found in the Schedule of Activities (with a reference to the SoA table)	
Agios	799	802	8	Although this section indicates that one should be careful not to duplicate what is in the SOA, the footnotes to the SOA can be excessive and really difficult to read particularly in relation to lab sampling. Consider expanding what is elaborated upon in Section 8.0 either in lieu of the footnotes or complementing the footnotes.	
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	800	802	8	For the section "TRIAL ASSESSMENTS AND PROCEDURES" the following is requested: "Describe the assessments and procedures required during each phase of the trial that are relevant to the stated endpoints. Provide details that are not already presented in the SoA, taking care not to duplicate information." In our opinion the information in this chapter should be also found in the SoA. Here, redundancy and precise comparison is useful, as the SoA is often used as a separate document for overview at the trial site.	
EFPIA	800	801	8	Instructional text in Bullet 1, sentence 1 is not clear. Revise for clarity.	Change to: "For the stated endpoints, describe the assessments and procedures that are required to be done during each phase/timeframe of the trial."
EFPIA	800	818	8	Please confirm it is the intent not to put text directly under Section 8.	Add "No text is intended here (header only)" (if confirmed that this is the intent).
Gilead Sciences	800	818	8	Suggest to include instructional text that "No text is intended here (header only)"; Rationale is consistency	
Gilead Sciences	800	818	8	Although instructional text already specifies not to duplicate info in the SOA, it may be helpful to specifically state that the frequency of the assessments need not be stated in Section 8.	
EFPIA	801	801		Suggest to clarify the meaning of 'that are relevant to the stated endpoints', or else delete it. All assessments will need to be described.	
EFPIA	802	802		With reference to ICH E8, we suggest to include a statement e.g. 'care should be taken to ensure all trial procedures and assessments are necessary from a scientific viewpoint and do not place undue burden on trial participants.'	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	803	803		Suggest to add 'data precision' be addressed for assessments related to key endpoints.	
EFPIA	803	803	8	General procedures (i.e. calibration of equiment, domiciling, etc.) which will be relevant to multiple sections, "8.1 Screening/Baseline" , "8.2 Efficacy" and "8.3 Safety" will be dupilcated.	Create a level 2 Heading (before 8.1) for general assessments and procedures.
Quotient Sciences	805	806	8	The text instructs the author to include information on timing of assessments. That information should be in the Schedule of Activities. It should not be repeated in the text, as that is unnecessary and it is very likely to lead to inconsistency between Schedule of Activities and the text as the protocol evolves.	Replace 'Include instructions on timing/conditions of assessments and if a specifically qualified person should be performing these assessments.' with the following: 'Refer to the Schedule of Activities for the timing of procedures. If a specifically qualified person should perform assessments, include instructions on the qualifications required.'
Quotient Sciences	807	808	8	The text instructs the author to include information on methods used to maintain blinding. However, that information is in Section 6.6.3. To avoid repetition, information on methods used to maintain blinding should be in either Section 6.6.3 or Section 8, with appropriate cross references.	Please specify that methods used to maintain blinding be included in either Section 6.6.3 or Section 8.
SÚKL CZ	807	808	TRIAL ASSESSMENTS AND PROCEDURES	Provide explanation if investigator is blinded to some results from any type of examination – if so, provide justification and evaluation on patient's health care and safety.	Provide explanation if investigator is blinded to some results from any type of examination – if so, provide justification and evaluation on patient's health care and safety.
EFPIA	809	809	8	Include guidance to indicate level of physician/patient burden in assessments and PROs (eg, expected duaration or time to complete assessments/PRO).	Expand guidance on PRO use to indicate level of physician/patient burden.
Gilead Sciences	809	809	8	Current instructional bullet states to reference the literature for "validation of scales/instruments/questionnaires…"; however, the current EU-CTR guidance states that patient-facing documents that are linked to the endpoints of the clinical trial shall be provided together with the protocol in part I of the clinical trial application. Has consideration been given for whether sample instruments/questionnaires be included with the protocol itself?	
Gilead Sciences	809	815	8	Suggest to clarify "All COA parameters should be fully integrated" to specify whether or not all instruments must be included as part of the protocol	
EFPIA	813	813		Suggest to address which COAs should be reviewed by investigator for potential AEs.	
Gilead Sciences	816	816	8	Suggest to remove volume of blood draw from examples, as this is typically specified as a maximum value	
EFPIA	819	819		Suggest to add that a subject card is handed out.	
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	819	819	8.1	The importance of the use of a controlled terminology should be explained and some examples or tools shold be proposed	
EFPIA	823	823	8,1	Please change the data field font from black to blue. Consider including multiple fields in the data field, eg, Screening/Baseline Assessment #1, Screening/Baseline Assessment #2, etc.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	823	825	8.2	For efficacy, different endpoints may be established for pediatric patients of different ages, so it is important to define this approach in the study protocol.	
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	824	835	8.2. and 8.3.	There are separate sections for "Efficacy Assessments and Procedures" and "Safety Assessments and Procedures", however there could be assessments that are relevant for both, efficacy and safety. It should be indicated in the protocol template where these should be described.	
CSL Behring	824	825		Include a statement to the effect that Level 3 headings can be added to the template as needed.	Level 3 headings can be added as needed.
EFPIA	824	824	8,2	The heading 8.2 only refers to "Efficacy assessment and procedures". For vaccine studies, immunogenicity could be the primary objective and therefore it is important to present it up-front rather than under section 8.10.	Suggest to change the heading 8.2 as "{Efficacy/Immunogenicity} assessment and procedures". Section 8.10 can be retained as it is and if immunogenicity is described in section 8.2, it can be cross-referred in 8.10.
Quotient Sciences	827	835	8,3	It's not clear whether any text should be included under the heading for Section 8.3. The instructions seem to describe information that would be included in the relevant subsections 8.3.1-8.3.5	Please clarify whether any text should be inserted under the heading for Section 8.3. If not, please add 'No text is intended here (header only)'.
EFPIA	830	832	8,3	Please clarify in the instructions it is not the intent to provide all the details on committees here but reference should be made to Section 10.2 for those details.	
EFPIA	830	835	8,3	Please clarify which text should be put directly under Section 8.3. the instruction bullets talk about committees and managemement of abnormalities (lines 830-834), but the data field (line 835) talks about Assessments and Procedures.	
CSL Behring	833	834		It is unclear from the instructional text whether the reference to 'management' should be taken to mean medical management (e.g., treatment) or the reporting mechanism (e.g., for clinically significant abnormalities as Adverse Events). We suggest that the intent of the statement be made clearer in the instructional text.	n/a
EFPIA	835	835	8,3	Please change the data field font from black to blue. Consider including multiple fields in the data field, eg, Safety Assessment #1, Safety Assessment #2, etc.	
Estimand Review team	842	842	8,3		Change to "Electrocardiogram (ECG)"
Estimand Review team	843	843	8,3	Consider adding: "This will include limits for ECG characteristics, e.g. QTc."	
SÚKL CZ	845	845	8.3.4 Clinical Laboratory Assessments	Add that is should be specified whether centrally assessed results will be provided to the Investigator.	Add that is should be specified whether centrally assessed results will be provided to the Investigator.
EFPIA	845	845		Consider adding "safety" to the heading, i.e. Clinical Safety Laboratory Assessments, to distinguish from other laboratory assessments.	
EFPIA	845	850	Section 8.3.4	There is guidance how to populate Secton 8.3.4 versus 13.2. At least a cross reference to Section 13.2 should be included here.	Consider adding such guidance

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	845	990		Sites need to know which types of samples are to be collected (e.g., blood, urine, tissue) and whether they are to be sent to the local lab or a central lab for testing. Yet biological samples are described in six separate locations: Section 8.3.4 ("Clinical Laboratory Assessments"), Section 8.7 ("Pharmacokinetics"), Section 8.8 ("Genetics"), Section 8.9 ("Biomarkers"), Section 8.10 ("Immunogenicity Assessments"), and Appendix 13.2 ("Clinical Laboratory Tests"). It is not helpful for sites to have to look in multiple locations to get a sense of which types of samples are to be collected. In addition, a single sample may be described in multiple locations, causing confusion for sites. For example: Genetic analysis is a type of biomarker analysis, and studies often collect a single tissue sample that is used for analysis of both genetic and non-genetic biomarkers. Mentioning these analyses in two separate sections has led to sites mistakenly believing that two tissue samples are to be collected: one sample for genetic biomarker analysis and one sample for non-genetic biomarker analyses.	List all samples in a single section entitled "Biological Samples for Laboratory, Pharmacokinetic, Immunogenicity, Biomarker, and Other Assessments." This section will list each type of analysis (e.g., hematology, chemistry, urinalysis, pregnancy test, pharmacokinetic, biomarker, immunogenicity), and sponsors can choose to cross-reference an appendix or a separate document for more detailed information about each type of analysis (e.g., "Clinical Laboratory Analyses," "Pharmacokinetic Analyses," "Biomarker Analyses").
TransCelerate BioPharma Inc.	845	850	8.3.4	The current instructions in this section appear to be the reverse of standard practice. The study-specific details around lab handling should go in the protocol body, and the appendix should simply be the list of panels for reference but is not needed for day-to-day conduct.	Recommend adding clarity to what is expected in this section versus Section 13.2 and also include a cross-reference to Section 13.2. Suggest including all details of collection and assessment of labs in Section 8.3.4 and make the appendix section 13.2 a simple table of the laboratory parameters to be included in the panels.
EFPIA	846	850	8.3.4	Consider including a crossreference to Section 13.2 and including instructions not to duplicate information that will go in Section 13.2.	
EFPIA	846	887		Section 8.4.6 Reporting of SAEs is redundant with Section 8.4.4.	Remove Section 8.4.6. and clarify instructions in Section 8.4.4. Recording of AEs and SAEs to include method of reporting SAEs to the Sponsor
EFPIA	851	852	8,3	Missing pregnancy testing section within 8.3. Pregnancy testing is a routine test in most clinical trials in practice and with the detailed description of pregnancy reporting in section 8.5, logically there should have a detailed description for pregnancy testing prior to that and section 8.3 is the right place for it along with other clinical testings.	Suggest adding a section 8.3.x after 8.3.4 for "Pregnancy Testing" since it's an important routine test for women of childbearing potential and it belongs to session 8.3 in practice. This addition will make the flow clearer since it describes pregnancy testing prior to pregnancy reporting in section 8.5. More details could be provided in Appendix 13.1 where pregnancy testing is mentioned.
Interpharma, Association of Switzerland's research-based pharmaceutical industry	851	852	8,3	Missing pregnancy testing section within 8.3. Pregnancy testing is a routine test in most clinical trials in practice and with the detailed description of pregnancy reporting in section 8.5, logically there should have a detailed description for pregnancy testing prior to that and section 8.3 is the right place for it along with other clinical testings.	Suggest adding a section 8.3.x after 8.3.4 for "Pregnancy Testing" since it's an important routine test for women of childbearing potential and it belongs to session 8.3 in practice. This addition will make the flow clearer since it describes pregnancy testing prior to pregnancy reporting in section 8.5. More details could be provided in Appendix 13.1 where pregnancy testing is mentioned.
EFPIA	853	855	8.3.5	Please add instructions in Section 8.3.5 to justify the need for suicidal ideation and behaviour risk monitoring in the study. A rationale could for example be that it is a known AE, a class effect or an adverse event of special interest (AESI). The justification will also need to be included (or referenced to) in the appropriate subsection of Section 8.4), for example in the case of an AESI.	If the trial meets any of the criteria requiring suicidal ideation and behaviour risk monitoring by the guidance/guideline in each region, include a justification for the need for suicidal ideation and behaviour risk monitoring in the study and add any specific instructions for the collection and interpretation of the assessment. In case this is an AESI in the study, justification will also need to be provided in the appropriate subsection of Section 8.4, or this section will need to be referenced to.'
Estimand Review team	855	855	8,3	Consider adding ". This might comprise overuse, misuse, and addiction/dependency."	
EUCROF - EU CRO Federation	857	857	Section 8.4.1	From a writer's perspective, it would be very helpful to have the ICH AE definitions already in the template.	Suggest adding definitions as per ICH terms.
EFPIA	857	857	8,4	In practice, protocol templates typically include a subsection on "Reporting on study treatment errors including misuse/abuse".	Consider including a similar section
EFPIA	857	857		[Major] As to align with EU-CTR/Article 41- Reporting of adverse events and serious adverse events by the investigator to the sponsor, for clarity, Amgen recommends to add a subsection in section 8.4 - Serious Adverse Events After the End of the Study/After the Protocol Required Reporting Period.	Amgen recommends to add a sub-section in section 8.4 - Serious Adverse Events After the End of the Study/After the Protocol Required Reporting Period:

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	857	857	8.4	It missing the description of the Periodic Reporting of Safety of the Clinical Study	Add a paragraph that describe the drawing up of the Annual Safety Report
Interpharma, Association of Switzerland's research-based pharmaceutical industry	857	857	8,4	In practice, protocol templates typically include a subsection on "Reporting on study treatment errors including misuse/abuse".	Consider including a similar section
EFPIA	858	858	8,4	In line 21, it is stated that level 3 headings may be deleted or modified as needed, except for level 3 safety headings (Section 8.4). Consider repeating this instrucion in Section 8.4.	
EFPIA	859	863	8.4.1	Propose to remove this subsection here and put all the details in sections 12.1 and 12.2 for more clarity. This way, it will be easier to retrieve all information on the definitions from one place.	There is no requirement to actively monitor study subjects after the study has ended with regards to study subjects treated by the investigator. However, if the investigator becomes aware of serious adverse events suspected to be related to investigational product, then these serious adverse events will be reported to Sponsor immediately/no later than 24 hours following the investigator's awareness of the event.
EFPIA	859	864	Section 8.4.1	Non-study-specific information such as the AE definition interrupts the flow of study-specific information.	Consider placing non-study-specific information such as the AE definition into the appendix (where there is already Section 12 on AEs). Consider deleting Section 8.4.1.
EFPIA	859	914	8,4	For all the level 3 headings under 8.4, where definitions, follow-up periods and reporting requirements are driven by GCP and/or regulations, can standard language be provided in the ICH M11 template? This will ensure common understanding and consistency.	
TransCelerate BioPharma Inc.	859	863	8.4.1	An option for efficiency in the protocol is to place the details for day-to-day study conduct in the main body of the protocol, and place more standardized reference-type information, such as definitions that are generally the same across studies, in the appendices. The CPT provides standard definitions in the appendix, rather than in the assessment section. The CPT has organized it this way for quite some time, and it has been well-received and there have not been issues or feedback from regulators with safety information being missed or de-prioritized in any way.	Recommend reorganizing this section to put standard definitions that are not specific to the current study in Section 12, including the definitions of AE and SAE.
ICON PLC	860	860	8.4.1	It would be beneficial to include a reference to ICH E2A here with the definitions of AEs and SAEs.	Add a reference to ICH E2A into the guidance text to direct the author.
EFPIA	861	863	8.4.1	Are the content control fields here supposed to have blue text to show they may be adapted? Even for "Additional details..." the appendix number may change.	Please check format.
Quotient Sciences	863	863	8.4.1	For improved clarity, please edit.	Please edit: 'Additional details of classification of Aes and SAEs are in Appendices 12.1 and 12.2.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
SÚKL CZ	865	865	Time Period and Frequency for Collecting AE and SAE Information	These should be collected at least during the period of relevant systemic exposure, i.e. 5 times the elimination half life - this should be added in the template.	These should be collected at least during the period of relevant systemic exposure, i.e. 5 times the elimination half life - this should be added in the template.
EFPIA	865	865	8.4.2	editorial	Time Period for and Frequency ~~for~~ of Collecting AE and SAE Information
ICON PLC	865	866	8.4.2	No instructional text regarding SAEs that may occur in screening or a timepoint for SAE collection i.e. first dose of IMP. Often see challenges with site reporting and understanding of these scenarios, so if there are instructional texts included so that protocol authors may think about including these parameters - it would be greatly beneficial for SAE reporting during conduct.	Include some instructional text regarding starting points for SAE collection (that should of course be tailored for the study as needed) and also screening events for the sponsor/author consideration.
CSL Behring	866			Please clarify if the use of "time periods" (instead of "time points") as used here is to indicate that there can be flexibility in start and end of Adverse Event reporting, as this is not clear.	n/a
EFPIA	866	866	8.4.2	Please consider adding guidance here for events that occur pre-IMP dosing, specifying that these are determined as non-TEAEs and that the Sponsor should define when to start collecting these. For example, some companies collect AEs from start of signing the ICF and other companies do not collect these AEs between ICF signing and first IMP dosing.	Please consider adding guidance here for events that occur pre-IMP dosing.
EFPIA	867	867	8.4.2	editorial	Time Period for and/or Frequency ~~for~~ of Collecting AEs and SAEs
CSL Behring	874			Propose to change "final outcome" to "outcome at last follow-up", as the definitive or true final outcome is sometimes not known in cases where a patient may be lost to follow-up.	final outcome outcome at last follow-up
EFPIA	874	874	8.4.4	Please consider adding an instruction around risk proportionate approaches to safety data collection and monitoring.	…, and the final outcome. Specify any changes to standard AE and SAE data collection requirements resulting from the application of risk proportionate approaches to the clinical study (eg, no longer collecting pre-determined non-serious AEs).
Quotient Sciences	876	877	8.4.4	Why are criteria for assessing severity and causality in appendices rather than the main body of the protocol? While it makes sense to provide further country/region-specific or indication-specific information in appendices, severity and causality must be uniformly assessed across the whole trial. Information on recording and categorisation of AEs is of high importance and should all be in one place. For phase 1 trials, for which there is unlikely to be any information in Appendices 12.1 and 12.2, having severity and causality ratings in an appendix will make the protocol disjointed and more difficult to use.	Include severity and causality criteria in Section 8.4.4. Make Appendices 12.3 and 12.4 optional, for use only where severity and causality criteria are complex and need additional explanation.
EFPIA	876	877	8.4.4	Is this a field?	Please check format.
EFPIA	880	881		The statement 'the duration of follow-up after appearance of the events' seems to be in conflict with '"until they are resolved or considered stable' above. Please align or clarify the difference.	
EUCROF - EU CRO Federation	881	881	Section 8.4.5	It is not very clear what is meant by "Specify any procedures to be used for trials in which death is not an endpoint."	Please add clarification.
EFPIA	881	882		Please clarify the meaning of 'Specify any procedures to be used for trials in which death is not an endpoint.'	
ICON PLC	884	887	8.4.6	Per EU CTR guidance, instructional text could be added with regard to identifying and reporting SAEs which do not require immediate reporting by the investigator.	Add text e.g., "Identify the categories of SAEs which do not require immediate reporting by the investigator to the sponsor and describe the procedure for reporting by the investigator to the sponsor of such SAEs."
ICON PLC	884	887	8.4.6	Per EU CTR guidance, the protocol shall describe the procedures for: (c) reporting of suspected unexpected serious adverse reactions by the sponsor to the Eudravigilance database.	Insert instructional text.
TransCelerate BioPharma Inc.	884	886	8.4.6	Similar to the above comment, the same applies for the SAE reporting details, which are not study specific.	Recommend moving the SAE reporting details to the appendix.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	886	886		Consider adding reporting timelines.	
EFPIA	886	886	8.4.6	Please consider adding an instruction around risk proportionate approaches to safety data collection and monitoring.	…to the Sponsor. Specify any changes to standard SAE reporting requirements resulting from the application of risk proportionate approaches to the clinical study (eg, deleyed reporting of pre-specified SAEs from the investigator to the Sponsor).
EFPIA	888	896	8.4.7/8.4.8	As the regulatory requirements differ from one country to another, we recommend keeping only this section "8.4.7 Regulatory Reporting Requirements for SAEs." to stay general. If a "Serious and Unexpected Adverse Reaction Reporting" section will have to be maintained, it would be recommended to have it as subsection and to clarify what is it expected as new information based on 8.4.7 It could be misleading on how it needs to be completed. For example, the USA version and ICH / EU do not have the exact same definition and reporting criteria (In ICH, SUSAR = Suspected and Unexpected Serious Adverse Reaction " reporting is based on investigator and/or company related ICSR, and in USA, SUSAR = Serious and Unexpected Suspected Adverse Reaction ", reporting is limited to company related ICSR). Providing too many details will not add value and may create some confusion for a study planned to be conducted in several countries.	Recommending to keep only this section "8.4.7 Regulatory Reporting Requirements for SAEs." to stay general and incorporating Section 8.4.8 as a subsection of 8.4.7.
EFPIA	888	896		Section 8.4.8 Serious and Unexpected Adverse Reaction Reporting is redundant with Section 8.4.7 Regulatory Reporting Requirements for SAEs since SUSARS are the SAEs that meet critiria for expedited reporting	Remove Section 8.4.8 and consolidate any relelvant instructions under Section 8.4.7 should this not be: Suspected Unexpected Serious Adverse Reaction (SUSAR)? see here: https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/reporting-safety-information-clinical-trials#reporting-susars-to-eudravigilance-section
ICON PLC	888	893	8.4.7	Suggest including information on unblinding procedure by the Sponsor / Sponsor representative to meet regulatory requirements on safety reporting which as such should not be mixed with emergency unblinding procedure.	Add sub section on unblinding for safety reporting purpose.
CSL Behring	890	893		Propose that the two bullet points presented in the draft template be inverted (i.e., appear in the reverse order) to reflect the usual order of reporting.	n/a
SÚKL CZ	892	893	Regulatory Reporting Requirements for SAEs	This is clarified in EC guidance document 2011/C 172/01 (CT-3), Section 4.3, paragraph 29, which states "Immediate reporting should allow the sponsor to take the appropriate measures to address potential new risks in a clinical trial. Therefore, the immediate report should be made by the investigator within a very short period of time and under no circumstances should this exceed 24 hours following knowledge of the serious adverse event".	This is clarified in EC guidance document 2011/C 172/01 (CT-3), Section 4.3, paragraph 29, which states "Immediate reporting should allow the sponsor to take the appropriate measures to address potential new risks in a clinical trial. Therefore, the immediate report should be made by the investigator within a very short period of time and under no circumstances should this exceed 24 hours following knowledge of the serious adverse event".
ICON PLC	892	893	8.4.7	Suggest including some instructional text regarding Non-IMP reporting for trials where authorized products are used in combination with sponsor IMPs and causality is assessed for both/multiple. Often Investigators will procure the medication but then should also be aware of reporting responsibilities of the NIMP involved in the clinical trial.	Suggest including some instructional text so that it is clear regarding NIMP reporting where such trial designs require.
EFPIA	893	893	8.4.7	Please consider adding an instruction around risk proportionate approaches to safety data collection and monitoring.	…their responsibilities. Specify any risk proportionate approaches to safety data collection and reporting applied to the clinical study.
Quotient Sciences	894	894	8.4.8	Please add 'Suspected' to the heading in line with international convention.	Please edit: '8.4.8 Reporting of Serious and Unexpected Suspected Adverse Reactions'
SÚKL CZ	894	895	Serious and Unexpected Adverse Reaction Reporting	SUSAR reporting is obligatory - must always be described in the Protocol and must be in line with applicable legislation	SUSAR reporting is obligatory - must always be described in the Protocol and must be in line with applicable legislation
EFPIA	894	894		This section implies describing sponsor pharmacovigilance reporting requirements (not relevant for investigator/site). Is this needed in the protocol?	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	894	896	8.4.8	The instruction 'Include this section, if applicable' seems in contradiction with the statement on line 21 'Do not delete or modify Level 3 safety subheadings (Section 8.4)'. Please clarify whether it is okay to completely remove Section 8.4.8 in case it is not applicable or wether the section heading should be kept, but 'not applicable' should be added.	
TransCelerate BioPharma Inc.	894	896	8.4.8	EU Clinical Trials Regulation 536/2014 asks for details to be included for procedures for reporting urgent safety measures, serious breaches, changing risk-benefit assessment due to unexpected events.	Recommend including this in the instructions to be included in this section to ensure the required elements are included.
EUCROF - EU CRO Federation	895	895	Section 8.4.8	If applicable" may suggest that the reporting is not mandatory.	Suggest removing if applicable or add clarifications.
CSL Behring	895			Within Section 8.4.8, we propose the addition of instructional text to include a reference to the Reference Safety Information section within the Investigator's Brochure (IB), or another applicable document.	n/a
Boehringer Ingelheim	895	898	8.4.8-8.4.9	Instructional text in these sections state, "Include this section, if applicable." which may imply section can be deleted if not applicable. However, text in Section 0.3 (Heading Structure and Flexibility) states that Level 3 headings in the safety section (Section 8.4) may not be deleted or modified.	Modify instructional text in either Section 0.3 or Sections 8.4.8 and 8.4.9 to clarify whether these sections may be deleted if not applicable, or whether "N/A" should be entered if sections are not applicable.
EFPIA	896	896	8.4.8	CTCG: Clinical trials Regulation (EU No 536/2014), procedures for reporting Urgent Safety Measures, Serious breaches, change risk/benefit due to unexpected event should be added.	Per CTCG consider adding procedures for reporting Urgent Safety Measures, Serious breaches, change risk/benefit due to unexpected event.
LFB Biotechnologies	896	896	8.4.8	AxMP is not mentioned in safety section while Eu CTR 536/2014 reports "In addition, the procedure for reporting of adverse events with suspected causal relationship with an AxMPs should be clearly defined in the protocol." This sentence should be added in Section AE/SAEs	add a section for the description of the reporting of Adverse events related to AxMP between 8.4.8 and 8.4.9
Estimand Review team	897	897	8,4	Add relevant acronym for clarity	Add "... (AESI)"
CSL Behring	897			Section 8.4.9 is titled "Adverse Events of Special Interest", whereas in the current ICH Guideline E3 this is called "Other Significant Adverse Events". We propose that the section title, as it appears in Line 897, be updated to align with the E3 guideline for consistency between guidance documents. This is important because once you have defined adverse events of special interest (AESIs) in the protocol, this labelling triggers the authoring of unnecessary narratives. On many occasions during clinical study report development, a study team may determine that many of the AESIs are not really AESIs. From experience, the placement of text in the protocol for standard medical queries (SMQ) allows for the Sponsor to determine if an event really is a true AESI.	Adverse Events of Special Interest Other Significant Adverse Events
ICON PLC	897	909	8.4.9	Regarding AESI reporting, suggest including some instructional text surrounding the reporting of AESIs and if AESIs would be captured within the Safety Database. If so, may wish to include a reference to follow the same process highlighted in section 8.4.6.	Add some additional instructional text so that the sponsor/author may consider directing the Investigator to report AESIs in a similar manner to SAEs, if AESIs are to be captured within the Safety Database.
ICON PLC	897	909	8.4.9	As per EU CTR medication errors, misuse or abuse in relation to the IMP should be recorded by the investigator and notified to the sponsor. Such events should be listed as mandatory to be collected by the Sponsor. As they might not fall under category of AE they should be discussed in the separate section on special situations.	Suggest to include mandatory text on special situation which are required to be recorded by investigator and notified to the sponsor.
EFPIA	898	909	8.4.9	Recommend that reporting of AESIs be fulfilled within 24 h of learning of the event.	Recommendation that reporting of AESIs be fulfilled within 24 h of learning of the event.
EFPIA	900	904	8.4.9	Drug abuse may be added in the list of AESIs in studies for which the Term 'Drug abuse' is applicable	Drug abuse may be added in the list of AESIs in studies for which the Term 'Drug abuse' is applicable
EUCROF - EU CRO Federation	903	903	Section 8.4.9	Other reportable events not already included in the previous sections, such as cardiovascular and death events,…" Death is included already in previous sections 8.4.6 and 8.4.7 as "Death" is an SAE per definition.	Delete "death" in this text.
EFPIA	903	903		Medical device incidents (including malfunctions) are not classified as adverse events and therefore should not be included under AESIs. Please delete or move to section 8.6 on medical device product complaints.	
ICON PLC	903	903	8.4.9	Remove 'death events' from the examples of other reportable events, given death is a serious criteria and these events will fall into an earlier category other than AESIs.	Remove 'death events' as an example from instructional text, so not to confuse.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	906	907		It is not always possible to define specific MedDRA preferred terms to capture an AESI. Suggest to add 'if applicable'.	
EFPIA	906	907	8.4.9	Please consider specifying the MedDRA version used rather than defining specific terms in the protocol.	Please consider specifying the MedDRA version used rather than defining specific terms in the protocol.
TransCelerate BioPharma Inc.	906	906	8.4.9	Avoid using MedDRA reference as this can be covered in the SAP as MedDRA version changes.	Recommend removing the second sentence in the first bullet.
CSL Behring	911			The Level 3 heading 8.4.10 Disease-related Events or Outcomes Not Qualifying as AEs or SAEs appears in blue. The general guidance stated that all Level 3 headings in Safety should be retained. Please clarify if this heading appears in blue (rather than in black) because it is truly additional/optional.	n/a
EFPIA	911	913	8.4.10	The fact that the section heading is in blue font seems to imply that this section can be removed if not applicable. This seems in contradiction with the statement on line 21 'Do not delete or modify Level 3 safety subheadings (Section 8.4)'. Please clarify whether it is okay to completely remove this section in case it is not applicable or wether the section heading should be kept, but 'not applicable' should be added.	
ICON PLC	911	913	8.4.10	There are some conditions under which a DRE may exceed acceptable limits and require reporting for safety monitoring. Recommend statement giving the caveat of DREs with severity / intensity limit. Section should refer to the protocol for these events and the limits so as to not contradict any information with the latest protocol version.	Should refer to the protocol section for both Disease-related events or outcomes that do not qualify for reporting and any conditions where these conditions may not apply.
Estimand Review team	912	912	8,4	Add relevant acronym for disease-related outcomes	Add "... (DRO), ..."
EFPIA	914	914	8.4.10	Please consider adding a section on other regulatory reportable events (eg, overdose) that are not necessarily resulting in an AE as these are currently missing.	section to be added
EFPIA	915	915		Consider putting in a reference to Appendix 13.1 somewhere in this section.	
ICON PLC	915	941	8,5	Suggest adding text on data protection/consent for both pregnant trial subjects and a pregnant partner of a trial subject.	For example: - Additional assent/consent forms that the subject and her parent/guardians (if appropriate) will be asked to sign to permit the collection of additional information throughout the pregnancy. - ICF that the study subject will need to give to their partner seeking approval to be contracted by the study staff to collect information bout the pregnancy - Additional consent required after the child is born to collect data.
EFPIA	917	917	8.5.1	Please remove redundancy in the term time period	use only period
SÚKL CZ	918	918	Participants Who Become Pregnant During the Trial	Add that it must be speficied whether study intervention must be stopped when becoming pregnant.	Add that it must be speficied whether study intervention must be stopped when becoming pregnant.
EFPIA	919	919	8.5.1	It is not clear from the instructions if the EWG intended this to be for "additional" assessments specific to the pregnant condition OR if this was specific to the existing protocol defined assessments that should be undertaken for a pregnant population specific efficacy/safety cohort analysis of the investigational product. The experts should consider that both could be relevant to these instructions.	It is not clear from the instructions if the EWG intended this to be for "additional" assessments specific to the pregnant condition OR if this was specific to the existing protocol defined assessments that should be undertaken for a pregnant population specific efficacy/safety cohort analysis. The experts should consider that both could be relevant to these instructions.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Interpharma, Association of Switzerland's research-based pharmaceutical industry	919	919	8.5.1	It is not clear from the instructions if the EWG intended this to be for "additional" assessments specific to the pregnant condition OR if this was specific to the existing protocol defined assessments that should be undertaken for a pregnant population specific efficacy/safety cohort analysis of the investigational product. The experts should consider that both could be relevant to these instructions.	It is not clear from the instructions if the EWG intended this to be for "additional" assessments specific to the pregnant condition OR if this was specific to the existing protocol defined assessments that should be undertaken for a pregnant population specific efficacy/safety cohort analysis. The experts should consider that both could be relevant to these instructions.
Estimand Review team	920	920	8,5	consider adding "of pregnant woman with embryo/fetus and woman after having given birth and child/children born"	
Estimand Review team	921	921	8,5	Grammar: "... collected for a participant...", is it rather "on" or "about"?	
EFPIA	921	923	8.5.1	Women of child bearing potential may be excluded on grounds of potential teratogenicity, with specific guidance regarding pregnancy prevention, this should be further captured here.	
EFPIA	921	923	8.5.1	The instructions states that what information should be collected (eg, treatment d/c) should be specified, but does not include instructions to specify whether a participant who becomes pregnant should be discontinued from the trial/intervention. If discontinuation needed, refer back to appropriate subsection of Section 7.	
CSL Behring	930			It is not uncommon for studies to define pregnancy, regardless of outcome, as an SAE. The instructional text in the draft template appears to indicate that such practice will not be allowable. Please clarify the intent of the text here, and reconsider language used as appropriate.	n/a
EFPIA	930	934		Original Text: "Specify that pregnancy is not an AE, unless a negative or consequential outcome occurs in the participant or child/foetus. If the negative event meets the seriousness criteria, then this is considered an SAE (for example, spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy, or pre-eclampsia) and reported per Section 8.4.5, Reporting of SAEs." The section number for "Reporting of SAEs" should be revised to 8.4.6 for accuracy. For completeness, we also recommend adding to record these SAEs as mentioned in section 8.4.4.	Recommendation for the following revision: "Specify that pregnancy is not an AE, unless a negative or consequential outcome occurs in the participant or child/foetus. If the negative event meets the seriousness criteria, then this is considered an SAE (for example, spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy, or pre-eclampsia) and recorded per Section 8.4.4 and reported per Section 8.4.5 8.4.6, Reporting of SAEs."
EUCROF - EU CRO Federation	933	933	Section 8.5.1	Incorrect section or name in cross-reference of text "Section 8.4.5, Reporting of SAEs".	Fix cross-reference to 8.4.6.
ICON PLC	933	934	8.5.1	Reporting of SAEs referenced here as section 8.4.5 whereas it is 8.4.6.	Update reference to section 8.4.6.
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	933	933	8.4.5	Incorrect section name/reference: and reported per Section 8.4.5, Reporting of SAEs…. but the Section 8.4.5 is "Follow-up of AEs and SAEs (Line 878)".	Correct the name/reference.
EFPIA	937	941	8.5.2	Please consider specifying that the ICF needs to be signed by the partner of a male study participant in order to allow pregnancy data to be collected and followed up, and that data from the pregnancy may be collected Y/N, such as data on the birth Y/N, data on the new born Y/N, and what maybe done with this collected data. Other guidance could include 1) how long the FU is required, or allowed per local laws and 2) if consent is given to store this data or only until successful live birth or until early termination. No collection maybe allowed without an ICF signed by the partner not treated with IMP in the trial.	Please consider specifying that the ICF needs to be signed by the partner of a male study participant in order to allow pregnancy data to be collected.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	938	941	8.5.2	Suggest to clarify pregnancy information is required if a female partner of a male participant becomes pregnant. Pregnancy information from a female partner of a female participant is not relevant.	If the investigator will attempt to collect pregnancy information for a male participant's partner, who becomes pregnant while the participant is in the trial.
EFPIA	938	939	8.5.2	The instruction "If the investigator will attempt to collect pregnancy information for a participant's partner, who becomes pregnant while the participant is in the trial." should also take into consideration the period that is specified in the eligibililty criteria for male participants related to pregnancy/sperm donation for reproduction.	
EUCROF - EU CRO Federation	943	943	Section 8.6	Section 8.6 is described as optional. Does this mean, the header may be deleted even if it is a leve2 header? Please clarify in the instructional text.	
EFPIA	943	943		The medical device product complaints for drug/device combination product section is listed as optional. Include instructions to state "not applicable" for this section, or delete entirely and renumber following subsections.	
EFPIA	943	943		Please clarify whether product complaints that are not related to devices should also be addressed.	
EFPIA	943	943	8,6	In EU CTR, all Medication Errors, Misuse and Abuse with and without AE are to be collected. Will a similar approach be taken at the ICH level? If so, then please consider adding a subsection on medication errors and misuse.	Per EU CTR, please consider adding a subsection on medication errors and misuse.
EFPIA	943	943	8,6	Please consider providing guidance to define where to collect information not linked to study participants.	
EFPIA	943	943		Please clarify whether this section should also address complaints with the use of an independent medical device (i.e. not a part of a drug/device combination product) that is being used for IMP administration, especially if it is investigational (e.g. used outside approval).	
EFPIA	943	962	8,6	For all the level 3 headings under 8.6, where definitions, follow-up periods and reporting requirements are driven by regulations, can standard language be provided in the ICH M11 template? This will ensure common understanding and consistency.	
LFB Biotechnologies	943	962	8.6	this section is only for medical device complaint? What about IMP complaint	clarify 8.6 targets medical device and IMP complaint, or add another section for IMP complaint
EFPIA	945	945		Please consider whether 'software as a medical device (SAMD)' should be addressed, and if so indicate where.	
TransCelerate BioPharma Inc.	946	947	8.6.1	Similar to the above comment regarding AE definitions, the definitions for medical device product complaints should also be placed in the appendix.	Recommend moving this section, Definition of Medical Device Product Complaints, to the appendix
Estimand Review team	963	963	8,7	PK studies are also susceptible of benefitting from the estimands framework, which could be used to better understand intercurrent events in this type of studies (e.g. partial meal ingestion, treatment discontinuation) and if/how the subsequent PK concentration values are used to derive PK parameters such as AUCs, etc.	Consider adding a reference to the estimand framework.
EFPIA	963	963		Please consider to add a section for Pharmacodynamics, or clarify where these assessments should be described.	Insert a section for pharmacodynamics.
EFPIA	963	963		The PK section does not include the PK endpoint definitions and is only centered on sample collection/handling and assay methods. Suggest including one more bullet in this template (see proposed change). This text is mostly taken from the Technical Specification.	"Add the following bullet after 969: Indicate definitions for the PK parameters of interest and how they will be calculated (for example, non-compartmental analysis). If population PK will be included, provide appropriate text. If PK will not be part of the trial, include a statement to this effect."
EFPIA	963	963	9	The instructional text at the beginning of Section 9 should indicate whether a separate statistical analysis plan will be written.	Indicate whether a separate SAP will be written.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	963	963	9.2.2	Editorial -- "Events *of* Primary Estimand(s)" should be "Events *for the* Primary Estimand(s)."	Change to "Events for the Primary Estimand(s)"
EFPIA	963	963	9,1	Why is the information on analysis sets split across two documents (protocol section 9.1 + the SAP)?	Put all analysis set details in a single place.
EFPIA	963	963	9,2	The instructional text here says that the SAP is introduced in this section. However, there is no mention of the SAP in the document text. In combination with the instructional text for Section 9.1, it isn't clear whether the SAP is a separate document or merely Section 9 of the protocol.	
EFPIA	966	969	8,7	Include a retention time for PK samples	
Estimand Review team	968	969	8,7	Add whether/when samples will be destroyed.	
SÚKL CZ	968	969	Pharmacokinetics	Generally, the Protocol should always address collected blood volumes for paediatric clinical trials - even if not intended for PK assessments, and justify whether the volumes are within the recommendations for maximum volumes to be collected. This section is missing in the template.	Generally, the Protocol should always address collected blood volumes for paediatric clinical trials - even if not intended for PK assessments, and justify whether the volumes are within the recommendations for maximum volumes to be collected. This section is missing in the template.
EFPIA	968	969	8,7	The PK section states the details for "processing samples" can be put in an appendix but how the samples are "handled" should be put in the protocol. These two terms have overlapping meanings. Could the intent of these two statements be more clearly stated?	Recommend using the bullet shown in 8.8 and 8.9 "Include the biological samples that will be collected (for example, serum, plasma, etc.) and the retention time for the samples (ensuring alignment with the ICF). [This would also address the previous comment.]
EFPIA	971	989		Recommend combining genetics and biomarker section into one. Suggest to separate operational details regarding biomarkers (incl genetics) from scientific rationale. Recommend only including sample collection supporting these biomarkers to be listed here, and any information regarding types of analyses or types of biomarkers to be included in scientific rationale (as suggested in comment below).	
EFPIA	971	971	8,8	Does the term 'Genetics' cover also 'Pharmacogenomics'?	If pharmacogenomics is not covered by genetics, consider adding this to the level 2 header.
EFPIA	979	979	8,9	Pharmacodynamics is mentioned as a subsection of 'Biomarkers'. However, Pharmacodynamics may be assessed via other ways than biomarkers for specific studies such as TQT, HAP and driving studies which collect PD measurements (primary endpoints) using other devices.	Consider adding a separate level 2 header 'Pharmacodynamics'.
Charité Research Organisation	979	989	8,9	Please consider changing this heading to 'biomarkers and pharamcodynamics' since biomarkers my not be identified in early studies	
Gilead Sciences	980	988	8,9	Suggest to include instructional text for considerations for biomarker sample collection for studies with sites in China.	
Estimand Review team	982	982	8,9	Is "tissue" worth to be added to the listing in brackets?	
EFPIA	985	986	8,9	Consider including details on the samples in Section 13.2 and crossrefering to Section 13.2.	
CSL Behring	987	988		Biomarker analyses may follow a separate detailed Clinical Study Protocol in the event that they are exploratory. Section 8.9 Biomarkers should be updated to include a statement to this effect, and we propose this be presented as an additional bullet point.	n/a
EFPIA	987	987		Consider if this is also relevant in section 8.8 Genetics	
CSL Behring	990			Suggest deleting "Assessments" from the header title for consistency with the other sub-sections within section 8.	8.10 Immunogenicity ~~Assessments~~
EFPIA	991	991		Suggest to address storage and analysis of samples as well.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	991	993	8. 10	Consider including details on the samples in Section 13.2 and crossrefering to Section 13.2.	
EFPIA	994	994		There is no section specifically covering the topic of biosamples collected/retained for future research purposes (i.e. research that is not restricted to the topic of the given study). While this can in principle be addressed within the sections above, clarification on this should be provided in the template, so that the protocols meet the requirements and expectations in relation to this topic.	
EFPIA	994	995	8	The template appears to be missing a section concerning "use of data and biosamples for future research". If applicable per local laws, it maybe required to have in the ICF a placeholder to confirm that samples maybe used for genetic testing, biomarkers, etc. A guidance should be added here, as some countries would require patients consent before collection, storage, testing, etc. may occur.	We recommend adding a section concerning "use of data and biosamples for future research".
Agios	995	1000	8,11	Clarify where in Section 8 qualitative interviews (exit interviews) should be included, whether just under Section 8 header or under a subsection of 8. It is not clear if this section should also include the qualitative interviews (e.g. exit interviews) referenced in line 812. Exit interviews asking the patients about their experience in the trial and with their assigned treatment are not traditional COAs, and would not necessarily focus on healthcare resource utilization or health economics. It is not clear exactly where such interviews should be described.	
Gilead Sciences	996	997	8,11	Suggest to clarify the instructional language here. Typically we would include PRO descriptions in this section.	
Estimand Review team	998	999	8,11	Consider adding "electronic device" to the listing	
EFPIA	1000	1000	8,11	Consider including multiple fields in the data field, eg, Medical Resource Utilization #1, Medical Resource Utilization #2, etc.	
EUCROF - EU CRO Federation	1002	1002	Section 9		Suggest addition of subsections for demographics/baseline analyses and PK analyses. See also general comment on early phase trials.
EUCROF - EU CRO Federation	1002	1002	Section 9	It is helpful to have a Level 2 heading called "General Considerations" as shown in the TransCelerate protocol template. This allows some flexibility in including study-specific Level 3 subheadings (e.g., "Descriptive Statistics", "Definitions", "Visit Windows") without changing the Level 2 heading structure (as the instructions in this document specifically state that Level 1 and Level 2 headings should not be changed).	Suggest adding as per comment.
EUCROF - EU CRO Federation	1002	1002	Section 9	Shouldn't the instructional text state that the writer should include "the level of significance to be used"? Note that the ICH E6(R2) document has a similar requirement (see item 6.9.3).	Add instructional text.
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	1002	1002	9	The title "STATISTICAL CONSIDERATIONS" should be changed to "STATISTICAL METHODS AND CONSIDERATIONS".	The title "STATISTICAL CONSIDERATIONS" should be changed to "STATISTICAL METHODS AND CONSIDERATIONS".
EFPIA	1002	1002		This section needs a level 2 section where topics that apply across objectives can be described, e.g., decision criteria, multiplicity adjustment, statistical implications of the choice of strategies to handle intercurrent events, handling of missing data, cf. more topics in the TransCelerate CPT.	
EFPIA	1002	1102	9	where is the "sequence of analysis" supposed to be described?	Add a subsection
EFPIA	1002	1106	9	Missed analysis plan for demographic /baseline characteristics, treatment exposure summary.	Propose to include subsection 9.x for demographic/baseline/treatment exposure summary or point to where it can be found in the SAP.
EFPIA	1002	1106	9	Recommend clarifying whether and how the data collected after primary analysis will be reported.	Propose to include 'State whether any additional data for participants continuing to receive study treatment past this time, as allowed by the protocol, will be further summarized in a final study report once these participants completed the study'.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	1002	1011	9 & 9.1	There are no instructions about linking analysis set definition and population attribute of the estimand(s), if estimands have been specified under Section 3. It would be important to include such link, to ensure consistency of analysis set with estimand(s) definition, as well as clarify the need for alignment with study objectives and endpoints.	Propose to include the following sentence in Section 9, "This section must be aligned with the objectives, endpoints and /or estimand being defined in Section 3." and the following sentence in Section 9.1, ''Ensure that the analysis sets align with the population attributes of any estimand specified in Section 3."
EFPIA	1002	1106	9	There is no decicated section for multiplicity. With the current structure of having separate sections for the analyses addressing the primary and secondary objectives, it is difficult to desscribe multiplicity adjustment in some settings (e.g. multiplicity adjustment across the primary and secondary endpoints).	Create a level 2 Heading (after 9.7) for multiplicity under Section 9. 9.1… 9.2 Statistical Hypothesis/Hypotheses 9.3 Multiplicity Adjustment 9.4 Analyses Supporting Primary Objective(s)
EFPIA/EFSPI Estimand Implementation Working Group	1002	1002	9	The section needs a level 2 section where topics that are relevant across objectives/analyses can be described. The instructional text should provide examples of which level 3 sub-section could be relevant. The rest of this section should be updated to reflect this section.	Add a section 9.1 section named “General Considerations” and add instructional text “Level 3 sub-section can be added as applicable to describe key topics such as decision-making criteria including type 1 error control, details of how intercurrent events and their strategies impact estimation methods, handling of missing data, etc.” Move sections 9.2.2 and 9.2.3 to new section 9.1 General Considerations and adjust instructional text accordingly, cf. general comment on proposed structure. Rename Section 9.2.1 to “Main Analysis” Provide the statement: “Further details will be provided in the Statistical Analysis Plan”.
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	1002	1102	9	Rules for defining and analyzing Derived Variables must be detailed.	
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	1002	1102	9	A section should be added: “Multiple Comparisons/Multiplicity” If there is more than one primary endpoint (outcome variable), more than one analysis of particular endpoint, or if there were multiple treatment groups, or subsets of the patient population being examined, the statistical analysis should reflect awareness of this and either explain the statistical adjustment used for type I error criteria or give reasons why it was considered unnecessary.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	1002	1102	9	It might be useful to add a specific section for the statistical analysis of Paediatric Population. It may be necessary to develop, validate, and employ different endpoints for specific age and developmental subgroups. Extrapolation of efficacy data from older to younger paediatric patients should be detailed.	
TransCelerate BioPharma Inc.	1002	1002	9	Including a general considerations section where topics that apply across the objectives/analyses can be described would avoid repetition in the following sections.	Recommend including a level 2 section on "General Considerations" (suggest this be Section 9.1)
Interpharma, Association of Switzerland's research-based pharmaceutical industry	1002	1106	9	Missed analysis plan for demographic /baseline characteristics, treatment exposure summary.	Propose to include subsection 9.x for demographic/baseline/treatment exposure summary or point to where it can be found in the SAP.
Interpharma, Association of Switzerland's research-based pharmaceutical industry	1002	1007	9	Recommend clarifying whether and how the data collected after primary analysis will be reported.	Propose to include 'State whether any additional data for participants continuing to receive study treatment past this time, as allowed by the protocol, will be further summarized in a final study report once these participants completed the study'.
Interpharma, Association of Switzerland's research-based pharmaceutical industry	1002	1011	9 & 9.1	There are no instructions about linking analysis set definition and population attribute of the estimand(s), if estimands have been specified under Section 3. It would be important to include such link, to ensure consistency of analysis set with estimand(s) definition, as well as clarify the need for alignment with study objectives and endpoints.	Propose to include the following sentence in Section 9, "This section must be aligned with the objectives, endpoints and /or estimand being defined in Section 3." and the following sentence in Section 9.1, ''Ensure that the analysis sets align with the population attributes of any estimand specified in Section 3."
Estimand Review team	1003	1003	9		Change to "...with current versions of the ICH E9 Guideline ..."
EFPIA	1003	1007	9	We suggest adding instructional text to clarify whether a statement should be provided indicating which general summary statistics will be provided for continuous or qualitative data.	Clarify whether a statement should be provided indicating which general summary statistics will be provided for continuous or qualitative data.
Agios	1004	1004	9	If data is collected by definition it is relevant	Delete the reference to "relevant data"
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	1006	1006	9	In the introductory part of section 9 it is described that a statement with regard to when the primary analyses will be conducted should be provided. We suggest that this information should be provided in a dedicated subsection instead of at the top level.	
EFPIA	1006	1007	9	Please consider adding more flexibility concerning what is reported in this statement. It may describe only the primary analysis, or an I/A if deemed more important, or both.	Adapt the statement concerning when the "primary analysis" will be conducted to allow more flexibility concerning which analyses are prioritized.
CSL Behring	1007			Within the section on statistical considerations, the existing text "at the time the trial ends" gives the impression that analysis is performed immediately. Theoretically (depending on the agreement with the health authorities and the study design), the primary analysis could be conducted before the end of study as soon as all primary endpoint data have been collected. We propose a rewording of this statement to reflect this.	The primary analysis will be conducted on all participant data ~~at the time the trial ends~~ after the last participant's final data have been collected and the trial is completed.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	1008	1008	Section 9	Some aspects for statistical analysis are relevant across multiple objectives, e.g. multiplicity adjustment. It would be helpful to describe such aspects independent of the Sections dedicated for specific objectives.	Consider adding a section that can possibly cover aspects that are relevant across objectives, e.g., type 1 error control across multiple hypotheses.
Estimand Review team	1009	1011	9,1	We have tranditionally had ITT/mITT/PPS/Safety/PK analysis sets, the role of the analysis sets is defined in E9. With the estimand framework, the analysis sets are specified as part of the estimand which would make the concept of analysis sets somehow obsolete. On the other hand, there are situations where estimands are not prominently used (safety) or in antibacterial drug development where trial participants are excluded if they do not have the disease. Also, the data sets may be the same or very similar, depending on the estimands chosen. Hence, we propose not to delete this section, but to shift it as a subsection to section 9.2.	Please consider "downgrading" it to a subsection under 9.2, e.g. as 9.2.1. Analysis sets
CSL Behring	1009	1012		We suggest that at least some Level 3 headings for the standard analysis sets, for e.g., Screened, Enrolled, ITT, PP, ATS should be included within this section of the template. This would further reduce the variability, whilst retaining sufficient flexibility.	n/a
EFPIA	1009	1010	9,1	Suggest using instead the term of 'Participant Analysis Sets' as this section refers to an analysis set as a set of study participants and not to the data points from each participant to be included in the analyses aligned with each estimand.	9.1 Participant Analysis Sets'
EFPIA	1009	1009		Should specification of data points to use in the estimations/analyses be specified in this section? Recommend to write instructional text that this is needed and can be specified in this section, in a section on the implications of the strategies chosen to handle intercurrent events or in the analysis section	
TransCelerate BioPharma Inc.	1009	1011	9,1	Data points selection is important and needs to be described in the protocol, so it should be clear the preferred placement for these details or at least general instruction that this is expected to be included.	Recommend clarifying if details on data points selection should be described here or elsewhere.
EFPIA	1010	1010		Please clarify the difference between "specified" and "described". Analysis sets for primary and key secondary endpoints/estimands should be fully specified in the protocol	
Estimand Review team	1010	1011	9,1	The Statistical Analysis Plan is a separate document. We discourage its use here because we think that all relevant information should be contained in the study protocol. Unfortunately, it has become (bad) practice for some sponsors to outsource relevant information to the SAP and to include only superficial or high-level information in the protocol as it gives them more flexibility to tweak or amend the analysis at later timepoints. The sentence, as it is currently written, can be misunderstood to engourage this malpractice.	delete any references to the Statistical Analysis Plan
EFPIA	1010	1011	Section 9.1	Analysis sets should be specified in the protocol. It is unclear what "and described in the Statistical Analysis Plan" is adding.	Consider deleting "and described in the Statistical Analysis Plan".
PTC Therapeutics, Inc.	1010	1011	9,1	PTC notes that the red colour used here is a different shade to the rest of the document.	PTC proposes colour consistency throughout for guidance text.
EFPIA/EFSPI Estimand Implementation Working Group	1010	1011	9.1	It is important not only to describe the participants whose data will be included in the analyses but also to describe the data points to be used. This could reasonably be described in one of at least three different sections: - The Analysis Sets Section - The General Considerations Section (e.g. Impact of Intercurrent Event Strategies Sub-Section) - The Analysis Section itself Currently, there is no agreement on where to describe this [see discussion in Principles and recommendations for incorporating estimands into clinical study protocol templates. Trials (2022) https://doi.org/10.1186/s13063-022-06515-2], so we recommend that M11 allows for the required flexibility to specify it where is makes most sense in the individual trials.	Add instructional text to section that makes it an option to specify either the participants only (and the data points in another section) or to specify both participants and data points in the Analysis Sets Section Add instructional text to the sub-section “Impact of Intercurrent Event Strategies” to General Considerations section that the impact of the strategy used to handle each intercurrent event on data selection can be described here or in one of the other two sections. Add instructional text to the Analysis Section that if not specified elsewhere, describe the data points to be used in the estimation/analysis.
EFPIA/EFSPI Estimand Implementation Working Group	1010	1011	9.1	It is unclear what the intention is behind saying that sets should be “specified” here and “described” in the statistical analysis plan. We recommend that analysis sets should be fully specified in this section (no need to mention SAP).	Remove reference to SAP here: “Analysis sets should be fully specified here and the intended use of each of them should be clear.”

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Agios	1010	1012	9,1	The reference to the statistical analysis plan should be moved to the preamble for Section 9 as it applies to every subsection of Section 9 not just to Section 9.1 and Section 9.2. Also template is missing general statistical considerations which apply across all endpoints.	Delete "and described in the Statistical Analysis Plan" from Section 9.1. Add to the preamble of Section 9 a reference to the statistical analysis plan "The statistical analysis plan (SAP) will be finalized <describe the timing> and will include a more detailed description of the statistical analyses described in this section." Change the Header of Section 9.1 to read "General Statistical Considerations" which will include the definition of analysis sets and any other definitions that apply across multiple endpoints so as to reduce redundancy in the protocol
EFPIA	1012	1012	9,1	Consider including multiple fields in the data field, eg, Analysis Set #1, Analysis Set #2, etc	
EFPIA	1013	1013		Suggest to add a level 3 heading on derived endpoints	
EFPIA/EFSPI Estimand Implementation Working Group	1013	1013	9.2	Sometimes the endpoint is not a straightforward measurement, but something that is derived in a complicated way. Suggest adding a level 3 section as a placeholder for such descriptions.	See General Comment on content structure Add: level 3 heading under Analyses Supporting Primary Objective(s) for “Endpoint Derivation(s)”
Agios	1013	1013	9,2	An analysis does not support an objective; the results of the analysis will inform whether or not the objective was met which is different than "suporting an objective". Section 9.2 header should be retitled as "Analyses of Primary Endpoints"	Retitle Section 9.2 Header as "Analyses of Primary Endpoints"
TransCelerate BioPharma Inc.	1013	1013	9,2	The endpoint could be a derivation and not straightforward, so this should be described here if applicable.	Recommend including a placeholder Level 3 section on endpoint(s) derivation(s).
Estimand Review team	1014	1014	9,2	For the reasons described above on line 1010, do not make any reference to the Statistical analysis plan. It would be prefereble to delete "plan", if you introduce the "statistical analysis" it should be fine.	Replace "Statistical Analysis Plan" with "statistical analysis"
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	1014	1015	9.2.	This section is called "Analyses Supporting Primary Objective(s) and it is described that this section introduces the Statistical Analysis Plan (SAP), with the detail to be provided in the subsequent subsections. It is unclear why the SAP should be introduced in a section on primary objectives, it should be rather referenced on the top level of chapter 9. It is unclear if the SAP is expected to be a separate document or included in the protocol.	
EFPIA	1014	1014		The Statistical Analysis Plan is most often referred to as a stand-alone document, so the sentence is confusing. Please consider to rephrase to 'This section introduces the statistical analyses…or planned analysis ...' to not confuse with the SAP.	
EFPIA/EFSPI Estimand Implementation Working Group	1014	1017	9.2	The SAP should not be introduced underneath a heading that relates specifically to analysis of the primary objectives, since the SAP relates to all analyses and in addition, “Statistical Analysis Plan” usually refers to a separate document. There could be an instruction to use labels/names of estimands from section 3 to ensure correct linking of the two sections. You have previously written that not all trials will have estimands defined.	Create a general analysis considerations section within section 9 to allow for cross-objective considerations such as multiplicity. This should be before the current section 9.2. See general comment on content structure. Modify text to accommodate trials without estimands defined. Proposed text: “This section describes the methods of estimation (analytic approach) in alignment with how the estimands are defined, if applicable. Sensitivity analyses should be aligned with how the estimands and estimators are defined. Labels or names of estimands introduced in section 3 could be used to reference in the following subsections to ensure consistent linking.”
Estimand Review team	1015	1015	9,2	Make clear that the analytic approach and the estimation are interlinked	"... method of estimation (and corresponding analytic approach)..."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Estimand Review team	1016	1016	9,2	Add cross-refences to remind and ensure that the sections are aligned throughout the document	Add "...how estimands are defined (defined in section 3.1 and justified in section 4.2)." to the sentence
EFPIA	1018	1018		What should be written before 9.2.1? The instructional text seems only to list topics that are already addressed in the sub-sections. Please clarify.	
EFPIA/EFSPI Estimand Implementation Working Group	1018	1018	9.2	Unclear what is meant to be written before 9.2.1. Is this supposed to be a summary of what is included in the subsection?	Clarification of intended content required. Suggest remove [Analysis Supporting Primary Objectives] as this will be covered in subsection.
EFPIA	1019	1021		Suggest adding text that indicates statistical hypotheses should be stated when applicable because some clin pharm studies may not have a formal hypothesis that is being tested.	
EFPIA	1019	1030	9.2.1	Section 9.2.1 can be renamed Main Estimator/Analysis. Specification of the main analysis should contain three subsections: Data Handling, Main Estimator/Analysis Specification and Assumptions, and Decision Rule(s). All these 3 subsections will ensure that all the needed information is specified. Data Handling subsection would specify the set of data points from each participant to be included in the analysis, including which data are not useful relative to intercurrent events and which data are missing. (The current subsection Handling of Intercurrent Events of Primary Estimand(s) could be misinterpreted as restating the strategies to handle intercurrent events, when its scope is data handling relative to intercurrent events. Specification of what data are missing would be included in the Data Handling section, while assumptions for missing data would be included in the Main Estimator/Analysis Specification and Assumptions section.) The subsection Main Estimator/Analysis Specification and Assumptions would include all specifications for the main estimator coresponding to the estimand, including assumptions for the model and the data that are either missing or not used. The subsection Decision Rule(s) would specify the analysis used for decision making for the corresponding objective and how it relates to the trial criteria for success. Sometimes, the analyses used for decision making could be different than the analyses that will produce an estimate for the estimand.	9.2.1 ~~Statistical Model, Hypothesis, and Method of~~ Main Estimator/Analysis 9.2.1.1 Data Handling 9.2.1.2 Main Estimator/Analysis Specification and Asumptions 9.2.1.3 Decision Rule(s)
EFPIA	1019	1019		Consider to rename this section "Main Analytical Approach" or "Main Analysis". Not all trials will test hypotheses. Sometimes the purpose is to estimate a treatment effect.	
EFPIA	1019	1030	9.2.1	Focus of this section is on statistical hypothesis testing. However, many Phase 1 studies are estimation-oriented. Please consider adding a few sentences at the end of the section to describe how estimation studies should be addressed.	
EFPIA/EFSPI Estimand Implementation Working Group	1019	1019	9.2.1	The heading should be renamed to be more general. Not all trials will test a hypothesis, cf. comments to lines 1002 and 1022-1027 .	Rename Section 9.2.1 to “Main Analysis (Estimand Label)”
Agios	1019	1030	9.2.1	the statistical hypothesis and statistical methodology to control type I error in the study should be provided as a whole and cannot just be provided for the primary endpoint. Further this section, as written, applies only to frequentist approaches and there should be an acknowledgement that other approaches (eg Bayesian approaches) may be used and should be described.	The Section for sample size determination should be moved up as the first subsection of Section 9 so that the statistical testing strategy (as applicable), interim analysis and method to control the type I error overall in the trial (which may go beyond just the primary objective (s)) can be introduced in a meaningful order
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	1019	1019	9.2.1	In longer term studies, paediatric patients may move from one age category to another; the study design and statistical plans should prospectively take into account changing numbers of patients within a given age category.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	1019	1029	9.2.1	Important features of the analysis including the particular methods used, adjustments made for demographic or baseline measurements or concomitant therapy, handling of drop-outs and missing data, adjustments for multiple comparisons, special analyses of multicentre studies, and adjustments for interim analyses, should be discussed.	
TransCelerate BioPharma Inc.	1019	1019	9.2.1	Not all studies are testing hypotheses and stating both "statistical model" and "method of analysis" may be redundant. The CPT uses the term “main analytical approach.”	Recommend reviewing and consider the best wording for this heading. Alternatively, could simplify to "Main Analysis"
EFPIA	1020	1029	9.2.1	A reference to the "population-level summary" used in the "estimands" framework appears to be missing.	Add a reference to the "population-level summary" used in the "estimands" framework.
EFPIA/EFSPI Estimand Implementation Working Group	1020	1021	9.2.1	The instruction tells authors just to align analysis with assumptions but not to provide them explicitly. More general text required in case a hypothesis is not to be tested.	Proposed text: "Ensure that the statistical analysis method is aligned with the primary estimand(s). List key assumptions that should be targeted in later sensitivity analyses."
Estimand Review team	1022	1024	9,2	Perhaps to add a table, if considered useful for the reader.	Add "A table might be added, if considered helpful for the reader."
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	1022	1024	9.2.1.	In this section it is described: "For all applicable objectives (for example, primary, secondary), under the appropriate header, state the null and alternative hypotheses, including the pre-planned type 1 error, or alternative criteria to define trial success and relevant operating characteristics if appropriate." This description presumes frequentist methods. We suggest to preface this paragraph with "Assuming the use of frequentist methods" or include guidance for Bayesian ones.	We suggest to preface this paragraph with "Assuming the use of frequentist methods" or include guidance for Bayesian ones.
CSL Behring	1022			As this section 9.2.1 of the template is for the primary objectives, we suggest to either put the statement “For all applicable objectives (for example, primary, secondary), under the appropriate header, state the null…” under each applicable subheading within Section 9.2, or delete “secondary” here and simplify the sentence to read “For the primary objecive(s), state the null…”	n/a
EFPIA/EFSPI Estimand Implementation Working Group	1022	1026	9.2.1	Add to instruction that "analysis data point sets" (or equivalent) should be provided or referenced. Decision making approaches that rely on estimation, probability of success (assurance) or Bayesian testing are now very common in Phase Ib and II trials. As this is meant to be a universally applicable template, it must be able to accommodate these very common approaches. Current instructions assume that frequentist approaches are used. Modify the instructions to support other (not only frequentist hypothesis testing) approaches to trial analysis such as estimation, go/no-go criteria or Bayesian methods. The decision criteria should be moved to the general considerations section.	Move to sub-section Decision Criteria to General Considerations section and include the following instructional text: “For all applicable objectives (for example, primary, secondary), under the appropriate header, state the null and alternative hypotheses, including the pre-planned type 1 error, or alternative criteria to define trial success and relevant operating characteristics if appropriate.” In this section (9.2.1), keep instructional text: “Describe the statistical model used and the factors that will be included (covariates and interactions) and any rules for handling these factors (for example, pooling of centres). Describe the data points to be used or reference analysis (data point) sets defined earlier.”
EFPIA	1026	1026		Recommend including specific criteria to exclude data.	"Update the last statement on 1026 to as follows: If applicable, state and discuss any pre-planned criteria for exclusion of data and any adjustments to account for multiplicity."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	1026	1027	9.2.1	Suggest adding details on statistical testing procedure. Testing procedure shows the details for Type-1 error control/multiplicity and it's important enough to be mentioned explicitly or add a separate section for testing procedure.	Suggest adding "including the details of testing procedure" after "If applicable, state and discuss any adjustments to account for multiplicity" or include a separate section 9.2.x to clarify the multiplicity adjustment.
EFPIA	1026	1027	9.2.1	Since multiplicity is an issue potentially involving not only the primary objective but also secondary objectives, multiplicity issues cannot be discussed in section 9.2.1. In addition, since multiplicity issues can sometimes be complicated, it would deserve a dedicated level 2 section.	Please consider describing multiplicity issues under a dedicated level 2 section.
EFPIA/EFSPI Estimand Implementation Working Group	1026	1027	9.2.1	Multiplicity by definition refers to multiple tests, and therefore goes across multiple objectives. In the current Section 9, all analyses are specified in different level 2 sections according to (type of) objective. It should be under a 'general' analysis / statistical considerations section, rather than under any single objective.	Create a general analysis considerations section within section 9 to allow for cross-objective considerations such as multiplicity. This may be a subsection (see general comment on content structure).
Interpharma, Association of Switzerland's research-based pharmaceutical industry	1026	1027	9.2.1	Suggest adding details on statistical testing procedure. Testing procedure shows the details for Type-1 error control/multiplicity and it's important enough to be mentioned explicitly or add a separate section for testing procedure.	Suggest adding "including the details of testing procedure" after "If applicable, state and discuss any adjustments to account for multiplicity" or include a separate section 9.2.x to clarify the multiplicity adjustment.
EFPIA	1027	1027		Please add instruction text stating that data points selection should be described here or referenced in case it has been defined elsewhere.	
TransCelerate BioPharma Inc.	1027	1027	9.2.1	Adjustments to account for multiplicity most often apply across primary and secondary objectives, so it may be misplaced under the primary objectives section.	Recommend moving this to the recommended "general considerations" section (see above comment for line 1002).
EFPIA	1028	1029		Not only in case of simulation should the underly ing assumptions be specified. This should always be the case, since they should be the targets for sensitivity analyses.	
TransCelerate BioPharma Inc.	1029	1029	9.2.1	The current instructional text states that underlying assumptions should be described if modelling and simulation methods are used; however, underlying assumptions in all cases should be included regardless of if the study uses modelling and simulation methods.	Recommend that underlying assumptions be separated and highlighted in a separate sentence.
EFPIA	1030	1030	9.2.1	Statistical Model, Hypothesis, and Method of Analysis should be separate data fields.	
Estimand Review team	1031	1031	9,2	The "handling" of intercurrent event could be read as how the i.e. is handled within the definition of the estimand which could be misunderstood here. This section is more about the handling of data in relation to Intercurrent events and estimand strategies, so the proposal is to delete Intercurrent events (as it is already incorporated by the primary estimand).	Change heading to "Handling of data in relation to Primary Estimand(s)"
EFPIA	1031	1038	9.2.2	The section does not specifically mention the handling of missing data related to intercurrent events, and missing data handling is specified under the next section 9.2.3. It would be helpful to specify the handling of missing data related to intercurrent events in Section 9.2.2, in order to create a link with the targeted estimand.	Propose to add "The handling of intercurrent events and missing data related to intercurrent events in statistical analysis should be aligned with the specific estimand strategies being used " to the following sentence on line 1034 and 1035.
EFPIA	1031	1031		Often there will be similarities across objectives, so to minimise repetitions, this section should be moved to a general considerations section. Also, suggest to avoid the term "handling of" in order not to confuse it with the strategies specified in section 3. This section should be about the implication on the estimation of the chosen strategies.	
EFPIA	1031	1031	Section 9.2.2	Flexibly adding stand-alone subsections on "Handling of Intercurrent Events of … Estimand(s)" associated with the description of the analyses supporting the defined estimand(s) with is highly welcomed. It has been proposed merging these aspects with analysis sets (="set of trial participants") but this does not work for all types of trials and endpoints. The instructional text could possibly be revised to clarify that this is not about explaining or justifying the strategies but rather about selecting the data points to be used for analysis and explaining the impact of strategies on estimation.	In the instructional text, consider clarifying that this is not about explaining or justifying the strategies but rather about selecting the data points to be used for analysis and explaining the impact of strategies on estimation.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA/EFSPI Estimand Implementation Working Group	1031	1031	9.2.2	It seems as if all estimands supporting (the) primary objective(s) are considered or summarized as “primary” estimands. It is likely that there will be supplementary estimands defined but also that estimands across objectives are similar and therefore, this subsection should be moved to the “General Considerations” section. Suggest re-wording to avoid repeating the choice of strategies as described in section 3, i.e., changing “Handling” to “Impact”	Reword subsection header to “9.2.2 Impact of Intercurrent Event Strategies” and move subsection to general considerations section.
TransCelerate BioPharma Inc.	1031	1031	9.2.2	Handling of intercurrent events is already discussed in Section 3, so the title should clarify that this is related to the analysis.	Recommend revising the title of this section to impact of intercurrent events and their handling strategies. This could also be placed in a general considerations section if it is added.
Interpharma, Association of Switzerland’s research-based pharmaceutical industry	1031	1038	9.2.2	The section does not specifically mention the handling of missing data related to intercurrent events, and missing data handling is specified under the next section 9.2.3. It would be helpful to specify the handling of missing data related to intercurrent events in Section 9.2.2, in order to create a link with the targeted estimand.	Propose to add "The handling of intercurrent events and missing data related to intercurrent events in statistical analysis should be aligned with the specific estimand strategies being used " to the following sentence on line 1034 and 1035.
EFPIA	1032	1032	Section 9.2.2	The wording "For each intercurrent event of the primary estimand(s) (Section 3.1, Estimand[s] for the Primary Objective[s])" requires alignment with what is expected in Section 3, i.e., listing all intercurrent events in Section 3?	Cross-check and align the header for Section 3.1, here given as "Estimand[s] for the Primary Objective[s]" which is different from the wording used in Section 3.
EFPIA	1032	1032		This requires a clear overview of all intercurrent events and not only the ones not captured by other attributes	
EFPIA/EFSPI Estimand Implementation Working Group	1032	1032	9.2.2	Cf. comment to line 417-421. A clarification of intercurrent events captured by other attributes is needed to meet this requirement.	
EFPIA/EFSPI Estimand Implementation Working Group	1032	1037	9.2.2	Estimands are defined in section 3 which includes the intercurrent events and the strategy to be used. In section 9 the implication of the strategy for the intercurrent event on the data should be described. So, it is not a repeat of the strategy itself but how this does or does not impact the observed data.	Replace original text by: Provide statistical details of intercurrent event handling beyond what has been specified in Section 3. Selection of relevant data points can be described here, in the Analysis Sets section 9.2 or in the main analysis section 9.3.2. Describe which summaries about intercurrent event occurrence are envisaged.
Eva Degraeuwe, Ghent University, BPCRN	1033	1034	9.2.2	Statistical analysis: From a data perspective, it should become mandatory for investigators to include the database contruct (and sharing) within their protocol. The use of data standards, timedrame DBL as a hard timeline point for the trial, which collection platform (internally developed, licensed) etc.	
Estimand Review team	1034	1035	9,2	See comment above	Change to "The handling of data in the statistical analysis..."
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	1034	1035	9.2.2.	It is unclear what an "estimand strategy" should be.	
EFPIA	1036	1036	Section 9.2.2	Section 9 is describing how the statistical analysis should be performed in alignment with the estimands defined in Section 3, whereas Section 3 should state and justify the clinical questions of interest.	A rationale for the choice of strategies to handle intercurrent events should be provided outside of Section 9, most likely Section 3, as part of a rationale for the defined estimand(s).
EFPIA/EFSPI Estimand Implementation Working Group	1036	1037	9.2.2	The wording is unclear. It seems to suggest that the rationale for the choices of strategies belongs to this section, but it rather belongs to section 3. The text should be updated to clarify this.	This section should describe how data is impacted as a consequence of the chosen strategies rather than repeating the guidance from the preceding sections.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUCROF - EU CRO Federation	1039	1039	Section 9.2.3	It was common to include "Handling of Missing Data" as a single Level 2 heading or as a subheading under a Level 2 heading called "General Considerations" rather than repeated as a Level 3 heading for each objective. This prevented unnecessary repetition.	Suggest restructuring as per comment.
EFPIA	1039	1039	Section 9.2.3	Flexibly adding stand-alone subsections on "Handling of Missing Data" associated with the description of the analyses supporting the defined estimand(s) with is highly welcomed.	Amend instructional text to explicitly state assumptions made for the handling of missing data. This will be helpful in conjunction with the subsequent Subsection on Sensitivity Analysis.
EFPIA	1039	1039		Often, the approach taken to handle missing data will be the same across objectives, so this sub-section should be moved to a general considerations section to avoid unnecessary repetition.	
EFPIA	1039	1048	9.2.3	In Clinical Pharmacology studies with PK as the primary objective, it may be difficult to stipulate in the protocol how missing data may be handled. There may be some missing PK concentration data which affect the estimation of PK parameters while other missing concentrations may have no impact. So, this section needs a few sentences added for Phase 1 studies.	
EFPIA	1039	1048	9.2.3	It would be preferrable to include in Section 9.2.3 that the section is only handling of missing data not related to intercurrent events and place the handling of missing data related to intercurrent events in Section 9.2.2, in order to create a link of the latter to the targeted estimand.	Please maintain Sections 9.2.2 and 9.2.3 separate from each other and modify section 9.2.3 title as "Handling of missing data not related to intercurrent events".
TransCelerate BioPharma Inc.	1039	1039	9.2.3	Details for handling of missing data would be better placed in a general section rather than under the primary objective, as it most often is similar across analyses/objectives.	Recommend placing this in the recommended "general considerations" section (see above comment for line 1002).
Interpharma, Association of Switzerland's research-based pharmaceutical industry	1039	1048	9.2.3	It would be preferrable to include in Section 9.2.3 that the section is only handling of missing data not related to intercurrent events and place the handling of missing data related to intercurrent events in Section 9.2.2, in order to create a link of the latter to the targeted estimand.	Please maintain Sections 9.2.2 and 9.2.3 separate from each other and modify section 9.2.3 title as "Handling of missing data not related to intercurrent events".
Boehringer Ingelheim	1040	1043	9.2.3	First sentence in Line 1040 is not needed and is repeated in Line 1042. "This section should describe how missing data will be dealt with. Refer to the E9(R1) addendum when estimand framework is used. The protocol should describe how missing data will be handled (for example, type of imputation technique, if any, and provide justification)"	"This section should describe how missing data will be handled (for example, type of imputation technique, if any) and the justification). Refer to the E9(R1) addendum when estimand framework is used."
EFPIA/EFSPI Estimand Implementation Working Group	1040	1041	9.2.3	Reference to ICH E9(R1) seems too vague; see proposed edit. More guidance is required.	Move subsection to General Considerations section Add instructional text: "This section should describe how missing data will be dealt with and distinguish between data not observed and data not selected due to occurrence of an intercurrent event. The latter should not be described in this section, but rather in the section Impact of Intercurrent Event Strategies. Refer to the E9(R1) addendum when estimand framework is used and ensure alignment of handling of missing data where possible, guided by the estimand's strategies for intercurrent events."
CSL Behring	1041			Typographical amendment.	…when the estimand framework is used.
Estimand Review team	1042	1042	9,2	It would be good to understand the rationale for the handling of missing data approaches	Change to "...should describe the rationale and how missing data ..."
Estimand Review team	1043	1043	9,2	To make sure that missing data handling is aligned with the considered estimand.	Add "Missing data handling needs to be aligned with the respective estimand."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
CSL Behring	1044			Typographical amendment.	In cases where the ~~P~~primary ~~O~~objective is related to safety, this section should also be completed.
EFPIA	1044	1044	9.2.3	The sentence about the primary objective being related to safety seems to be misplaced in the section on missing data.	Move the sentence to the instructional text below current header 9.2.
EFPIA/EFSPI Estimand Implementation Working Group	1044	1044	9.2.3	The sentence "In cases where the Primary Objective is related to safety, this section should also be completed" seems to be misplaced in Subsection 9.2.3 Handling of Missing Data. Does it rather belong to Section 9.2 Analyses Supporting Primary Objective(s)?	Move to instructional text below section 9 heading and rewrite text to apply across objectives: "The topics listed below in Sections 9.3.1-9.3.4 should be considered regardless of the type of objective, such as efficacy, safety and pharmacokinetics". Note that section numbers as per the general comment on content structure.
EFPIA/EFSPI Estimand Implementation Working Group	1045	1047	9.2.3	This paragraph supports a General Considerations section where this can be described more logically.	Create a "Section 9.1 General Considerations" and move section 9.2.3 to that section (as per general comment on content structure).
EFPIA	1049	1052		Recommend using "if applicable" language because not all studies should be assumed to have sensitivity analyses.	
EFPIA	1049	1052	9.2.4	Definition of supplementary analysis and how it is different from sensitivity analysis is unclear. It is important to clarify this, to make clear which analyses need to be described under Sections 9.2.4 and Section 9.2.5 respectively.	Propose to include following instructional language "A supplementary analysis is any planned, presented or requested analysis beyond a sensitivity analysis in order to more fully investigate and understand the treatment effects. These analyses may be directed to an estimand targeting a new treatment effect definition, or an estimand anchored to another endpoint."
EFPIA	1049	1049		Add instructional text that for each sensitivity analysis it should be explicitly described which underlying assumption in the main analysis it targets.	
TransCelerate BioPharma Inc.	1049	1049	9.2.4	Further instructional text would be helpful in this section to ensure it is clear which of the assumptions underlying the main analytical approach each sensitivity analysis is targeting.	Recommend that the instructional text should state that it should be clear which of the assumptions underlying the main analytical approach each sensitivity analysis is targeting.
Interpharma, Association of Switzerland's research-based pharmaceutical industry	1049	1052	9.2.4	Section does not clarify that sensitivity analyses target the same estimand as primary analysis; it would be important to clarify this, in order to create a link to the primary estimand.	Propose to include following instructional language: "Sensitivity analyses are a series of analyses conducted with the intent to explore the robustness of inferences from the main estimator to deviations from its underlying modelling assumptions and limitations in the data. For studies with estimand definition, it targets the same estimand as for primary analysis."
Interpharma, Association of Switzerland's research-based pharmaceutical industry	1049	1052	9.2.4	Definition of supplementary analysis and how it is different from sensitivity analysis is unclear. It is important to clarify this, to make clear which analyses need to be described under Sections 9.2.4 and Section 9.2.5 respectively.	Propose to include following instructional language "A supplementary analysis is any planned, presented or requested analysis beyond a sensitivity analysis in order to more fully investigate and understand the treatment effects. These analyses may be directed to an estimand targeting a new treatment effect definition, or an estimand anchored to another endpoint."
CSL Behring	1050			Typographical amendment.	Sensitivity analyses are (a series of) analyses….
EFPIA/EFSPI Estimand Implementation Working Group EFPIA/EFSPI Regulatory ESIG	1050	1052	9.2.4	1) Question: This definition is coming from ICH E9(R1). Should it be applied also in studies that don't use the estimand framework? If so, please add this to the instruction (see right column). 2) The section currently defines a Sensistivity analysis, but should contain the instruction to describe the purpose and details of the proposed sensitivity analyses. Suggest adding instruction to list explicitly state the assumptions related to each sensitivity analysis (see right column).	Describe any proposed sensitivity analyses, if applicable, and the assumptions targeted for each sensitivity analysis. Sensitivity analyses are a series of analyses conducted with the intent to explore the robustness of inferences from the main estimator to deviations from its underlying modelling assumptions and limitations in the data. This definition is used irrespective of using the estimand framework.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	1054	1054		Does this section also include estimation of supplementary estimands? If yes, please specify and if not please specify where to describe it.	
Agios	1054	1054	9.2.5	This section should be optional	Make section optional
TransCelerate BioPharma Inc.	1054	1054	9.2.5	Many trial protocols include supplementary estimands. It is unclear whether a supplementary analysis targets the same estimand as the main and sensitivity analyses, or if it targets a different estimand. Currently, it is not clear from the template where to describe the estimation of supplementary estimands.	Recommend adding clarification as to where analysis of the supplementary estimand is to be provided.
EFPIA/EFSPI Estimand Implementation Working Group	1055	1055	9.2.5	Supplementary analysis should also be defined similarly to sensitivity analysis (see right column, taken from ICH E9(R1)	Describe any supplementary analysis if applicable. Supplementary analyses are conducted in addition to the main and sensitivity analysis with the intent to provide additional insights into the understanding of the treatment effect.
EFPIA/EFSPI Estimand Implementation Working Group	1055	1055	9.2.5	Does this section also include estimation of supplementary/additional estimands? If yes, please clarify and if no, where should the estimation of such estimands be described?	Add instructional text "Estimation of supplementary estimands can be described here or in a separate level 3 sub-section."
EFPIA	1057	1061	9,3	Please include guidance on the structure of Section 9.3. If there are multiple secondary endpoints, would each of the endpoints be addressed in a subsection, each with the structure of Section 9.2? Please also include guidance on how the user can structure the subsections for the secondary endpoints used in the multiple testing procedure (for which estimands are defined) versus the other secondary endpoints.	
EFPIA	1057	1057	9,3	Change to plural, to align with the header of Section 9.2	Replace "Analysis" by "Analyses".
Agios	1057	1057	9,3	An analysis does not support an objective; the results of the analysis will inform whether or not the objective was met which is different than "suporting an objective". Section 9.3 header should be retitled as "Analyses of Secondary Endpoints"	Retitle Section 9.3 Header as "Analyses of key Secondary Endpoints" and add a Section for "Analyses of Other Secondary Endpoints" (which will often include Safety, PK and PD endpoints as an example)
TransCelerate BioPharma Inc.	1057	1057	9,3	There is a need to distinguish between objectives that are part of confirmatory testing and those that are only supportive. It is unclear in the current instructions provided and there are different requirements to the two types.	Recommend instructional text distinguishing between objectives that are part of confirmatory testing and those that are only supportive.
EFPIA/EFSPI Estimand Implementation Working Group	1058	1060	9.3	1) What if the study does not use estimands? (see proposed edit) 2) The protocol should make clear which secondary analyses are confirmatory. See e.g., ICH E9, section 2.1.3: "The protocol should make a clear distinction between the aspects of a trial which will be used for confirmatory proof and the aspects which will provide data for exploratory analysis." Also, instructional text should be added to clarify that the confirmatory analyses should be described with the same level of detail as for the primary objective including specification of sensitivity analyses.	"This section should focus on estimands/endpoints for Secondary Objectives. It should be clear in the protocol which analyses supporting secondary objectives are planned as confirmatory. These analyses should be described with the same level of detail as the analyses supporting primary objective(s) and specification of sensitivity analysis should also be provided. In this section describe statistical analyses, corresponding to each secondary estimand/endpoint."
Estimand Review team	1059	1059	9,3	Clarification	Change to "... analysis, the rationale and handling of ..."
CSL Behring	1060			Section 9.3 Analysis Supporting Secondary Objective(s) does not discuss multiplicity, which is also relevant for secondary endpoints. Line 1026-1027 includes a sentence relevant to multiplicity, and we recommend this sentence be added to section 9.3.	If applicable, state and discuss any adjustments to account for multiplicity.
EFPIA	1061	1061	9,3	Please change to blue font.	
EFPIA	1062	1062		Please consider changing to "Analyses supporting exploratory objectives".	
EFPIA	1062	1062	Section 9.4	Change to plural, add "supporting", to align with the header of Section 9.2	Replace "Analysis" by "Analyses Supporting".

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA/EFSPI Estimand Implementation Working Group	1062	1062	9.4	Is there a reason why this section does not say: 9.4 Analysis Supporting Exploratory Objective(s)? Suggest alignment with sections on analysis supporting primary and secondary analysis.	Analysis Supporting Exploratory Objective(s)
EFPIA/EFSPI Estimand Implementation Working Group	1062	1062	9.4	Add instructional text	Addition: "Analyses related to exploratory objectives can be described in less detail than those of primary and secondary objectives."
Agios	1062	1062	9,4	One cannot analyze an objective. This section should be retitled as "Analyses of Exploratory Endpoints". Further, the analysis of exploratory endpoints should be at the end of all other sections for analysis of other endpoints	Retitle Section 9.4 as "Analyses of Exploratory Endpoints" and move to the end of Section 9
TransCelerate BioPharma Inc.	1062	1062	9,4	The title for this section is slightly inconsistent with previous sections. This is likely a typo.	Recommend correcting the title to "Analysis Supporting Exploratory Objectives" to be consistent with the previous sections.
Quotient Sciences	1064	1066	9,5	Safety is a primary endpoint in most phase 1 healthy volunteer trials. As level 2 headings should be retained, what would we enter in Section 9.5 (Safety Analyses) if we have described the safety analysis in Section 9.2 or 9.3?	
Agios	1064	1067	9,5	The purpose of this section is not clear. Per the instruction safety analayses of primary and secondary objectives should be discusssed in Section 9.2 and 9.3. Exploratory safety analyses would be discussed in Section 9.4. Unclear what safety analyses should be described here.	Delete this section
EFPIA	1067	1067	9,5	Please change to blue font.	
EFPIA	1068	1068		9.6 Other Analyses – this section does not include language indicating that this is the preferred site for description of PK, genetics, biomarkers, and immunogenicity. Just as there is a specific section in prescribing information for these data that are distinct from safety and efficacy, so too, because they are so commonly collected and analyzed they should have a designated spot in protocols.	We suggest adding subsections so that these common analyses have a consistent place in the protocol, such as 9.6.1 PK, 9.6.2 genetics, 9.6.3 biomarkers, 9.6.4 immunogenicity. We suggest having an overall text of direction that these subsections should describe how these specific types of data will be analyzed.
CSL Behring	1069			Typographical amendment.	Describe ~~O~~other ~~A~~analyses such as Subgroup analyses, Adjusted analysis if needed.
EFPIA	1069	1069		Recommend to include PK analyses, immunogenicity analyses, pharmacodynamic analyses as examples.	
EFPIA	1069	1069		This would be described under the appropriate objective section; if not please clarify what is meant by this. Suggest clarifying that this is related to analyses not covered by any of the other analysis section, e.g., subgroup analyses, PK/PD modelling, etc and consider inserting level 3 headings for the examples provided.	
EFPIA/EFSPI Estimand Implementation Working Group	1069	1069	9.6	Insert suggested level 3 heading and clarify that the content relates to topics not already addressed elsewhere in analysis sections supporting primary, secondary and exploratory objectives.	Modify instructional text: "Describe Other Analyses such as Subgroup analyses, if not already covered by analysis supporting either primary, secondary or exploratory objectives. Add appropriate sub-section headings, e.g., 9.7.1 Subgroups."
Agios	1069	1069	9,6	Subgroup analyses should be described together with the analyses for the corresponding endpoints. Similarly for adjusted analyses. This section should cover analyses for any other endpoints that were not already described in the previous sections but there should be none left as there are already sections for primary, secondary and exploratory endpoints which span all the endpoints for a study	Delete the section
TransCelerate BioPharma Inc.	1069	1069	9,6	Additional instructions providing more clear guidance as to what would be included as "other analyses" would be helpful.	If needed, adjusted analyses should be described together with other analyses supporting a specific objective. Consequently, it should not be described in this section.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Quotient Sciences	1071	1092	9,7	Interim Analyses: Dose decision criteria and stopping criteria should not be specified in this section, but in dedicated sections as described above. Likewise, authority to stop the trial should be covered in Section 10.5. This section should describe the analyses, who is responsible, when they will be done, and how blinding will be preserved. For interim PK analyses done to support dose escalation in phase 1 healthy volunteer trials, it should be specified how the interim report will ensure that blinding of the investigator will be maintained, particularly in the event that an incomplete dataset is available (eg an incomplete group was enrolled, a participant withdrew, or PK blood samples were not taken).	Instruct the author to cross refer to relevant rules and procedures for dose escalation and stopping the trial. Include instructions to explain how blinding will be maintained in interim reports.
EFPIA	1071	1071	9,7	Instead of only describing the interim analyses here, consider describing all planned analysis in the study so there is one section here where all this info is in one place.	
EFPIA	1071	1071		Some of the topics requested in the protocol may jeopardise trial integrity, e.g., bullet nos: 2, 4, 5 and 10. These should be described elsewhere and kept confidential. Please consider revising or deleting these.	
EFPIA	1071	1092	9,7	Some of the items listed in the instructions go beyond statistical considerations on how to perform an interim analysis, eg, who will perform the analyses or decision bodies.	Move aspects not directly related to statistical considerations to another place in the protocol, e.g., Section 10.
EFPIA	1071	1093	9,7	There's a need to mention software used in the interim analysis calculation.	Propose to include one additional item: "Mention the software (and version) used in the calculation. Reference the method if non-standard."
Interpharma, Association of Switzerland's research-based pharmaceutical industry	1071	1093	9,7	There's a need to mention software used in the interim analysis calculation.	Propose to include one additional item: "Mention the software (and version) used in the calculation. Reference the method if non-standard."
EFPIA	1072	1072		Please add instructional text to remind that information on intercurrent events shoud be as complete as possible at time of interim analysis.	
EFPIA	1072	1072		While stopping criteria have a relation to interim analyses, trial stopping rules and guidance are already covered in section 7.4. It would be expected that since stopping rules will often be related to safety findings, the governance, decision making (including involvement of the DMC) will be covered in section 7.4. Suggest to modify the bullets here and refer to section 7.4 instead.	
EFPIA	1072	1093	9,7	In this section, is the expectation to list all IAs planned or should the analyses that will be performed for each IA be described?	
EFPIA	1072	1093	9,7	All information about blinding could be redundant with section 6.6.3. Please consider omitting here and cross referencing to the appropriate section.	Please consider deleting information concerning blinding that is already described in Section 6 (redundant).
EFPIA/EFSPI Estimand Implementation Working Group	1073	1073	9.7	Add instructional text	Add bullet: specify which information should be collected as completely as possible for the interim analysis including information for the main analysis variable but also relevant intercurrent event information.
TransCelerate BioPharma Inc.	1073	1073	9,7	The description for interim analysis should also include instruction that data on the endpoints to be included and the intercurrent events should be collected as completely as possible.	Under the Interim Analyses instructions, a bullet should be added to specify that data on the endpoints to be included and the intercurrent events should be collected as completely as possible.
EFPIA	1082	1086	9,7	The term adaptation is used twice, while the rest of the document uses adaption for this matter.	strive for consistency
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	1087	1088	9.7.	If the trial will be overseen by a Data Monitoring Committee (DMC), there must be a DMC Charter which must be referenced here. The ultimate authority to stop or modify the trial has only the sponsor as the responsible person.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	1089	1089	9.7.	It is unclear how "stopping guidelines" differ from "decision criteria...for early stopping" described earlier.	
EFPIA	1089	1089	9,7	Stopping criteria are explicitly called for in this section. This may be considered proprietary and require redaction when the protocol is posted to CTIS.	
CSL Behring	1090	1092		We recommend the final bullet point relating to pre-specified interim analyses be moved such that it appears in front of describing how the trial integrity will be protected (ref: Lines 1085-1086), as the strategy for protecting trial integrity may depend upon the adaptations planned.	n/a
CSL Behring	1094	1097		Section 9.8 Sample Size Determination notes that the section should detail the methods used for the determination of the sample size etc. We recommend that when the sample size is based upon complex simulations, that it is more appropriate to describe those simulations in an appendix.	n/a
EFPIA	1094	1094		Please add instructional text to specify estimands in reference trials, if possible and if applicable. Also, the expected frequency of each intercurrent event and their expected impact on effect size and precision should be specified	
EFPIA	1094	1101		Suggest starting the statistical considerations section with the sample size. Currently, it is too buried down in the section. The suggested order would be statistical hypotheses, sample size, analysis sets and then statistical analyses for primary, secondary, etc.	
Agios	1094	1101	9,8	The sample size determination considerations should be upfront in Section 9 as Section 9.2.1 and 9.7 are informed by this section	Move Section 9.8 as Section 9.1
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	1094	1094	9.8	Section "Sample size determination" (9.8) should be moved to the top of the statistics section, before "Analysis set" (9.1)	"Sample size determination" as point 9.1
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	1094	1102	9.8	The method by which the sample size is calculated should be given in the protocol, together with the estimates of any quantities used in the calculations (such as variances, mean values, response rates, event rates, difference to be detected). The basis of these estimates should also be given.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	1094	1102	9.8	A possible estimate of the drop-out rate must be detailed.	
EFPIA/EFSPI Estimand Implementation Working Group EFPIA/EFSPI Regulatory ESIG	1095	1097	9.8	1) Add hints about historical estimands and expected intercurrent event frequencies, see edit) 2) For some adaptive or complex designs, sample size determination and confirmation of statistical operating charcteristics are carried out by computer simulation and may not be immediately reproducible. This section should refer appropriately to this and state whether simulations have been carried out.	This section should detail the methods used for the determination of the sample size and a reference to tables or statistical software used to carry out the calculation. Sufficient information should be provided so that the sample size calculation can be reproduced or described. For adaptive or complex designs, state whether detailed trial simulations have been carried out, the software used, and if applicable, refer to the Trial Simulation Report If prior study results are used in the sample size calculation in the given study, make sure that these are referenced and the estimands from the prior studies have been adequately considered. State whether the impact of expected intercurrent events have been considered in sample size calculations, e.g., assumptions relating to effect size and variability
TransCelerate BioPharma Inc.	1095	1097	9,8	Reference trials used in the sample size determination should mention the underlying estimands, if possible. The impact on effect size and precision of the intercurrent events and their handling strategies should be described.	Recommend including instruction to include the underlying estimands of reference trials used in the sample size determination, if applicable.
EFPIA	1096	1096	9,8	What does the following mean: “Sufficient information should be provided so that the sample size calculation can be described.”	
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	1098	1100	9.8.	It is described in the template: "If the planned sample size is not derived statistically, then this should be explicitly stated along with a rationale for the intended sample size (for example, exploratory nature of pilot trials; pragmatic considerations for trials in rare diseases)." However, the clinical assumptions (e.g., effect size) on which the statistical sample size calculation is based have to be justified, and any evidence supporting these assumptions has to be discussed. See also SPIRIT item 14.	We suggest to add the following text: “ The clinical assumptions (e.g., effect size) on which the statistical sample size calculation is based have to be justified, and any evidence supporting these assumptions has to be discussed”
EFPIA	1098	1100	9,8	Including criteria such as precision of the estimator or length of CI’s would provide a good example for justifying the sample size for pilot studies.	
EUCROF - EU CRO Federation	1103	1103	Section 9.9	The reporting of serious breaches from trial protocol or ICH GCP or legislation are not addressed, but only protocol deviations.	Revise section “9.9 Protocol Deviations” in title and contents in order to capture also reporting of serious breaches from trial protocol or ICH GCP or legislation, “as per local or regional requirements”.
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	1103	1105	9.9.	In the section Protocol Deviations "Plans for detecting, reviewing, and reporting any deviations from the protocol should be described." Further details might be helpful: Detection - A subsection Statistical Monitoring should be considered Reporting - If a per Protocol analysis is used either primarily or as a sensitivity analysis the protocol violations that are not in the per protocol set should be defined. Deviations from the protocol - Should be described (e. g., eCDFs of % dose given, distribution of delay between treatment blocks etc.)	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
CSL Behring	1103			Detecting, reviewing, and reporting deviations is not only or predominantly a statistical topic. With this in mind, we question whether the information within this section should sit elsewhere in the template. Alternatively, should the guidance text be revised/expanded to focus it more on the statistical aspects of this activity. We recommend this be considered when advancing the draft of this template document.	n/a
EFPIA	1103	1105	9,9	Even though describing the plan for identifying the protocol deviation can be described in general, there may be circumstances that arise in Clinical Pharmacology studies based on PK concentration and parameter values. So, it may be difficult to describe all possible situations in the protocol itself.	
EFPIA	1103	1106	9,9	Suggest moving the section (9.9) to another location since it is not just a statistical issue - potential other locations could be in chapters 10 (oversight) or 11 (quality assurance)	
EFPIA/EFSPI Estimand Implementation Working Group	1103	1103	9.9	Protocol deviations are an element of quality of trial conduct and should not be described in the Statistical Considerations section. Not all PDs are intercurrent events, but those that are should be described within the estimand framework.	Move to Section 11
Agios	1103	1106	9,9	This sub section should belong to Section 8	Move this sub section under Section 8
TransCelerate BioPharma Inc.	1103	1103	9,9	Protocol deviations are more of an operational aspect than a statistical one. In addition, there is no requirement to provide all the details about detecting, reviewing and reporting protocol deviations in the protocol. A reference to a separate plan where this is described is adequate.	Recommend moving protocol deviations out of the statistical section and under the operational details in Section 10 or 11. Also recommend clarifying that the protocol does not need to include all details on deviation handling; a brief/general statement for deviations with a reference to the plan where further information is available is adequate
Interpharma, Association of Switzerland's research-based pharmaceutical industry	1103	1106	9,9	This section seems out of place. The reporting part of this section should be placed in earlier part of Section 9 and detecting and reviewing part of this section should be integrated with Section 11.1 Quality Tolerance Limits.	Please create a subsection in the earlier part of Section 9 for plan for reporting protocol deviations. Move and integrate plans for detecting and reviewing protocol deviations to Section 11.1.
EFPIA	1104	1105		The current text is more directed toward the sponsor. Suggest to rephrase to: 'Instructions to the investigator on responsibilities for detecting and reporting any deviations from the protocol should be described.'	
EUCROF - EU CRO Federation	1107	1107	Section 10	As per DoH No. 22, the following should be included: "In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.". A subheading under Section 10 for issues related to treatment of patients who have study-related injuries (e.g., insurance for study) would be helpful. Please note that the ICH E6(R2) document also has the following protocol requirement (see item 6.14): "Financing and insurance if not addressed in a separate document". A subsection under Section 10 regarding Dissemination of Clinical Trial Data, with instructional text specifying the requirements above would be helpful. ICH E6(R2) states that the protocol should include the publication policy, if not addressed in a seperate document.	Add instructional text as per comment.
Quotient Sciences	1107	1159	10	Please add a subsection for protocol amendments to specify how changes may be made to the protocol and to confirm that regulatory and ethical approval will be obtained before implementation of those changes, as applicable.	Add a new level 2 heading: 'Amendments to the protocol'
EFPIA	1107	1107	10	Should an optional section on financial disclosure be included as a subsection of section 10? (to be included in case this info is not included in another document)? Likewise, should (optional) sections be included on 'long-term retention of samples', 'record retention' or 'publication policy/dissemination of clincal study data' and/or 'CRF completion'?	
EFPIA	1107	1107		Please consider whether subsections covering Document Retention, Financial Disclosure, Insurance and Indemnity are needed, or where such information should be placed.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	1107	1107	10	Level 2/3 headings on recruitment strategy, financial disclosure, dissemination of trial data and publication policy appear missing from the template. Suggest to include these headings as it is important to comply with regulations.	
EFPIA	1107	1158	10	For all level 2 headings under section 10, where standard language is needed to comply with GCP and/or regulations, can the text be provided in the ICH M11 template? This will ensure common understanding and consistency.	
PTC Therapeutics, Inc.	1107	1107	10	Given the transparency and disclosure requirements, PTC considers whether guidance around specific references be made to public databases, such as EudraCT, should be detailed here.	PTC proposes consideration of this additional content.
Freeline Therapeutics	1107	1183	10 & 11	All of what is in Section 11 could be described as 'Trial Oversight' (Section 10). It is clearer to keep all 'General Considerations' like these together in 1 section.	Combine sections 10 & 11 into 1 section 'General Considerations'
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	1107	1144	10	A section on the future uses of samples and data, if any, should be included. It might be optional	[Future uses of samples and data]
TransCelerate BioPharma Inc.	1107	1107	10	The following elements are required by EU CTR to be included in the protocol: Recruitment strategy, Dissemination of trial data and results, Use of biological samples/data for future research.	Recommend including the following sections within Section 10: Recruitment strategy, Dissemination of trial data and results, Use of biological samples/data for future research
TransCelerate BioPharma Inc.	1107	1107	10	Financial disclosure and publication policy (including transparency requirements) are expected to be included in the protocol, so the template should clarify placement and instructions for these elements.	Recommend including 3rd level sections within Section 10 for financial disclosure, publication policy including transparency requirements
CSL Behring	1110	1119		Line 1119 states 'List the investigators' and sponsors' responsibilities 'in this regard'', and it is not clear to us to what this is referring to. The list of responsibilities resulting from all the guidelines above is very extensive. Is the intent that all the responsibilities should be listed here? Furthermore, we find the section heading on Line 1110 "regulatory and Ethical Considerations" to be somewhat vague. To make it clear that this section relates to investigator and responsibilities, we recommend either changing the section title or otherwise including an appropriate sub-heading within the section.	10.1 ~~Regulatory and Ethical Considerations~~ Investigator and Sponsor Responsibilities
EFPIA	1110	1111	10	Section on recruitment strategy is missing	Consider adding such item.
EFPIA	1110	1123	10,1	Per CTCG: Since 2016, the Declaration of Taipei on Ethical Considerations regarding Health Databases and Biobanks has complemented the Declaration of Helsinki. This could be added here.	Add a statement referring to Ethical Considerations regarding Health Databases and Biobanks.
EFPIA	1110	1123	10,1	Addition of standard text on Investigator and Sponsor responsibilities would be useful for the authors.	
EUCROF - EU CRO Federation	1113	1113	Section 10	Is it correct that this line is shaded in grey? Is this mandatory universal text, or a text field?	Please either delete grey shading or add square brackets.
Estimand Review team	1114	1115	10,1	The World Medical Association should be mentioned	Insert "World Medical Association (WMA)" in the text
EFPIA	1114	1118	10,1	Please check the format - why is the black font a field and the blue font not between braces or fields?	Please check the format.
TransCelerate BioPharma Inc.	1114	1118	10,1	EU PEARL received feedback from CTCG to include the "Declaration of Taipei on Ethical Considerations Regarding Health Databases and Biobanks".	Recommend including the "Declaration of Taipei on Ethical Considerations Regarding Health Databases and Biobanks" here along with the Declaration of Helsinki.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Estimand Review team	1115	1115	10,1	Add article	Change to "... the Council for ..."
ACRO (Association of Clinical Research Organizations)	1119	1119	10,1	The "Note for guidance on Coordinating Investigator signature of Clinical Study Reports" CPMP/EWP/2747/00 dated Oct 2001" includes guidance that "The co-ordinating investigator or the process of designating the signatory co-ordinating investigator should be defined in the protocol". ACRO suggest including provision for this within section 10.1 of the Protocol Template and the associated section of the Technical Specification.	Line 1119. Add "Coordinating Investigator responsibilities should be included under Investigator Responsibilities"
EFPIA	1124	1124		Section 10.2 ("Committees") should be broadened to include additional information that can be transferred to the "Study Administrative Structure" section of the clinical study report. In addition to providing information about committees, this section should indicate whether the sponsor or a vendor (e.g., contract research organization) is responsible for activities such as the following: monitoring, study management, IxRS, laboratory assessments, ECGs, data management, statistical analysis, and medical writing.	Add instructions stating that this section should indicate whether the sponsor or a vendor (e.g., contract research organization) is responsible for activities such as the following: monitoring, study management, IxRS, laboratory assessments, ECGs, data management, statistical analysis, and medical writing. Commitees are part of study design and should be described elsewhere (Section 4).
EFPIA	1124	1129	10,2	Suggest that the instructions under committee structure to also include details when a centralized committee such as an adjudication committee is involved in evaluating endpoints.	
ICON PLC	1124	1129	10,2	Recommend referencing Adjudication Committee too, so the author is reminded to reference the Adjudication Committee and respective Charter, if included in the trial design.	Please include reference to Adjudication Committee as an example.
EFPIA	1127	1127	10,2	"Data Safety Monitoring Board" should be "Data *and* Safety Monitoring Board."	Change to "Data and Safety Monitoring Board"
SÚKL CZ	1131	1131	Informed Consent Process	Indicate that the consent must be obtained prior to any other trial-specific activity.	Indicate that the consent must be obtained prior to any other trial-specific activity.
EFPIA	1131	1138	10,3	Pediatric subjects who have failed to reach the age of majority in their local jurisdiction can only provide informed assent, while their parent or guardian provides informed consent (often called parental permission). Please amend this instructional text to provide guidance that is also applicable to this study population. Refer to ICH E11 for contextual background to inform your approach.	Pediatric subjects who have failed to reach the age of majority in their local jurisdiction can only provide informed assent, while their parent or guardian provides informed consent (often called parental permission). Please amend this instructional text to provide guidance that is also applicable to this study population. Refer to ICH E11 for contextual background to inform your approach.
EFPIA	1131	1138	10,3	This section should also provide guidance that adolescents who previously assented for participation and have turned the age of majority after they have been randomized (i.e., now of the legal age for consent due to a birth date anniversary), will require a new consent to be obtained.	This section should also provide guidance that adolescents who previously assented for participation and have turned the age of majority after they have been randomized (i.e., now of the legal age for consent due to a birth date anniversary), will require a new consent to be obtained.
EFPIA	1131	1160	10	The following sections appear to be missing: 1) Dissemination of clinical study data and results and 2) Use of biological samples and data for future research (EU CTR requirement) 3) Financial Disclosure.	Consider adding sections for: 1) Dissemination of clinical study data and results and 2) Use of biological samples and data for future research (EU CTR requirement).
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	1131	1131	10.3	Incorrect section name/reference: Sponsor's discretion in the separate space provided. Committees listed here should be fully described in Section 10.3, Committees Structure…. but the Section 10.3 is "Informed Consent Process (Line 1131)".	Correct the name/reference.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	1131	1131	10.3	The title should include assent, as well	Informed Consent and Assent Process
Interpharma, Association of Switzerland's research-based pharmaceutical industry	1131	1138	10,3	Pediatric subjects who have failed to reach the age of majority in their local jurisdiction can only provide informed assent, while their parent or guardian provides informed consent (often called parental permission). Please amend this instructional text to provide guidance that is also applicable to this study population. Refer to ICH E11 for contextual background to inform your approach.	Pediatric subjects who have failed to reach the age of majority in their local jurisdiction can only provide informed assent, while their parent or guardian provides informed consent (often called parental permission). Please amend this instructional text to provide guidance that is also applicable to this study population. Refer to ICH E11 for contextual background to inform your approach.
Interpharma, Association of Switzerland's research-based pharmaceutical industry	1131	1138	10,3	This section should also provide guidance that adolescents who previously assented for participation and have turned the age of majority after they have been randomized (i.e., now of the legal age for consent due to a birth date anniversary), will require a new consent to be obtained.	This section should also provide guidance that adolescents who previously assented for participation and have turned the age of majority after they have been randomized (i.e., now of the legal age for consent due to a birth date anniversary), will require a new consent to be obtained.
EUCROF - EU CRO Federation	1132	1132	Section 10.3	The protocol should include detailed description of the recruitment and informed consent procedure, especially when subjects are incapable of giving informed consent.	The instructional text should state that the recruitment procedure should be described under certain circumstances.
EFPIA	1132	1137	10,3	Please consider adding a dedicated section here for specific ICF requirements: partner pregnancy, genetic sample collection and testing, biomarkers, immunogenicity, and other examples of collection, storage, testing, and further use in or outside the period of the clinical trial, determination of approval of use of samples for future use as maybe required by local laws, and that patients/participants in specific countries be re-consented on the further use of their samples during, or after clinical trial closure. Privacy guarantee with respect to these samples, etc. needs to be specified here.	Please consider adding a dedicated section here for specific ICF requirements.
EFPIA	1132	1137	10,3	Per CTCG: EU legislation is leading for the part of the trial conducted in EEA, so please refer to CTR and GDPR in addition to the mentioned requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements. Before signing an agreement to allow any remaining specimens to be used for exploratory research, the participant must be informed on the purpose of this procedure. A broad consent not specifying the purpose is not acceptable.	Please provide instruction to explain that before signing an agreement to allow any remaining specimens to be used for exploratory research, the participant must be informed on the purpose of this procedure
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	1137	1138	10.3	A new sub-section should be added to include details on the assent process in case of paediatric trials	[Informed Assent Process]
EUCROF - EU CRO Federation	1138	1138	Section 10.3	Rescreening should be in square brackets, blue font color and shaded in grey.	Please change as per comment.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	1138	1142	10.3.	In our opinion the section on "Rescreening" doesn't fit here and should rather be mentioned in chapter 5 (Trial Population).	
EFPIA	1138	1138		Suggest to add a cross-reference to section 5.6 Screen Failures	
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	1143	1144	10.3.	In this section there should be also suggested fields for additional frequently used ICFs: - Additional ICF text for secondary use of clinical trial data - Additional ICF text for pregnancies/pregnant partner	
EFPIA	1143	1144		The field: 'Additional ICF text for Use of Remaining Samples in Optional Exploratory Research' does not belong under the heading 'Rescreening'. This should be placed in a section related to Exploratory Research (which is currently not included in the template). Please rectify.	
EFPIA	1144	1144		Please add a section on 'Recruitment and information to participants'. Info on Recruitment is required under EUCTR.	
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	1145	1147	10.4.	Data Protection requirements are very different based on the applicable national/regional law. The following should be added to the description of this section: "Take into account national/regional law and relevant additional national/regional requirements for the content of a protocol (e.g., sponsor declaration of data protection within EU trials)."	The following should be added to the description of this sections: "Take into account national/regional law and relevant additional national/regional requirements for the content of a protocol (e.g., sponsor declaration of data protection within EU trials)."
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	1145	1145	10.4	Reference to confidentiality should be added	Data Protection and Confidentiality
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	1145	1148	10.4	Reference to the applicable data protection regulations should be added	"This trial will be conducted in accordance with the following data protection regulation(s):…"

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	1145	1148	10.4	Reference to the data subjects' rights, to the data storage period and to any possible transfer of data should be added	It could be a bullet point list as for the other sections
PTC Therapeutics, Inc.	1146	1147	10,4	PTC requests clarification on the sentence "measures that should be taken in case of a data security breach" and whether this refers to a "personal data breach" when subject di-identified information is compromised or whether this is also for "confidential" (eg, results/finding) data leak. These are two distinct processes (one is security-driven and one is privacy-driven), and PTC seeks clarification of whether both are required to be detailed.	PTC requests additional guidance is provided on this section content.
EFPIA	1148	1148		A separate section on publication and/or disclosure policies for the study and study results is needed to meet multiple regulatory requirements.	
EFPIA	1148	1148		It would be helpful to have additional guidance on what should be addressed in the protocol itself and the level of detail generally expected, to align across trials and companies. Some data protection experts request many details in the protocol itself, while others believe the protocol should be high level, only referring to compliant methods that are documented in detail elsewhere, in the TMF and IT system documentation, e.g. in relation to which parties, vendors, laboratories etc. have access to each aspect of participant data. Please provide additional guidance.	
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	1148	1148	10.4	A new sub-section should be added to include details on the measures to ensure confidentiality	[Confidentiality]
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	1148	1148	10.4	Cite the data reuse under dta protection	
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	1149	1158	10.5.	The section "Early Site Closure Or Trial Termination" should rather be added section 7 (Discontinuation of Trial Intervention and Participant Withdrawal from Trial).	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	1149	1158	10,5	Consider not grouping 'early site closure' and 'trial termination' as these are different concepts. Please consider rather combining a section on trial termination with Section 7.4 Trial Stopping Rules.	Provide details and subsequent activities in case of study closure or in case of abandoing of planned study parts.
CSL Behring	1150			Within section 10.5, we interpret the reference to "close a site" to mean early or prematurely. Elsewhere throughout the template, references are made to 'early' site closure, and we propose that this section be updated for consistency with the remainder of the template.	List the decision rights of sponsor or designee to close a site early or….
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	1159	1159	10.6	A new sub-section should be added to include details on the incidental finding policy, where applicable (e.g. when genetic analyses are foreseen)	10.6 Incidental finding policy
EUCROF - EU CRO Federation	1161	1162	Section 11	General Considerations: Risk Management and Quality Assurance Comment 1: Risk Management measures consist of in- process quality control measures and independent quality assurance measures. The umbrella term would be "Quality Management".	Change to: General Considerations: Risk and Quality Management"
EUCROF - EU CRO Federation	1161	1183	Section 11	Sections on Monitoring and Auditing would be welcome.	
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	1161	1161	11	A new section before GENERAL CONSIDERATIONS: RISK MANAGEMENT AND QUALITY ASSURANCE should be added to deal with the policy on the communication and publication of study results	Communication of study results
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	1161	1161	11	Title "General Considerations: Risk Management And Quality Assurance" does not reflect the content: risk management is not mentioned in the following paragraphs	Add a paragraph in which risk management is deepened.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	1164	1167	11.1.	It doesn't seem reasonable to include Quality Tolerance Limits in the protocol as they cannot be defined for many risks anyway.	
EFPIA	1164	1164		Section 11.1 is entitled "Quality Tolerance Limits," but some studies may not apply quality tolerance limits. In addition, ICH E8 introduces Critical to Quality Factors and the current draft ICH E6 (R3) doen not use the term QTLs,	Section 11.1 should be entitled "Management of Study Quality." Instructions should state that quality tolerance limits or critical to quality factors should be addressed in this section.
EFPIA	1164	1164	11,1	If QTLs are to be included in the protocol, should it be somehow aligned with expectations from the investigator on how to ensure quality measures, otherwise, it seems this is not necessary in a protocol but a quality plan maintained outside the protocol.	
PTC Therapeutics, Inc.	1164	1164	11,1	PTC considers it is unclear as to what is required for this section.	PTC requests specific guidance on what content is required in this section.
EFPIA/EFSPI Regulatory SIG	1164	1167	11,1	Central statistical monitoring for data quality is now commonplace and should be referred to in this section	Indicate where Quality Tolerance Limits will be predefined, how they will be monitored during the trial, details of any central statistical monitoring, and expected discussion in the clinical trial report
Gilead Sciences	1165	1166	11,1	Suggest to provide more structure for the information required for Quality Tolerance Limits. Current instructions are not clear.	
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	1165	1165	11.1	The meaning of Quality Tolerance Limits is not clear and unambiguous	Please specify the meaning of Quality Tolerance Limits
TransCelerate BioPharma Inc.	1165	1166	11,1	The CPT has suggested text with a proposed approach to defining QTLs based on the available regulatory guidance. Something similar would be helpful here.	Consider additional instruction here on expectations of QTL information, or at minimum provide example text for this in the training materials.
LFB Biotechnologies	1167	1167	11.1	'Serious breach' is not mentioned while Guideline for the notification of serious breaches reports the sponsor and investigator responsibilities 'The principal investigator should have a process in place to ensure that the site staff or service providers delegated by the principal investigator/institution are able to identify the occurrence of a (suspected) serious breach; a (suspected) serious breach is promptly reported to the sponsor or delegated party, through the contacts (e-mail address or telephone number) provided by the sponsor or delegated party.	The following sentence could be proposed to be added "Describe sponsor and Investigator responsibilities for detecting, reviewing, and reporting of serious breach"
EUCROF - EU CRO Federation	1168	1168	Section 11.2	Data Quality Assurance A section on Data Handling and Record Keeping is missing (see ICH E6 6.13). Please note: "Data Handling" would describe the quality control measures planned for the trial data.	Consider changing the heading to Data Handling, Data Quality Assurance and Record Keeping. Alternatively, the Heading could be "Data Management" and Data Handling, Data Quality Assurance and Record Keeping could be 3rd level headings.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	1168	1170	11,2	This section does not emphasize the link between data quality and estimand(s) of interest for the trial. It is important to mention this link since data collection and quality should be directly related to the target effect of interest.	Propose to include "Efforts should be made to collect all data that are relevant to support a statistical analysis aligned with the estimand of interest. If the estimand that are required to support regulatory decision making do not require the collection of the variable after an intercurrent event, then the benefits of collecting such data for other estimand should be weighed against any complications and potential drawbacks of the collection."
Interpharma, Association of Switzerland's research-based pharmaceutical industry	1168	1170	11,2	This section does not emphasize the link between data quality and estimand(s) of interest for the trial. It is important to mention this link since data collection and quality should be directly related to the target effect of interest.	Propose to include "Efforts should be made to collect all data that are relevant to support a statistical analysis aligned with the estimand of interest. If the estimand that are required to support regulatory decision making do not require the collection of the variable after an intercurrent event, then the benefits of collecting such data for other estimand should be weighed against any complications and potential drawbacks of the collection."
EUCROF - EU CRO Federation	1169	1169	Section 11.2	This section should have instructional text that says to provide "a statement from the sponsor ... confirming that the investigators and institutions involved in the clinical trial permit clinical trial-related monitoring, audits and regulatory inspections, including provision of direct access to source data and documents". Please note that the ICH E6(R2) document has similar requirements (see ICH E6(R2), 4.1, 4.9.7 and 6.10).	Add instructional text as per comment.
EUCROF - EU CRO Federation	1172	1172	Section 11.3	As per ICH E6(R2) 6.4.9: "The identification of any data to be recorded directly on the CRFs (i.e., no prior written or electronic record of data), and to be considered to be source data." should be included in the protocol. This doesn't seem to be fully addressed.	Add instructional text as per comment.
EFPIA	1172	1172		Please clarify where information on CRFs and and other forms of data capture should be addressed.	
EFPIA	1174	1174		Suggest to address protocol compliance including methods to monitor and assess this, and recording of protocol deviations, in this section (rather than in the statistics section).	
EFPIA	1180	1180		Please clarify where retention of trial documentation should be addressed (both source data and CRF data at site and for sponsor.)	
EFPIA	1183	1184	12	Consider adding a separate appendix with a brief 2-pager scientific summary that is needed for the CTIS portal, as well as a brief lay summary that could be utilized for several disclosure deliverables	
EUCROF - EU CRO Federation	1184	1184	Section 12	All information related to AEs/SAEs should be in one place of the protocol. We suggest to include the sections 12.1 Further Details and Clarifications on the AE Definition and 12.2 Further Details and Clarifications on the AE Definition in the already existing sections about AEs and SAEs. As it is now, there is a lot back and forth for the sections. There is also the danger that the Appendix will not be read.	
Quotient Sciences	1184	1208	12	As noted above, 12.3 and 12.4 would be better placed in Section 8.4.4.	Move 12.3 and 12.4 to Section 8.4.4
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	1184	1207	12	It does not seem to be useful to have an Appendix on Adverse Events and Serious Adverse Events. We suggest including all information in section 8.4 "Adverse Events and Serious Adverse Events."	
EFPIA	1184	1185	Section 12	"Severity" may not be the proper (CDISC) term	Consider using "intensity".
EFPIA	1184	1199	12.1-12.2	Clarification and consistency.	Consider adding a crossreference to Section 8.4.10 Disease-related Events or Outcomes Not Qualifying as AEs or SAEs

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	1184	1207	12	For all level 2 headings under section 12, where standard language is needed to comply with GCP and/or regulations, can the text be provided in the ICH M11 template? This will ensure common understanding and consistency.	
PTC Therapeutics, Inc.	1184	1185	12	PTC considers that this section should be included within Section 8.4 as the content is extremely important to the study conduct.	PTC proposes moving this into the main body of the protocol rather than as an appendix.
Freeline Therapeutics	1184	1208	12	AE information is so important it should be within the main body of the protocol under the AE section	Move text to the main body of the protocol under the AE section
EFPIA	1185	1185		Since the main definitions appear to be in section 8.4 the title here is misleading. Suggestion to delete this part, or change to 'Further details' The subheadings below are self-explanatory	
TransCelerate BioPharma Inc.	1185	1185	12	Per CDISC terminology, “Intensity” is used rather than “Severity.”	Recommend replacing "Severity" in this section title with "Intensity."
CSL Behring	1187	1189		As this section 12.1 relates to Adverse Event (AE) definitions, the statement “Any relevant regional AE requirements” would appear to be out of place and we question if this really belongs here i.e., can there be regional differences in how an AE is defined? If the intent is to specify AE “requirements” then it appears that such information better belongs in the sections on documentation, reporting, follow-up etc. If retained in the current location, it could be considered to make the section sub-headings for 12.1 and 12.2 more general in nature by referring to AE definitions and requirements.	n/a
EFPIA	1187	1187		It may be problematic for site personnel comprehension and compliance to have the SAE definition spread across two sections, i.e. a standard definition in section 8.4 and a trial-specific one here. Suggest that this should be more integrated, so site personnel are not confused or misled.	
ICON PLC	1187	1194	12,1	Suggest include some guidance text here that for "death events", death is an outcome of an SAE, so please report the cause of death which had the outcome of death as the SAE.	Insert guidance text: death is an outcome of an SAE, so please report the cause of death which had the outcome of death as the SAE.
Gilead Sciences	1187	1208	12	Suggest to keep AE and SAE definitions in a single section and cross-reference	
CSL Behring	1190			Whilst appendices are an integral part of the protocol and Adverse Event (AE) reporting is standard, we question whether key AE information is too important to be placed in an appendix at the end of the document. We suggest this point be reconsidered.	n/a
CSL Behring	1192			It is not clear that if an overdose is not associated with any adverse signs or symptoms, should the overdose itself be considered as an AE as is suggested in the text. Propose a revised definition to provide further clarity around this point.	· The trial-specific definition for AEs associated with an overdose (of IMP or any concomitant medications)
EFPIA	1199	1199		It may be problematic for site personnel comprehension and compliance to have the AE definition spread across two sections, i.e. a standard definition in section 8.4 and a trial-specific one here. Suggest that this should be more integrated, so site personnel are not confused or misled.	
EFPIA	1200	1202	12,3	Please consider including specifics to ensure that the scale is harmonised across sponsors.	
EFPIA	1203	1206	12,4	Please consider including specifics to ensure that the scale is harmonised across sponsors.	
EFPIA	1203	1207	12,4	What is the ICH preferred recommendation, binary or WHO criteria, as this is not clear and not agreed upon between individual health authorities? Guidance is needed for the Sponsors. • ICH E2A extraction - Many terms and scales are in use to describe the degree of causality (attributability) between a medicinal product and an event, such as certainly, definitely, probably, possibly or likely related or not related. Phrases such as "plausible relationship," "suspected causality," or "causal relationship cannot be ruled out" are also invoked to describe cause and effect. However, there is currently no standard international nomenclature. The expression "reasonable causal relationship" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.	Recommendation is to provide a guidance similar to ICH E2A to avoid different terms and scales to describe the degree of causality.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUCROF - EU CRO Federation	1209	1209	Section 13	All information related to Contraception and Pregnancy and Clinical Lab Tests should be in one place in the protocol. The Appendices should only contain items that are unique to that protocol, e.g., QOL scales.	Keep all related information together in the body of the protocol. Otherwise, it is back and forth for the reader and makes reading of the protocol more difficult.
EUCROF - EU CRO Federation	1209	1209	Section 13		Suggest moving the Appendix section below the References section; this is standard document structure.
Quotient Sciences	1209	1226	13	As noted above, 13.1 would be better placed in Section 5.5.	Move 13.1 to Section 5.5.
EFPIA	1209	1227	13	suppose that other appendices can be added beyond the ones listed, for example for ECG (similar as the one for lab safety)	flex to add more appendices
PTC Therapeutics, Inc.	1209	1210	13	PTC considers that this section should be included within Section 8.4 as the content is so important to the study conduct.	PTC proposes moving this into the main body of the protocol rather than as an appendix.
EFPIA	1210	1241	13	Please consider adding definition sections for AESIs, medication errors, overdose, misuse, abuse, wrong technique in application or administration, etc.	Consider adding definitions.
EFPIA	1210	1241	13	Consider adding a section for decentralized trial activities.	Consider adding a section for decentralized trial activities.
PTC Therapeutics, Inc.	1212	1212	13,1	Given the global nature of some trials, PTC seeks clarification on how regional guidance such as CTFG should be included within the protocol.	PTC requests additional guidance is provided on this section content.
Freeline Therapeutics	1212	1251	13.1-13.3	All important information for the conduct of the trial should be kept together within the main body of the protocol. Any other supporting information is better placed (and is usually in practice) in separate document such as study manuals to avoid needing a protocol amendment if details change during the study.	Move these sections into the relevant parts of the main body of the protocol where the topics are already mentioned.
EFPIA	1214	1218	13.1.1	Can the definitions of child-bearing potential be provided in the ICH M11 template to ensure consistency and common understanding?	
SÚKL CZ	1219	1219	Contraception	Indicate that a separate list for male and female participants should be provided.	Indicate that a separate list for male and female participants should be provided.
SÚKL CZ	1219	1219	Contraception	It should be indicated that the contraception measure must be in line with available nonclinical/clinical knowledge and cover the whole period of relevant systemic exposure (5 elimination halflives) and when relevant, longer due to other drug characteristics (genotoxicity etc.).	It should be indicated that the contraception measure must be in line with available nonclinical/clinical knowledge and cover the whole period of relevant systemic exposure (5 elimination halflives) and when relevant, longer due to other drug characteristics (genotoxicity etc.).
PTC Therapeutics, Inc.	1219	1219	13.1.2	PTC considers that this should be a mandatory section.	PTC proposes changing this to a mandatory section as every protocol should include this information.
EFPIA	1224	1225	13.1.3	Consider including details on pregnancy testing in Section 13.2 and crossrefering to Section 13.2.	
CSL Behring	1227	1238		Propose to add "Reporting mechanism for lab results considered clinically significant" as an additional bullet point within section 13.2 Clinical Laboratory Tests, as there could be special criteria/requirements (for e.g., pre-defined changes) that are relevant to be noted here.	· Reporting mechanism for lab results considered clinically significant
EFPIA	1227	1240	13,2	For Clinical Laboratory tests, the usage of CDISC controlled terminology for test naming should be encouraged in the explanatory text	Encourage the usage of controlled terminology according to CDISC wherever possible in the explanatory text
LFB Biotechnologies	1227	1240	13.2	Section 13.2 only provides information on clinical laboratory tests. Shouldn't information on specialized Bioanalytical labs performing PK/Biomarkers/Immunogenicity assays be included for completeness ?	Name section 13.2 "Laboratory tests" and include information related to both clinical and bioanalytical lab activities
Agios	1227	1251		The appendices from 13.2 onward are noted as optional but are not marked blue.	Make headers for Sections 13.2 and onward blue text.
EFPIA	1228	1240	13,2	Include instructions as to whether this should be presented by epoch (eg, baseline, treatment, follow-up) and/or type (hematology, chemistry, urinalysis)?	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
LFB Biotechnologies	1232	1232	13.2	"equations and references for locally calculated labs" : sentence to be corrected	equations and references for locally calculated lab results
Quotient Sciences	1235	1237	13,2	The author is instructed to consider situations where central lab results are not available owing to severe disruption; however, the effect of severe disruption on other aspects of the trial, such as disruption of supplies of IMP and restrictions on participants' travel, are not mentioned in the template.	
EFPIA	1238	1238		Suggest to add: retention and destruction of samples, including any special handling of residual samples.	
EFPIA	1240	1240		Suggest to add: any test results that will not be shared with the sites, e.g. to avoid unblinding.	
PTC Therapeutics, Inc.	1242	1242	13,3	With the introduction of submission through CTIS, PTC is concerned that if this section is to include specific national requirements it could be extremely confusing and long.	PTC requests additional guidance is provided on this section content and considers inclusion of roadmaps that cover these specific national requirements could be useful.
Gilead Sciences	1245	1247	13,3	Instructions are not aligned with CTIS requirements. Suggest to delete this sentence.	
KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS Network), Germany	1252	1266	13.4.	Detailed information on change history and amendments are already asked for at the very beginning. Mentioning them again in this chapter seems redundant.	
EFPIA	1252	1252	Section 13.4	"Prior" in the title is misleading as this section should cover ALL amendments.	Consider removing the term "Prior" from the title
Freeline Therapeutics	1252	1267	13,4	Protocol amendments history should be in an appendix of its own to keep all the information about amendments together. An appendix is the appropriate place to keep information which is not required for the daily management of the trial at the site.	Move information in Section 13.4 (and all amendment history information) to an appendix of its own called 'Protocol Amendment History'.
TransCelerate BioPharma Inc.	1252	1252	13,4	The reference to this section in the "current protocol amendment" section in the front of the document uses a slightly different title (likely a typo.)	Recommend updating the title of this section to "History of Prior Amendments"
EUCROF - EU CRO Federation	1268	1268	Section 14	This is titled as a glossary. It has been standard to list an abbreviation and the term. For a glossary, a writer would include the definition of the term. Will this additional information become mandatory with this new template?	
EFPIA	1268	1278	Section 14	Section title does not indicate that abbreviations are to be expected here.	Consider adding "abbreviations" to the section title
EFPIA	1268	1278	Section 14	List of abbreviations and definitions may be overlooked if placed in the appendix.	Consider moving list of abbreviations and definitions to the beginning of the document.
PTC Therapeutics, Inc.	1268	1278	14	PTC considers that this section should be included directly before the TOC as it is so materially important to the protocol content and readability. Additionally, PTC is concerned that it is not mandated to define all abbreviations at first use.	PTC proposes moving this into the main body of the protocol directly after the table of contents rather than as an appendix. PTC also consider that it should be mandated that all non-standard abbreviations should be defined at first use to avoid confusion.
TransCelerate BioPharma Inc.	1268	1268	14	It is common practice for most documents to place the abbreviation list at the front of the document; the CPT also follows this approach. The abbreviations should be covered in a list at the beginning of the document to serve as first use to avoid having to define in-text.	Recommend clarifying that this section is just to define specialized terms, not serve as the abbreviation list. Placement of the list of abbreviations should also be clearly identified in the front matter of the template.
Charité Research Organisation	1268	1269	14	Since a table for abbreviations is proposed at the beginning (line 62), the suggestion to define abbreviations an the end of the protocol is confusing.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	1269	1269	14	"Define abbreviations and other terms used in the protocol", this section should be inserted at the beginning of the study protocol.	Move this section.
Claudia Pansieri, Adriana Ceci, Donato Bonifazi, Viviana Giannuzzi, Mariagrazia Felisi, Annalisa Landi, Giorgio Reggiardo, Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and Fondazione Per La Ricerca Farmacologica Gianni Benzi Onlus (FGB)	1272	1272	14	Some terms have an ambiguous and unclear meaning	Clearly define some expressions such as: Auxiliary Medicinal Product, Rescue Medicament, Concomitant Medicinal Product, Deviation, Serious Breach, Violation.
EFPIA	1274	1277	14	Please clarify that these terms should be defined in the appropriate sections in the protocol (not necessarily in Section 14).	
EFPIA	1277	1277		Not clear why product complaint is included on this list. This should be driven by regulatory guidelines. Please clarify or delete.	
EUCROF - EU CRO Federation	1279	1279	Section 15		Do not include the Reference section as an appendix; remove "Appendix" after the Section number.
EFPIA	1282	1282	15	Consider including multiple fields in the data field, eg Reference #1, Reference #2, etc.	