EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

04 December 2019
EMA/542003/2019

Overview of comments received on 'ICH guideline E8 (R1) on general considerations for clinical studies' (EMA/CHMP/ICH/544570/1998)

Comments from:

Stakeholder no.	Name of organisation or individual
1.	Medical Research Council Clinical Trials Unit at University College London
2.	Medicines for Europe
3.	European Society of Clinical Microbiology and Infectious Diseases
4.	The COMET Management Group
5.	ECRIN (European Clinical Research Infrastructure Network)
6.	Novo Nordisk A/S
7.	Standing Committee of European Doctors (CPME)
8.	European Respiratory Society (ERS)
9.	GKV-Spitzenverband
10.	Health ad Youth Care Inspectorate (team GCP), the Netherlands
11.	State Institute for Drug Control, Czech Republic
12.	Clinical Trials Facilitation and Coordination Group (CTFG)
13.	EFPIA
14.	German Pharmaceutical Industry Association (BPI)
15.	European Hematology Association (EHA)
16.	European Organisation for Rare Diseases (EURORDIS)
17.	Simbec-Orion
18.	ACRO (Association of Clinical Research Organizations)
19.	Fimea inspectorate
20.	ACRP – Association of Clinical Research Professionals
21.	Association of Medical Ethics Committees in Germany
22.	GQMA – German Quality Management Association
23.	Joint comments of Arbeitsgemeinschaft Angewandte Humanpharmakologie (AGAH), Germany, and Deutsche Gesellschaft für experimentelle und klinische Pharmakologie und Toxikologie (DGPT), Germany
24.	European Forum for Good Clinical Practice (EFGCP)

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

Stakeholder no.	Name of organisation or individual
	With input from Members of its Working Parties, from Institutional Members and collaborating organisations like, e.g., the Swiss Clinical Trial Organisation (SCTO)
25.	European Federation for Exploratory Medicines Development (EUFEMED)
26.	European Organisation for research and treatment of cancer (EORTC)
27.	Lymphoma Coalition
28.	Research Quality Association (RQA) – GCP Committee
29.	European Association of Hospital Pharmacists (EAHP)
30.	AGES – Austrian Agency for Health and Food Safety
31.	EUCROF - European CRO Federation
32.	ASOCIACIÓN ESPAÑOLA DE FARMACÉUTICOS DE LA INDUSTRIA (AEFI)
33.	KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien (KKS-Network), Germany
34.	Prof Martin Landray on behalf of Nuffield Department of Population Health, University of Oxford
35.	MHRA UK
36.	National Institute of Health and Care Excellence (NICE) - England
37.	Centre for Human Drug Research (CHDR) - The Netherlands
38.	Pharmaceuticals and Medical Device Regulatory Science Society of Japan
39.	Voisin Consulting Life Sciences(VCLS) - France
40.	From an individual – no affiliation provided

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

1. General comments

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1	The term clinical study is used throughout but given this refers to the study of a medicinal product in humans, the term trial would be more appropriate, as this will always be in early or late-phase trial settings if being trialled in humans. Patient input into study design section – perhaps should broaden to patient and public involvement (PPI) and define the broad range of members who may contribute to PPI. Can also mention how PPI can contribute to interpretation of trial results and wider dissemination of findings following reporting of main results.
2	Throughout the document, clinical studies are referred to as any studies conducted in humans on drugs, considered synonymous with medicinal products. As medicinal products can also contain device components (e.g. pre-filled syringes, inhalation devices, etc.), and furthermore, clinical investigations on medical devices are following the same principles in study design, it should be clarified if these principles apply to these types of medicinal products as well. We notice the inconsistent use of the terms "compliance" and "adherence" across different ICH guidelines, which at times can be confusing. For example, in ICH E8(R1) the term "protocol adherence" is consistently used, while in ICH E6(R2) the term "compliance with the protocol" is used. Our suggestion is to use both terms consistently in all ICH documents; to stay in line with the ICH E6(R2) we propose the term "compliance" when referring to the compliance with the documents, regulations and procedures (e.g. protocol, GCP, regulatory requirements etc.), while the term "adherence" can be used only when referring to patients adherence to the study treatment (IMP, treatment procedures etc.) On similar note, it would also be useful to add a short definition of the difference between "deviations", "violations" and "breaches", which is also often unclear in clinical research terminology. Possible separation of the three terms: breaches are major violations affecting patient's safety and/or data integrity on a study level; violations are major deviations affecting patient's safety and/or data integrity on a patient or site level; deviations are all other minor deviations which cannot be classified to any of the two prior definitions. There are a few possible grammar/typing errors, which should be corrected during the revision.
3	Very helpful document.

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	My only general comment stems from my perspective: that of communicable diseases background. Most treatments in most areas of medicine have effects on individual patients only. In communicable diseases, effects may extend to contacts of the infected patient. Outcome selection in study and other design features should consider the need for not-individual outcomes (e.g. spread of pathogens resistant to antimicrobials). Other instances where the medicinal product might impact on other-than-the-patient-prescribed-the-drug are when it alters the reproductive capacity, or impacts the offspring.
4	Relevant outcomes are needed for the development of a drug (and other interventions) during their life cycle There is increasing recognition of the value of core outcome sets (COS) as a means of improving the relevance of outcomes in research, particularly to patients. COS represent an agreed minimum set of outcomes that should be measured and reported in all trials in the specific topic area defined by the scope of the COS. A well-developed COS will have included all relevant stakeholders, including patients or their representatives, in the determination of the most important outcomes to be measured. Minimum standards for the development of COS ensure that COS appropriately reflect outcomes that are important to a range of groups, particularly patients, healthcare professionals and those who will use the COS in their research (https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002447). This Guideline on general considerations for clinical studies highlights the need for relevant outcomes to be present throughout the drug development lifecycle (studies phase 1-4). As noted (lines 337-338), early phase studies should include 'potential study endpoints for further study' in later phase trials. The development and uptake of COS by researchers will ensure that relevant outcomes are included earlier in the research lifecycle, as discussed in the SBU podcast (www.youtube.com/watch?v=PGMhUkdoZag), and we are pleased that the EMA is seeking to increase awareness of COS, encourage COS development and support uptake of COS (see podcast from Hans-Georg Eichler, Senior Medial Officer, European Medicines Agency, www.comet-initiative.org/assets/downloads/Hans-Georg%20Eichler_COMET.mp4). The COMET Initiative is facilitating work to help COS to improve healthcare research, health care and health, in part by the identification of COS that have already been developed, or are in development, and their inclusion in an online free database (www.comet-initiative.org/studies/search). Many organisations now actively endorse the use of COS and the COMET database, including the EMA (see www.comet-initiative.org/cosuptake).
5	Clear document providing a comprehensive and detailed overview of the challenges raised by current practice in clinical research, including secondary use of data. In the academic sector, personalised medicine research programmes are now developed as a paradigm for drug repurposing,

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	centred on the patient (what is the best treatment option for this subgroup of patients ?) rather than on the product. Therefore the identfication of patient clusters is a critical step in these programmes, that typically include three steps : i) patient stratification, using data and biosamples from a stratification cohort, followed by a validation cohort, and subsequent identification of homogenous clusters based on conventional or machine learning methods; ii) a translational step to determine the treatment options to be tested in each cluster ; and iii) multiarm trials (umbrella, etc) to test these treatments options in each cluster, and to assess the personalized vs. the non-personalized approach. Such programmes may lead to new indication for drugs. However this raises two critical questions : 1 – the validity of the new indication for a subgroup of patients defined through biomarkers requires a validation of the stratification (design and data quality of the cohorts, reliability of the clustering method, including algorithms in case of complex biomarker profiling) 2 - the multiarm trials (umbrella, basket) may raise specific issues (the CTFG produced a document on multiarm trials, and this is also valid for 'platform' trials sharing a common control arm). These questions will be addressed in a H2020 project (PERMIT, GA 874825, coordination ECRIN) whose objective is to discuss methodological standards for personalized medicine research programmes (EMA will be a partner in this project).
7	The document is of great interest for stakeholders organising, conducting or participating to clinical studies. The principles of ethical conduct of clinical studies and the protection of subjects including special populations are presented in § 2.1 as stated in other ICH guidelines. Nevertheless, it would be of great interest to further emphasize the role of ethics committees in the different steps of organising and conducting clinical trials. Likewise, the CPME would like to formulate cautions concerning the participation of pregnant and nursing women to clinical trials.
8	The European Respiratory Society (ERS) has read with great interest the novel ICH guideline E8 (R1) on general considerations for clinical studies, and wants to congratulate the European Medicines Agency (EMA) for this excellent and clear guideline. In addition to the comprehensive text on efficacy, the ERS would like to highlight the increasing importance of real life effectiveness. Indeed, whereas efficacy and (short-term) safety data from exploratory and confirmatory trials are crucial for decisions with respect to *approval of the drug* by regulatory authorities such as EMA, these data are often insufficient to develop clinical practice guidelines, providing appropriate evidence-based guidance to physicians, patients and payers for the *optimal use of the drug* in clinical practice. To this end there is a huge need for additional studies investigating the real life effectiveness and comparative effectiveness of the newly approved drug, not only compared with other drugs (from the same class or another class of drugs),

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	but also compared with non-pharmacological treatments (e.g. psychotherapy, physiotherapy, radiotherapy or surgery). The ERS is very supportive of the vision of the EMA to expand its authority to the entire product lifecycle, since many research questions still need to be addressed after approval of the drug. Does the drug work in unselected patients (in real life) and in non-specialist settings (in real world)? How does the *effectiveness* of the novel drug compare with that of existing drug treatments? What is the safety of the drug in vulnerable patients, e.g. elderly patients and/or patients with comorbidities and polypharmacy? What is the long-term safety of the drug, e.g. if used over prolonged periods of time (or even life-long) to treat chronic non-communicable diseases? Although real life effectiveness and comparative effectiveness can be investigated via observational studies, pragmatic trials and large simple trials offer the advantage of reducing the risk of confounding bias thanks to the randomization of subjects. The ERS also wants to highlight the need for *patient-centred clinical research*, in addition to drug-centred research, as put forward in the recent position paper of the BioMed Alliance members (please see the white paper by Denis Lacombe et al, Moving forward from drug-centred to patient-centred research, European Respiratory Journal 2019). To maximise the potential of precision medicine and personalized medicine, new drugs reaching the market should not be considered as an end but as a start of clinical studies. The ultimate aim is to provide clinical evidence of real life effectiveness, comparative effectiveness, cost-effectiveness and long-term safety of drugs as well as individual predictors of (non)response in order to offer accurate guidance for the optimal use of different drugs in individual patients.
11	Usage of the term "Quality by design" in this document is somehow misleading. This term is used to explain that the research and development planning should be focussed on quality of gained data but it is not clear whether it has any additional meaning when compared to the term "quality" only. Alternative term could be used to describe this type of approach. Rewording is recommended (see also specific comments below) to make the text more readable and understandable. Additionally, the term quality is used in different meanings and it should be specified whether it refers to quality of data, quality of study, quality of design or any else.
12	In general, the document is written with commercial sponsors in mind, without really addressing the non-commercial/academic aspects of clinical research, which can have an impact on prescribing practice and an impact on public health. This document must be applicable to both commercial and non-commercial research or there is the potential that alternative forms of GCP may be followed for non-commercial work in the future such as the ICH version being proposed by the Bill and Melinda Gates Foundation. https://wellcome.ac.uk/news/pivotal-moment-clinical-trial-regulations.
13	We welcome the opportunity to comment to this important guideline. We are in agreement with the guideline broadly and

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	appreciate the introduction of flexibility in this guideline to take into consideration the diversity of clinical trial design and data sources, quality by design and patient input in clinical studies. In general, the guideline E8 is very good. It is a clear description of all considerations for a well-designed and -executed clinical study and includes an up-to-date view on clinical studies. New insights of this guidance are regarding quality control measures. However, the guideline is extremely general and does not consider the new flexibility we have gained in many areas. Issuing this now cements the status quo. For example, - The guideline still distinguishes between exploratory and confirmatory trials while in practice the transition from exploratory to confirmatory is more and more fluid these days - It continues to use the traditional framework for the logical progression of drug development in phases 1 – 4 providing appearance of operating in the old paradigm. It is recommended that this document resets the framework on the approach to drug development. Scientific methodologies have evolved. A multitude of methodologies (e. g., adaptive designs, master protocols, observational research, pragmatic research) is available to be used to provide evidentiality for drug development. We recommend lessening the focus on phases 1 - 4 and instead focus on answering the research questions using appropriate methods at the suitable time - The use of Complex Clinical Trials (CCTs) is mentioned in one sentence only (lines 358 – 360). Pointing out the possibility of using CCTs would be a suitable contribution to section "2.2 Scientific Approach in Clinical Study Design, Conduct, and Analysis" and "4.3 Clinical Studies", and could be further elaborated in "4.3.2 Exploratory and Confirmatory Studies …". In particular, their role in dose-finding (adaptive phase 2/3 trials) or efficacy in different indications (basket trials) could be mentioned - Basket - and umbrella trials are mentioned marginally only - Orphan drugs and Advanced Therapy Medicinal Products (ATMPs) are not taken into consideration. In order to reflect innovations in clinical development and technology, the scope of the guideline should be expanded to include discussion of the application of real-world data (RWD) and artificial intelligence (AI) (e. g., RWD in phase 3 safety studies and for the study design; AI as a part of trial design for the stratification of patient populations which also introduce interesting numbers of ethical AI issues, like bias in training data and being able to justify algorithmic decisions). The need to assess for potential futile use of subjects, e. g., that an entire study or a treatment arm may potentially be

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	considered futile research, is not mentioned. Some guidance on this topic would be helpful. With respect to control groups, additional guidance on ethical considerations could be provided (e. g., which criteria define an unethical control group, etc.). The guideline E8 covers drugs as well as vaccines and biologics (lines 32-33). However, throughout the document reference is made to "patients" mainly, whereupon "(healthy) participants" in preventive vaccine studies and programs should also be included. Therefore, the text should be amended to refer to "participant(s)" rather than patient(s). Consistent language (terminology, descriptions) should be used throughout the ICH Efficacy Guidelines to prevent confusion. An opportunity for harmonization between E8 and E6 arises at the upcoming review of ICH E6 (R3). E. g., most of the Quality by Design (QbD)-related process described in E8 is redundant compared to section 5.0 of ICH E6 (R2), whereas E8 describes the QbD process slightly differently and introduces new terminology. For instance, the expression "critical to quality factors" appears to convey the same intent as the phrase in E6(R2) "critical data and processes." Repetitions of some content/phrases were noted in several sections of the document (e. g., lines 227-229 describing involvement of stakeholders). Cross-referencing between sections throughout the document would reduce redundancies. Adaptive clinical trial designs (in our opinion a very powerful way to develop faster early phase trials without "wasting" patients) would be appropriately covered in the planned ICH guidance on adaptive clinical trial designs and hence would not need to be detailed here. A reference would be sufficient. The order of sections should be changed to enhance clarity on expectations related to Clinical Studies: start with Drug Development Planning (4.) as introduction, followed by section 5, then 1-3 as well as 4,6, 7. The meaning of Annex 3 is unclear: the table does not provide insights in the use of the "critical to quality factors" concept. In case the table should serve as a cross-reference to other ICH guidelines, completion is required (e.g., dissemination of study results does not include E3, structure and content of clinical study reports). To clearly communicate the intended use of the table the title should be reworded.
14	In principle we believe that the GCP-renovation would be a useful guidance updating the current version of the ICH GCP and we welcome the efforts to bring about a revision. However, in the present draft variant we only see a presentation and summary of the current situation. Techniques and practices

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	as well as theoretical knowledge are listed, as it is usually used for quite some time. In this respect, the draft does not appear to be in line with the announced GCP renovation.
15	The document mentions patients, physicians, investigators and sponsors as stakeholders. Clinical Research Organizations (CROs) should also be mentioned in the text as one of the stakeholders, and it should be clear that they should follow the guidelines as all the other stakeholders. Moreover, in some parts of the document, some examples of adequate measures that are used to protect subjects' rights, safety, and welfare are provided. We consider that one important measure to protect subjects' safety is clarifying that, although the sponsor can delegate tasks to third party providers (CROs), they remain ultimately responsible (and liable) for the study. Mentioning this in the Guidelines may protect other clinical trial stakeholders (such as investigators) from being requested to over-report or provide excessive documentation by CROs, which may have a negative impact on patient safety, as truly important signals are lost, diluted in an unmanageable number of trivial queries and unfiltered notifications of suspected unexpected serious adverse reactions (SUSARs), for instance. In addition to the above, some specific suggestions have been provided in the specific comments below to reduce this risk. The aim of the document is clear. In some parts, however, more specific information could be helpful to prevent an overload of information for individual participating doctors and patients. Section 2.3 describes the benefits of involving patients in the design and conduct of clinical trials. However, the question is not whether patient organizations should to be involved (they have to be), but which parts of the protocol should be reviewed/approved by them. Regarding patient involvement throughout the text, there are several additional aspects that could be addressed: - What should be done if there is no patient group available with sufficient resources and/or knowledge – especially, how to judge early, often in complex trials? - What should be done if a lack of advice hampers the start of the study? - Should this be a review process, what would be the timelines? what would be the difference to the review by the ethics committee, which claims to focus specially on this point? What should be done if the ethics committee and the patient organizations disagree?

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	- There is a high risk to establish a proforma approach. Regarding the study population, some issues are worth mentioning. Currently, especially in oncology trials, the inclusion and exclusion criteria define a selected patient population that does not represent the real-life patient population. Medicine approval, however, does not restrict the use to the patients who would have fulfilled the study criteria. This results in a lack of important information for patients with a variety of organ dysfunctions that would have prevented them from fulfilling the inclusion criteria. Therefore, either trials for this population should be performed, or overly restrictive in- and exclusion criteria should be avoided.
16	Excellent revision. Important aspects added such as interaction with stakeholders and notably the patients are welcome. Here a few additional comments that do not directly relate to any line in the document: 1. High-intervention versus low-intervention studies Although this concept might be EU specific, it is useful. For example treatment strategy trials to explore when in the course of the disease it is best to treat, or which products should be used first line, and other second line, are all using authorised products, and patients can be randomised to different treatment modalities. A sentence could be added to explain this guidance also includes intervention studies using non-investigational drugs 2. Advanced therapies medicinal products This guidance focuses pretty much on chemical entities, classical drugs, and does not at all address specific aspects to the development of advanced therapies. Some guidelines were published by FDA and EMA, if not ICH, and they could be mentioned. 3. Patient recruitment There is no mention of clinical studies recruiting subjects from different regions or countries than country or region of residence, particularly needed in rare diseases, and reminding that the study sponsor should cover all expenses. The alternative would be to open centres closer to where subjects live, however this is not always possible (e.g. advanced therapies). 4. Study reporting The guidance rightly encourages the publication of objective and unbiased information (pubic posting of clinical trial results). It would be useful to recommend sharing clinical trial data with research organisations, e.g. individual patient data from placebo and standard of care arms, as they can constitute relevant information on the natural history of the disease during the trial period, or

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	can be used to pool placebo data/standard of care data for other purposes. See for example the PSoC Initiative and the creation of a platform that enables TransCelerate Member Companies to share placebo and SoC data. Such data is also of interest to other research organisations than industry. 5. Access to study data for study subjects Study subjects who wish to access their own data at the end of the study have to struggle to access these data. In the EU this is in contradiction with the objectives of the General Data Protection Regulation (GDPR Reg (EU) 2016/679) where part of the expanded rights of data subjects is the right to obtain confirmation from the data controller as to whether or not personal data concerning them is being processed, where and for what purpose. Further, the controller shall provide a copy of the personal data, free of charge, in an electronic format.
18	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 and pharmacovigilance research. In 2018, ACRO member companies managed or otherwise supported a majority of all biopharmaceutical-sponsored clinical investigations worldwide. With more than 130,000 employees engaged in research activities in 114 countries, the member companies of ACRO advance clinical outsourcing to improve the quality, efficiency and safety of biomedical research. ACRO welcomes the draft revision of ICH E8, and in particular the emphasis on inclusion of all relevant stakeholders, particularly the inclusion of patient groups, in the design of clinical studies, and the emphasis placed on identifying the critical to quality factors necessary to achieve the study objectives and the protection of study subjects, while also enabling flexibility in study design and promoting efficiency in study conduct. The latter is based on the risk-proportionate approach to clinical trial conduct described in ICH E6(R2) and, although it is discussed, we would encourage ICH to include a greater emphasis on risk control in the final text. We welcome the focus on QbD principles but feel the guidance is very high level, but we would like to see more detail around the practical implementation of QbD e.g. using some of the guidance found in the CTTI QbD principles document and toolkit Given that patient-reported outcomes (PROs) now play a significant role as study endpoints in the development and evaluation of

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	new therapies, it was disappointing that the draft guideline did not address the specific challenges to be considered when PROs are used, and we recommend that this should be included in the final guideline. Similarly, although truly "virtual" (or "decentralised") clinical studies are still extremely rare, it is now common for individual features within a clinical trial to be managed in a virtual way in order to realise more efficient data collection and central monitoring and/or to improve convenience for study subjects and encourage participation in clinical studies. Consequently, although the draft guideline includes references to electronic health records and digital tools, we were surprised that the unique challenges of conducting study activities virtually are not addressed. Consequently, we recommend considering inclusion of a robust discussion of decentralised trials and the increasing digitisation of clinical trials in the final guideline. The term clinical study has been adopted throughout the ICH E8R1 document. From a regulatory perspective, this is important as clinical studies can be studies other than clinical trials, see EMA and FDA definitions below: - **Non-Interventional Study:** Means a clinical study other than a clinical trial (as per Article 2.2(4) of Regulation EU/536/2014). - **Observational Study: A non-interventional clinical** study design that is not considered a clinical trial [As per Glossary of Framework for FDA's Real-World Evidence Program - Dec 2018 According to section 1.12 of ICH E6 (R2), "The terms clinical trial and clinical study are synonymous". However, based on the legal definitions provided above this is not the case and clinical study does not equal clinical trial. The work carried out by ICH under the Efficacy heading is also listed as being concerned with the design, conduct, safety and reporting of clinical trials. Although reference is made to observational studies in Appendix 1, the objectives are aligned with those of a clinical trial and the study types do not extend to those such as Disease Registries or studies which don't include medicinal products. • Revert to using the term "trial" and "clinical trial" throughout Revision 1 of ICH E8 or, if intent is to expand the scope of ICH E8R1 (and subsequent E6R3) to the continuum of studies beyond clinical trials of an IMP (as inferred by the renovation paper) then this needs to be a formally adopted definition change by the ICH body/stakeholders and language in other documents such as ICH E6R2 and the ICH website as a whole needs updating to reflect this. Otherwise this will lead to further confusion. See also comment on line 413. 479and 488 **Proposed change:** Revert to using the term "trial" and "clinical trial" throughout Revision 1 of ICH E8 or, if intent is to expand the scope of ICH E8R1 (and subsequent E6R3) to the continuum of studies beyond clinical trials of an IMP (as inferred by the renovation paper) then this needs to be a formally adopted definition change by the ICH body/stakeholders and language in other

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	documents such as ICH E6R2 and the ICH website as a whole needs updating to reflect this. Otherwise this will lead to further confusion. See also comment on line 413. 479and 488
19	Great to see that quality by design aspects have been incorporated This guide encompasses both interventional and observational trials and research data collection methods? For example, the ICH E6 mentioned in section 6.1.1 is the bible for interventional medicinal trials, but if the scope of this guide is also observational trials, should one mention that other relevant (non-ICH) guidances should also be considered? E.g. instead of ICH E6 section 6, protocols may be designed based on the ENCePP guide on methodological standards in pharmacoepidemiology. Although this guide recommends that studies should be simplified in order to improve study efficiency, to answer specific research questions and to target resources to critical areas, the reality is the opposite: sponsors try to obtain data as much as possible within a study (several secondary and exploratory objectives, sub-studies, HTA-data etc). Could this trend of extremely complex studies be addressed in this guide? Update the ToC
20	<u>General Comment #1</u> The majority of the document could apply not only to pharmaceutical studies but also to investigational medical devices. Additionally, the conclusion of chapter 1 "Objectives of the document" (lines 31 to 34) seems to limit the field of application of the global document to pharmaceutical products excluding medical devices. If exclusion of medical devices from the field of E8 is intentional from ICH, this should be clarified. Proposal of clarifications may include: - Amendment of document title to "General considerations for pharmaceutical clinical studies" - Addition in line 34 to specify that "Clinical studies on medical devices have to be included/excluded from the field of application of the document". <u>General Comment #2</u> Introduction of risk-based language and critical to quality factors is positively received. However, by being overly broad and allowing latitude interpretation, it may end up not being as useful as intended. Because of possibly too wide interpretations,

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	implementation especially for the Industry and Authorities can be jeopardized and lead to several pushbacks. General Comment #3 Attention should be raised on the possible challenges introduction of quality by design may add for Investigator Sponsored trials involving non approved drugs provided by the industry, but not directly sponsored by the Industry. Investigators, and more largely university hospitals which may run such type of trials may not have sufficient resources (either financial, technical or human) to fully comply with these new requirements, especially in the fields of orphan drugs, rare disease or paediatrics. General Comment #4 "Critical-to-quality" is a singular descriptive term. To facilitate global understanding and improve readability, it is suggested to hyphenate all occurrences of the term throughout the document.
21	We appreciate that issues regarding data monitoring committees are considered. Given that a blinded and standardized assessment of endpoints is highly important for the robustness and validity of the results of many trials we suggest to add relevant points to consider regarding Endpoint Adjudication Committees. Given that Contract Research Organisations and other types of vendors play an ever increasing role in the planning and conduct of clinical trials a short section on ‚Selection and qualifications of CROs and vendors' could be helpful too. Since many years physicians are expected to comply with the principles of Evidence-based Medicine. Thus it is time to use this concept for the regulation of clinical trials too. Therefore ICH should encourage and promote the independent scientific evaluation of its guidelines and their respective revisions. In particular it is important to identify and subsequently abandon requirements which failed to provide added value for the protection of research subjects and the quality of the data and subsequently the results of the trial. We appreciate that the role of patients and patient representatives is emphasized (see section 2.3 and 3.3.3).
23	Emphasis of Clinical Development Plan before the beginning of development is encouraged. In order to optimise the clinical trials, to allow adequate planning of resources and to set-up reliable planning procedures a clinical development plan should be drafted the latest after meaningful results from proof-of-concept trials are available. In those cases when enough knowledge about mechanism of action is already deduced from animal experiments and from other similar compounds the clinical development

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	plan can already be drafted prior to first-into-human trials. It is recommended to explain the term "quality by design" already in the first paragraph, as this term is not broadly known to those who perform clinical trials. Minimal interventional studies should be actively addressed including adapted ICF procedure This document is designed exclusively to cover studies carried out for the purposes of obtaining and maintaining marketing authorization by pharmaceutical companies. It does not address studies conducted by independent researchers, but it would also be binding for such studies. This causes major and unnecessary obstacles for independent research which provides an essential contribution to the understanding and appropriate use of many drugs. It is in the best interest of patients, the public and the researchers to separately address this issue in the document. In early phase clinical trials alternative study designs become more and more important. Especially in First-in-Human trials it is common to work with adaptive designs in regards to dosing steps and sample size per dosing group where interim decisions are based on safety, tolerability and pharmacokinetics. Not only in oncology, studies with adaptive design including healthy subjects and patients are of increasing relevance. Several reasons like acceleration of development process but also reduction of drug exposure for healthy subjects and early detection of efficacy-related effects including adequate surrogate endpoints are of increasing relevance for modern drug development. Thus, today separation of phase 1 and phase 2 trials is no longer the only practical option. Such trials should be actively mentioned as option and the necessity of adequately defined decision procedures should be addressed. The draft guideline addresses the integration of quality into clinical studies, considering the diversity of clinical study designs and data sources used. Besides individual studies, meta-analyses have been used to provide a comprehensive overview of study outcomes. Furthermore, pharmacometric methodologies, such as modelling and simulations, have become an integral part of modern drug discovery and development to quantify the relationships between the dose of an administered drug, its exposure, and its clinical efficacy and safety in individual patients and in certain populations. This methodology has been used successfully to identify the most appropriate dosing regimen of a medicine, by describing variability between individuals that may be associated with lack of efficacy in certain patients or with toxicity in others. Reference to meta-analyses, pharmacometric methodologies and other in silico investigations should therefore be included in in the general principles to consider in planning a drug development programme (Section 4) and in the Annex. Several bullet points in Annex 1 are not actively addressed in the main body of the guideline, here it is recommended to care for

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	completeness (general comment), the "missing" terms should be specified (see also specific comments); Safety pharmacology is missing in Appendix 1 as well as in main text, Pharmacoeconomic and effectiveness studies are mentioned in the Annex, but not discussed in the text. Patient-reported outcomes (PROs) can be important clinical study endpoints for regulatory approval studies, including effectiveness studies. These have been mentioned in Annex 1, but their relevance and proper planning of validation studies should also be addressed in the text, for example following the paragraph on validation of biomarkers (lines 237-239) and/or in the context of the discussion of patient involvement which is especially important for development, validation and application of PROs. Following Regulation (EU) 2017/745 (MDR) combination products such as integrals are regulated by Directive 2001/83/EC or Regulation (EC) 726/2004 as medicinal products. The draft ICH E8 has no reference to combination products at all. As those products are a significant part of medical applications they should be considered in this guideline as well. Due to the growing importance of companion diagnostic devices it is considered meaningful to address the specificities of device development, validation and its interference with clinical trials and clinical development programs.
24	This draft text provides guidance to a very traditional model of drug development. It does not sufficiently include modern and future approaches including technologies (e.g., Modelling & Simulation, Real-World Data use) or drug development concepts (e.g., personalised medicine) This draft text does not provide guidance on the early, parallel development of the drug for vulnerable populations, e.g., paediatrics, although this is even legally required in some regions. This draft guideline limits its scope to drug studies. But in expectation of an increasing number of combination product and companion diagnostic developments such limitation is not helpful. This draft guideline primarily uses the term “studies” but there is no clear definition of this term and the type of studies covered by this term. This draft text does not put any emphasis on the need for competence (defined as knowledge + skills + attitude) of all involved staff. Training on study specific tasks alone is not sufficient. And it does not emphasise on the prerequisite of competent staff in authorising/reviewing bodies supporting the investigator in fulfilling his/her responsibilities in protection of subjects and

Stakeholder number	General comment (if any)
	generation of reliable data. "Subjects" may be replaced by "participants" (this remark would concern all ICH guidelines) Other ICH Guidelines should be referenced more consequently (give title of guidelines). The need to build in considerations for good data management practices and for those to be funded appropriately is an important concept in the quality by design process, which should be considered throughout, not only in §5.2 (suggested additions made) In the interest of future reduction of trial costs and complexity it should be considered under which conditions direct patient/sponsor data collection could be acceptable, e.g., if the Sponsor had adequate medical oversight and qualified physicians conducting blinded data analysis with data captured direct from the patients. This could be potentially important for future technology studies.
25	The term and strategy "quality by design" is not broadly known to the clinical study community. We recommend that this concept gets explained in the very first paragraph and not only in lines 62 to 65 and 86ff, to avoid confusion. This draft guideline mostly uses the term "patient". To ensure the validity for the guidance for studies from early and late phases and to foster the awareness that also the patients in clinical studies are "volunteers" we propose to consistently replace "patient" and "volunteer" by "subject". The draft guideline's description of the scientific approach to drug development is very traditional and the selection of mentioned relevant aspects is not clear. Important aspects like contributions of Modelling & Simulation, genetic testing, Real World Data, innovative study designs, etc., are not presented.
26	EORTC welcomes the revision of this guideline (initially adopted in 1997), part of the "GCP renovation" endorsed by ICH assembly in January 2017. Indeed, the clinical research landscape has radically changed over the last two decades and the revision was long awaited by numerous stakeholders. As the progress in science accelerates, EORTC would like to suggest, in the spirit of quality by design proposed in the revision, to add a provision on the mechanisms and frequency of further updates (e.i. every 5 years).
27	The draft Guideline on General Considerations for clinical studies is written in very general terms and the interpretation is not always clear and easy.

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	After having read the draft, I ended up with the following questions. This guideline describes the standard development of a product. I wonder how this can be applied to the development of cancer drugs, that are in many cases given in combinations, where a single drug is not effective. I´m well aware there are other guidelines that tackle this. However, this aspect is not mentioned and could be added around line 352 where combinations are mentioned or under line 434 additional development. Another aspect that I find hard to see in this guideline is the development of drugs for orphan indications or orphan diseases. In that case it is hard to include enough subjects and the program may have to be adapted and may have to include post approval or observational studies. Something about such indications could be mentioned around line 475, enough subjects. In chapter 7, line 733, Considerations in identifying critical to quality factors, I would like to add an extra point about the material to be used to inform the patients, including the Informed Consent. It is essential that the information is understandable for the patients and that the patient understands/agrees with the critical aspects of the study and the choices that will be made. This can improve the patient compliance and thus the quality of the data and the study. When talking about Protection of Clinical Study Subjects we should be thinking not only on clinical aspects but also to include a mention to the information patients receive prior to the study, informed consent forms where benefit vs risks is well described in lay language. In the table that summarizes ANNEX 3: SELECTED EXAMPLES OF CRITICAL TO QUALITY FACTORS I cannot find any mention to patient input into the study design, I would like to see this included as a quality factor.
28	Comment: In general, the E8 text regarding Critical to Quality (CtQ) Factors does not relate clearly to the steps in the new E6 section 5.0. It would be logical that E6 would reference the critical to quality factors as part of step 5.0.1; Critical process and data identification; since the advice provided in E8 sections 3.2 and 3.3 regarding critical to quality factors and how to determine them is helpful. Similarly, E8 3.3.4 Reviewing Critical to Quality Factors; would be sensible to reference the E6 quality tolerance limits as a mechanism to manage the risks associated with the critical to quality factors. A further example is in line 136, where determining impact and likelihood of a risk is discussed but not the ability to detect issues (as stated in E6 R2 5.0.3). Proposal: Ensure that content and key terminology for risk-based quality management aspects are fully aligned between E6 and E8, even delaying the finalisation of E8, if necessary, to achieve this. This will help the reader to more readily understand what is important and determine how to put it into practice. Alternatively, both E6 and E8 document could reference a third common

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	document which would be dedicated to quality risk management in clinical trials. Comment/proposal: We suggest there should be a new section in E8 dedicated to unintentional bias and unblinding, e.g. extending current section 5.1.5 Methods to Reduce of Assess Bias. There are already several areas within the document where the risk of unintended unblinding or other potential bias is mentioned or an activity covered where it might occur. For example: 685-690; 6.1.3 Data Management should include centralised monitoring and, if it did, then there should be consideration given to the type of data review and any analysis and the impact it could have in terms of unintentional bias and unblinding. 695; Interim analysis and ongoing monitoring of data could cause unintentional bias and unblinding. 700-707; Safety Monitoring. Where safety reports are unblinded, care needs to be taken to ensure blinded staff do not receive unblinded information. 720 Data Monitoring Committee may receive unblinded information and therefore care needs to be taken to ensure blinded staff do not receive unblinded information. Comment: Annex 3 does not give enough specific indications of factors that could be practically determined as critical to quality. As such, they rather list areas where factors may lie but don't help much to recognise common examples. Proposal: More specific examples would make this annex easier to translate into practice. Furthermore, guidance or examples showing how to represent a CtQ factor would be helpful too, either in this document or a related FAQ document. In any case, while more detail would help, it would be appropriate to add a further statement that any such list cannot be exhaustive and that sponsors and investigators should establish and build a list of factors that are relevant to them and each particular study. Only ICH guidelines seem to referenced, many of which have not been revised for many years and therefore may not represent the current thinking. Proposal: Where other ICH guidelines are referenced, a caveat could be useful to encourage the reader to consider what technological and methodological advances in clinical trial conduct have been made in the meantime and how to apply the principles to current-day studies.

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29	Overall, EAHP agrees with the content of the document. Specific comments have been provided below.
31	EUCROF welcomes the opportunity to provide comments on this revised ICH E8 Guideline. The Guideline is important as medicinal products have advanced and the drug development process has progressed over the recent decades. New approaches (e.g., new study designs, use of post-approval data for regulatory purposes) have evolved and need to be taken into consideration when designing, planning, conducting, evaluating and reporting clinical trials and non-interventional studies. EUCROF has reviewed the draft guideline from a higher trial phase perspective as well as early phase perspective and submits the following comments: EUCROF suggests to include a section "SCOPE OF THE GUIDELINE", explaining that interventional and non-interventional (observational) studies (NIS) are covered in this document. This becomes clear when reading but at a relatively late timepoint. This should be clarified early on as it is not the norm for ICH guidelines. In addition, E6 explicitly states in 1.12 "The terms clinical trial and clinical study are synonymous." which is not the case for this Guideline as the term "clinical study" includes non-interventional studies. Clear terminology is a prerequisite for generating quality. Question: why is the term "non-interventional" (as used by FDA and many other authorities) not used, but only "observational"? NIS is widely used by the "post-approval community". Section 3 "Designing Quality into Clinical Studies" is overlapping to large extent with E6 section 5.0. However, there is not a single reference to E6. E6 offers more precise procedures regarding the consideration of "Critical to Quality" factors (risks), for example, the consideration of probability, impact and detectability. The latter is missing in this guideline. Section 3 of this guideline should be harmonised with E6 section 5.0 in order to avoid confusion. Adaptive study designs are mentioned only one time in the context of confirmatory (Phase 3) trials (section 4.3.2). This is not sufficient as adaptive designs can be applied across all phases of clinical research, from early-phase dose escalation to confirmatory trials. In addition, more innovative study designs (basket, umbrella, platform trials) are not mentioned at all. In general, there should be more referencing to early phases throughout the document. Early phase clinical trials in healthy volunteers has not been given much attention and this therefore renders the guideline not applicable in some sections. ICH E6 is mentioned solely in the context of "conduct" of a clinical study. Examples: 1. Line 37-39: Important principles of ethical conduct of clinical studies and the protection of subjects, including special

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	populations, are stated in other ICH guidelines (ICH E6 Good Clinical 38 Practice, Risk based quality management R2) 2. Annex 2: Table **Conduct and reporting:** E3 Clinical Study Reports E6 Good Clinical Practice However, E6, especially after the enforcement of R2, contains important elements for the design and planning of a clinical study (so does E19). It is not correct to limit the scope of E6 to the conduct of a clinical study. Along the same line, E19 cannot be limited to safety reporting. Any guideline addressing a risk-proportionate approach to a clinical study also addresses the design and planning of that study. What is the audience of the revised guideline? The guideline is teaching basic knowledge about clinical trials to a broad audience. Many sections contain descriptions of long-used "middle-of-the-road" principles and practices. It would be very helpful to also learn about new approaches that mirror the more recent developments. What is the purpose of the revised guidelines? As mentioned above, the draft seems to concentrate on standard approaches in clinical development. It therefore meets its first objective (to describe internationally accepted principles and practices in the design and conduct of clinical studies that will facilitate acceptance of data and results by regulatory authorities) only to a limited extent. The guideline seems to focus on trials in small molecules and only rarely and punctually mentions newer and advanced therapies. EUCROF would like to bring to the attention of the expert group that there is ongoing discussion about the term "subject" (for example in the UK, but also in the US). To talk about trial/study participants as "subjects" is increasingly seen as disrespectful by patient organisations, ethics committees and - of course – individuals themselves who make a valuable contribution to clinical research. EUCROF is well aware that this terminology has been used from the outset of the ICH initiative, however times have changed and the involvement of patient representatives in the design and planning of clinical studies is increasing. It is understandable that an individual does not want to be called a "subject". Maybe ICH should start thinking about an alternative terminology (e.g., study/trial participants).

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33	We very much appreciate the proposed renovation of the "ICH guideline E8 (R1) on general considerations for clinical studies" and its strong focus on quality of design and of risk based approaches. However, as an academic network, we have some general concerns. As we already expressed in our comment to the "ICH Reflection on "GCP Renovation": Modernization of ICH E8 and Subsequent Renovation of ICH E6", the ICH guidelines, and especially E8 and E6 are perceived as the standard setting guidelines for clinical trials in general, without restriction to drug development and purely regulatory aspects. In the absence of other guidelines / international standards and induced by the title "good clinical practice", which is overarching, ICH E6 (and in consequence E8) are applied to all interventional clinical research (e. g. by legal bodies, funders or inspectors). In our opinion, the proposed text focusses too much on clinical development programmes. We would very much appreciate broadening the focus, taking into account academic, publicly funded research involving drug therapies, but also other therapeutic options. The current ICH E8 guideline explicitly states in its objectives: "The principles established in this guideline may also be applied to other clinical investigations (e.g. radiotherapy, psychotherapy, surgery, medical devices and alternative therapies).". We wonder why this statement has been skipped. The vast majority of medicinal products are intended for treatment. However, medicinal products may also used for diagnostic purposes (e.g. tracer or contrast agents in imaging). The specific issues of diagnostic trials (as addressed e.g. by Sackett et al, BMJ 2002;324:539) should be at least mentioned.
34	There are two significant changes in this document by comparison with the original version. The first is a **welcome emphasis on the principles of Quality-by-Design**, focussing on issues that matter (to the participants in the study and the results that will influence care of future patients). The second is an **unhelpful change in scope from clinical trials to clinical studies**. This is problematic for a number of reasons: First, it makes the contents of the rest of the document less clear (bouncing between interventional and observational studies, randomized and non-randomized designs, etc); secondly it strays into areas beyond regulatory decision-making (for example "other health policy decisions" [line 7]) without including the relevant stakeholders; and thirdly, it invites application of these guidelines to areas of epidemiological and clinical research for which these guidelines were never initially intended (e.g. studies of risk-prediction, disease causality, biobanking). Much of the document is taken up with simply listing and describing (at a fairly superficial level) the types of study that can be

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	done (section 4), the elements of design (section 5) and conduct (section 6). In each case, the information is not much more detailed than that which can be found from a quick internet search of lay-focussed websites and there is little or no guidance on the pros and cons of different approaches. (For example, why do randomized designs deal so effectively with bias and what is the influence of different types of error on the reliability of the results in this context?). The impact of these pages and pages of descriptive non-guidance is that the importance of quality-by-design gets lost. Quality-by-Design starts with focussing on what matters – unfortunately this guideline fails to do that! **The guideline would be greatly improved by (A) reverting the focus to clinical trials and (B) deleting much, if not all, of sections 4-6 so that the final contents includes General Principles, Designing Quality into Clinical Studies, and Considerations in Identifying Critical to Quality Factors.**
35	In general, the document is written with commercial sponsors in mind, without really addressing the non-commercial/academic aspects of clinical research, which can have an impact on prescribing practice and an impact on public health. This document must be applicable to both commercial and non-commercial research or there is the potential that alternative forms of GCP may be followed for non-commercial work in the future such as the ICH version being proposed by the Bill and Melinda Gates Foundation. https://wellcome.ac.uk/news/pivotal-moment-clinical-trial-regulations
36	We welcome the revision of the ICH E-8 guidelines on 'General Considerations for Clinical Trials'. We have identified a number of areas where we would like to see further development, particularly regarding recognition of the roles and perspectives of health technology assessment bodies in medical decision making, and the level of detail concerning study quality. Detailed comments are provided below. Health technology assessment The clinical development of medicines aims to address the needs of both regulators by demonstrating the efficacy and safety of new medicines, and health technology assessment (HTA) agencies and payers by demonstrating the value of these medicines to healthcare systems around the world through relative effectiveness and sometimes also cost-effectiveness analyses. The revised guideline does not currently adequately reflect the roles and perspectives of HTA bodies in medical research and regulatory decision making. Internationally, HTA bodies have an important role in informing decisions about the reimbursement of medical technologies [1]. HTA bodies are heavily dependent on the evidence generated on treatment effectiveness from randomised controlled trials (RCTs)

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	in their assessments [2]. It is therefore essential that the evidence generated from RCTs is relevant not just to regulators but also to HTA bodies. While regulators are primarily concerned with treatment efficacy and safety, HTA bodies are also interested in the clinical and, sometimes, cost effectiveness of the medical technology in routine clinical practice compared to the next best alternative. This difference in focus can lead to important differences in evidence requirements, including in the comparator(s), outcomes, and estimands [3]. The importance of reflecting these differing perspectives in study design is well recognised. Since 2010, the European Medicines Agency (EMA) and EUnetHTA, an umbrella organisation to which many HTA bodies in Europe belong, have established a program of joint scientific advice, in which manufacturers can receive advice on study design and evidence requirements from both the EMA and multiple HTA bodies simultaneously [3]–[5]. Failing to provide appropriate evidence to HTA bodies means that they must often rely on real world data sources to supplement the evidence base, which may be subject to bias [6]. Accounting for the evidence requirements of both regulators and HTA bodies in study design avoids the need for duplication of evidence, provides more robust evidence, and will ultimately lead to better decisions being made. We therefore call for the explicit incorporation of the HTA perspective into the revised ICH E-8 guidelines. Specific changes we recommend are as follows: • Page 1, line 7. Amend to read: "...support regulatory, health technology assessment, and other health policy decisions." • Page 1, line 27. Add "health technology bodies and healthcare professionals" to the list of stakeholders. • Page 3, line 60. "decision making" should be defined and include regulatory decisions (i.e. marketing authorisation) and reimbursement decisions, when applicable. • Page 3 line 76. The heading should be rephrased "Stakeholders input into study design", and an additional paragraph added recognising the importance of consulting other stakeholders, including HTA bodies and regulatory authorities, during the clinical development process, particularly in the design of pivotal trials. • Page 7 section 3.3.3. "Engaging with stakeholders in study design". The first sentence line 190 should be changed as follows: "Clinical study design is best informed by input from a broad range of stakeholders, including HTA bodies, patients, treating physicians and informed by certified clinical guidelines (from HTA agencies and learned societies)."

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	• Page 4 line 215. After "with regulatory authorities" add "and other relevant stakeholders (e.g. health technology assessment bodies)." • Page 8, line 204. The following sentence should be added: "The technology value proposition should be devised early in the clinical development process. Evidence aimed at informing reimbursement decisions should be integrated early in the clinical development, and companies should consider engaging with HTA bodies to realise this." Study quality Discussion of study quality in sections 3.1 to 3.3 would benefit from a more concrete definition of quality and greater detail as to how quality can be assured. The quality of study conduct and the protection of patients are fundamental elements of the conduct of clinical trials, however these do not guarantee that studies will provide robust answers (especially unbiased estimates of treatment effects) to meaningful scientific questions. Other criteria pertaining to study quality which should be better defined and more fully addressed in the guidelines are: description and justification of the trial design, maintenance of the scientific integrity, quality assurance of trial conduct and optimisation of clinical feasibility, assurance of the safety of the trial participants, maintenance of data integrity, reassessment of benefit-risk balance at critical steps throughout the clinical trial, validation of companion diagnostics (when appropriate) and data transparency. The trial design should be described and justified in a clear, practical, and focused protocol. Key elements of study design include the magnitude of the expected benefit, its justification and sample size, planned analyses (including interim analyses), randomisation (whether fixed allocation or adaptive), strategies to avoid unblinding by patients and investigators, strong justifications for any cross-over or treatment switching during the study, study setting, study duration, the rate of withdrawal and follow-up of patients, and the method of ascertainment of key outcomes. These aspects are not currently discussed in sufficient detail. Greater emphasis should be placed on data collection to ensure complete and high-quality data. This relates to baseline characteristics of patients, adherence to study interventions, use of concomitant interventions, study outcomes (primary, secondary, and other), and adverse events. Concrete proposals should be provided for minimising missing data, data errors, excess variability, and delayed data submission, which could include the design of protocol and manual, the development of forms and data entry tools, training and certification, techniques to reduce variability including central adjudication of events, data entry

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	and electronic source data. Another important aspect to study quality, which should be acknowledged, is the use of results from previous studies to inform trial design. For example, the dose selection in a pivotal efficacy study should be informed by dose-finding studies. There is an important element of continuity and logic in the clinical development which is not currently reflected in the guideline. Other comments Below we list additional comments: • The terms "interventional studies", "observational studies", and "decision makers" need to be explicitly defined. • It is important to clarify that this guideline addresses clinical trials as defined in ICH E6, i.e. "Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy." • It may be important to highlight that not all the medicinal products follow the traditional clinical development described in the guideline. Some products may be licensed on the basis of early (e.g. phase 2) trials. Other products are developed in other clinical development approaches (e.g. adaptive designs, seamless phase 2/3 designs and master protocol studies) which pose specific issues during the design, conduct and analysis, which should also be mentioned in the guideline. • Pages 2, lines 54-56. The expressions "sound scientific principles" and "important questions" are too vague. • Page 3, section 2.3 "Patient input into study design". Line 77: the sentence should read as follows: "Consulting with patients, carers and/or patient organisations in the design, planning and conduct…". Line 83: the sentence should be changed as follows: "meaningful to patients including measurement of the healthy related quality of life, selection of the…". • Page 4, lines 107-108. Is it not clear what constitutes "appropriate subjects". The sentence should be rephrased as follows: "the eligibility criteria should be devised to ensure the selection of patients with the disease or molecular/genetic profile of interest, and at the correct point in the treatment pathway. The criteria should both ensure that the clinical trial has a good internal and external validity (i.e. the generalisability of the trial results to the patients treated in clinical

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	practice)." • Page 4, line 111. The bullet beginning "endpoints that are well-defined and measurable" should be rewritten as "biological endpoints or clinically relevant endpoints that are well-defined and measurable…" • Page 4, line 113. An additional bullet should be added "unless proven unethical or not feasible, studies should be comparative and include an inactive or an active comparator which reflects the current standard or best supportive care. The conduct of non-comparative studies should be avoided and the rationale for conducting non-comparative studies should be duly justified." • Page 4, line 113. An additional bullet point should address the question of study duration and follow-up of patients. • Page 5, line 141. Recommendations regarding proactive communication should be explicit about which stakeholders this communication should be with, and what information should be communicated. • Page 10, line 274. Replace the word "temporal" by "sequential". • Page 11, line 313. The sentence should be amended to read "If a potential for drug-drug interaction is suggested by the adverse reactions, pharmacological (e.g. prolonged QTc) or metabolic profile..." • Page 16, line 455. Add "The eligibility criteria should be balanced to ensure an appropriate internal and external validity of the trial. In that respect, the selection criteria should use consensual criteria to define the disease, recruit patients who have followed a clinically relevant treatment pathway and reached the point in the treatment pathway at which the new investigational product is intended to be used. The exclusion criteria concerning other underlying conditions should be limited to ensure the generalisability of the trial results and that important populations of patients are not unduly excluded from entering the trial (e.g. HIV positive patients). It is recognised that the efficacy of medicines can be difficult to establish in frail patients. However, frail patients can constitute an important part of the patient population in some conditions, therefore, patients with poor performance status should not be systematically excluded from entering clinical trials. Finally, patients recruited in the trial should be offered a standard of care which reflects the clinical practice usually offered to the patients to whom this product is intended to be used." • Page 17, line 477. After reference to ICH E9, add: "However, only focusing on reaching statistical significance should not be the only purpose of a clinical study. The clinical studies should also be designed to provide meaningful clinical benefits, therefore, the magnitude of the effect size should also be considered in the primary hypothesis of the trial and therefore

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	in the sample size calculations." • Page 19, line 521. Add "feasibility of conducting indirect treatment comparisons" after feasibility of conducting the study. • Page 19, line 544. The following sentence should be added: "Assessments of the effects of interventions on patients' (and sometimes carers) functioning and quality of life are critical components of clinical trials. The outcomes used in the clinical studies should therefore include a set of health-related quality of life measurements. Ideally this should include both a generic and a disease specific quality of life scale". • Section 5.1 "Study design". A paragraph on the study duration should be added. As a general rule, the duration of the study should be long enough to ascertain the efficacy of the product (both in responders and non-responders), the maintenance of the treatment effect and should ideally reflect the treatment duration in clinical practice and provide information on the long term outcomes of the disease. The follow-up of the patients should document the course of the disease after the withdrawal of the treatment. • Page 18, section 5.1.3, "Control group". The guideline should emphasise that comparative randomised clinical trials still represent the gold standard which allow an unbiased estimate of the treatment effect. Therefore, any deviations from this design (e.g. single arm trials) should be duly justified. • Page 20, section 5.1.5. "Methods to reduce or assess bias" should discuss all the possible sources of bias including the randomisation and blinding (including the measures put in place to minimise the risk of unblinding by investigators), the deviations from intended interventions, the missing outcome data, the measurement of the outcomes and the selection of reported results. • Page 21, line 596. The sentence should be redrafted as follows: "The study protocol should be finalised before the start of the study. The statistical analysis plan needs to be finalised before the unblinding of study data especially if (unblinded) interim analyses are conducted during the study. In the case of an open-label study, it should be finalised before the start of the study." • It should be recognised that some products are developed in other clinical development approaches (e.g. adaptive designs, seamless phase 2/3 designs and master protocol studies) which pose specific issues during the design, conduct and analysis. It would be relevant to define these different study types and address the issues which are specifically posed by some of these studies (see e.g. Sudhop et al. 2019 [7]).

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	• Current debates over the role and interpretation of the P-value should be addressed in the "statistical analysis" section of the guideline (i.e., section 5.1.6). The guideline should also put the emphasis on the effect size and its clinical relevance. • Finally, a clinical trial development programme should be supplemented by an assessment of the evidence gaps and a programme aimed at addressing them. Such programme should be jointly approved by regulators and HTA bodies. References [1] L. Barnieh et al., "A Synthesis of drug reimbursement decision-making processes in organisation for economic co-operation and development countries," Value Heal., vol. 17, no. 1, pp. 98–108, 2014. [2] A. Makady, R. ten Ham, A. de Boer, H. Hillege, O. Klungel, and W. Goettsch, "Policies for Use of Real-World Data in Health Technology Assessment (HTA): A Comparative Study of Six HTA Agencies," Value Heal., vol. 20, no. 4, pp. 520–532, 2017. [3] G. Tafuri et al., "How aligned are the perspectives of EU regulators and HTA bodies? A comparative analysis of regulatory-HTA parallel scientific advice," Br. J. Clin. Pharmacol., vol. 82, pp. 965–973, 2016. [4] M. Berntgen, A. Gourvil, M. Pavlovic, W. Goettsch, H. G. Eichler, and F. B. Kristensen, "Improving the contribution of regulatory assessment reports to health technology assessments - A collaboration between the european medicines agency and the european network for health technology assessment," Value Heal., vol. 17, no. 5, pp. 634–641, 2014. [5] T. Wang, N. McAuslane, L. Liberti, H. Leufkens, and A. Hövels, "Building Synergy between Regulatory and HTA Agencies beyond Processes and Procedures—Can We Effectively Align the Evidentiary Requirements? A Survey of Stakeholder Perceptions," Value Heal., vol. 21, no. 6, pp. 707–714, 2018. [6] D. A. Grimes and K. F. Schulz, "Bias and causal associations in observational research," Lancet, vol. 359, no. 9302. pp. 248–252, 2002. [7] T. Sudhop, N. C. Brun, C. Riedel, A. Rosso, K. Broich, and T. Senderovitz, "Master protocols in clinical trials: a universal Swiss Army knife?," The Lancet Oncology, vol. 20, no. 6. pp. e336–e342, 2019.
37	General comment. The intention of this document is to serve as a guideline. However, it contains abundant educational information; chapter 4 discusses general principles of drug development and chapter 5 discusses the elementary ingredients of a clinical study; all this

Stakeholder number	General comment (if any)
	can be found, and in much more detail, in books. Other sections like chapter 2.1, about the protection of subjects, is already covered by other ICH guidelines like E6 and E7. We have the opinion that such didactic sections should be limited as it distracts from the purpose of this document. Being economical with information would make this guideline more workable. Also, it can be assumed that this information is known to scientists; the targeted group for this document. Moreover, limiting the document to guideline information provides the opportunity to describe other sections in more detail; e.g. page 6 mentions that "a culture that values and rewards critical thinking and open dialogue", page 7 mentions "encouragement of a proactive dialogue", but does not indicate how this can be achieved. More guideline on the practical implementation of these otherwise vague advices would improve this document.
38	Comment received on the ICH Admin box: Comment 1: **Pharmaceuticals and Medical Device Regulatory Science Society of Japan** The scope of "clinical study" targeted by E8 guideline has been broadened from the previous E8 description focusing on Clinical Trial to Clinical Study including observational study. However, the scope in this document is unclear only from "1.OBJECTIVES OF THIS DOCUMENT". Therefore to clearly show the scope of the guideline first by appending the following is important: "In this document, Study Data refer to Primary Data and Secondary Data (existing electronic health records etc.)."
40	Various comments received on the ICH Admin box: Comment 2: **From an individual – no affiliation provided** I reviewed the draft for information on the difference between Phase IIIb and IV in clinical trials and this sub division is not considered in the guide (4.3.2 Exploratory and Confirmatory Studies (usually referred to as Phase 2 or Phase 3)). It would be important to include this in order to have a basis on which to observe the correct phase with which the pharmaceutical industry presents the protocols for its evaluation. Stakeholder no. 40

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes
1	13	**Comment:** Consider change in title. **Proposed Change:** "General Considerations for Clinical Development Planning and Clinical Studies"
1-20	26	**Comment:** Term "studies" is used in the line three and throughout the entire document. Previously, ICH was using a narrower term of trials, which only refers to the interventional studies, while current revision use the larger terms of studies on purpose, to cover not only interventional studies, but also observational research. Though ICH work is centred on the process of drug approval, not all clinical studies serve this purpose. Many clinical studies (not only the phase 4) may be conducted by sponsors different from marketing authorisation holders (MAH), including non-for profit organisations, university hospitals etc… for the purpose of ensuring continuous progress of the quality of healthcare. Proposed revision does not specifically state that it only applies to studies part of the drug registration dossier and seems to target a larger application. However, despite the risk based approach and "fit for purpose" principle, some recommendations are still too restrictive and can hinder clinical research in its current diversity. If the intention is to cover the entire lifecycle of the product (referred in several lines) and to regulatory and other health policy decisions, other stakeholders (such as academia, HTA bodies, patients etc…) shall be deeply involved in the drafting of the new version of the guideline from the onset (as opposed to the indirect implication through the public consultations). In case, this is not acceptable, ICH shall clearly state its documents apply for studies aiming to be part of the regulatory submission dossier and only to be considered if applicable for studies with different purposes. **Proposed change:** EORTC would suggest composing a multi-stakeholder group to re-design the proposed revision in order to have a comprehensive and consistent document addressing the entire product lifecycle, taking into account roles, requirements,

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		specificity and value of contributions of different stakeholders. If this is not possible in short term, ICH shall be clear current revision shall only apply as such to the marketing authorisation and follow-up.
Table of contents	8	**Comment:** Please add a glossary of key terms **Proposed change:** Please add definitions of key terms into a glossary; Efficacy: does the drug work in selected patients in specialised centers? Comparator is most frequently placebo; drug adherence is high. Effectiveness: does the drug work in unselected patients in real world settings? Comparator is most frequently other active treatments (drugs or non-pharmacological therapies); drug adherence is low(er).
3	20	**Comment:** Specification of "medical interventions" may create confusion on the field of application of E8R1 and reader may understand it only applies to interventional trials. E8R1 also address in section 4.3.3 and section 5 situations applicable to observational studies. **Proposed change:** Removal: "Clinical studies are conducted to provide information…"
3-4	3	**Comment:** Medical interventions and drugs/medicinal products do not necessarily coincide. **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		ultimately improve access to safe and effective TREATMENTS with meaningful impact on patients
3-4	16	*"Clinical studies of medical interventions are conducted to provide information that can ultimately improve access to safe and effective drugs with meaningful impact on patients."* **Comment:** The word "safe" might be misleading, as the objective is to improve access to drugs that have a positive benefit/risk ratio, or for which the benefits outweigh the risks. But no medicines are safe. **Proposed change:** Clinical studies of medical interventions are conducted to provide information that can ultimately improve access to drugs whose benefits outweigh their risks with meaningful impact on patients.
3-4	33	**Comment:** Medical interventions are not limited to drug application alone, but include a broad range of other therapeutic options. **Proposed change:** … access to safe and effective **therapies** (instead of "drugs")…
3-5	9	**Comment:** Clinical studies are not only used to improve access to drugs. Although this may be the focus of pharmaceutical companies when performing clinical trials in preparation of marketing authorisation applications, the definition of the purpose of clinical trials is wider. **Proposed change:** Change sentence: Clinical studies of medical interventions are conducted to provide objective information on the efficacy and harms of applying these interventions to participants with the overarching aim of concluding on the effects this intervention will have when used in patients.
3-5	13	**Comment:** On line 3, the objective of the guideline is written as "Clinical studies of medical interventions are... ", which can be read that

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		scope of the guidance is interventional trials. On the other hand, line 31 describes that the term "clinical study" in this document is meant to refer to a study of a medicinal product in humans, conducted at any point in a product's lifecycle; which can be read that the guidance scope is not limited to interventional trials. In addition, the subsequent content seems to describe guidance for clinical studies including observational research. If the "clinical study" referred to in this guideline includes not only interventional studies but also observational studies, we propose revision of the description of "Objectives of this Document". **Proposed Change:** "Clinical studies of medicinal products are conducted to provide information that can ultimately improve access to safe and effective drugs with meaningful impact on patients, while protecting those participating in the studies."
4	1	**Comments:** "access to safe and effective drugs" – perhaps limits documents to clinical studies and trials only of medications. **Proposed change**: "access to safe and effective interventions. These interventions may include but are not limited to drugs/medications, surgical operations, diagnostics, medical devices, screening programmes and healthcare therapies"
4	20	**Comment:** Improvement of the access to safe and effective drugs is a continuing improvement process. **Proposed change**: " …improve access **to safer and more effective** drugs…"
4	24	**Comment:** As the guideline refers to the general term "clinical studies" it should principally be applied to all type of clinical research in humans. This also includes medical devices, radiotherapy, etc and therefore not only the term "drug" should be used.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: Clinical studies of medical interventions are conducted to *collect information in a systematic and scientific sound manner* that can ultimately ~~improve~~ broaden access to safe and effective ~~drugs~~ *treatments* with meaningful impact on patients,….
5	20	**Comment:** " protecting those participating" can be clarified. **Proposed change:** " …protecting **safety, integrity and confidentiality of research participants**."
5	31	**Comment:** The term quality in clinical trials/studies should be defined (protection of trial/study participants and robustness and reliability of trial/study data) to remind everybody what this document is about.
5-7	13	**Comment:** In addition to quality, it is important that clinical studies enable sufficient flexibility in their approaches to accommodate modern trial designs and technological advances. **Proposed change:** "This document focuses on designing quality and flexibility into clinical studies, considering the diversity of clinical study designs and data sources used to support regulatory and other health policy decisions."
7	3	**Proposed change:** add "for example, development of clinical practice guidelines".
7	36	**Proposed change:** *Page 1, line 7*. Amend to read: "...support regulatory, health technology assessment, and other health policy decisions."

Line no.	Stakeholder no.	Comment and rationale; proposed changes
9-11	24	**Comment:** Today the need for acceptance of clinical research study results is not limited anymore to regulatory authorities but also to HTA Bodies, the healthcare professional community and the health-interested public. This would then also include IITs performed to investigate treatment optimisation options relevant for life-cycle aspects. **Proposed change:** … by regulatory authorities*, Health Technology Assessment bodies, healthcare professionals and the health-interested public*
9-20	33	**Comment:** Focus is too restricted to drug development and regulatory aspects
13-14	20	**Comment:** Objective 2 appears to be vague and may not always be easily understood. Proposal of rephrasing for clarification. **Proposed change:** " …including the identification of factors that are critical to the quality of the study **during study planning**, and the management of risks to those **critical** factors during study conduct **and after**."
14	24	**Comment:** The need for quality considerations are equally relevant for the executing professionals, not just for the planning. **Proposed change:** …during study planning *and execution* …of factors that are critical to….
17-18	20	**Comment:** Objective 3 may not always be easily understood. Proposal of rephrasing for clarification. **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		” …and describe **the characteristics that support the determination of critical quality factors for those studies to ensure the protection of study subjects**….”
17-20	24	**Comment:** Sentence is too long. Please make shorter sentences to ease understanding.
18	1	**Comments:** “study subjects” - Preferred term would be participants. **Proposed change:** “study participants”
21-22	23	**Comment:** “Provide a guide to the ICH efficacy documents to facilitate user's access…”. Mentioning the ICH safety seems to have been forgotten. **Proposed change:** “Provide a guide to the ICH efficacy *and safety* documents to facilitate user's access
21-22	25	**Comment:** “Provide a guide to the ICH efficacy documents to facilitate user's access…”. Mentioning the ICH safety seems to have been forgotten. **Proposed change:** “Provide a guide to the ICH efficacy and safety documents to facilitate user's access
27	7	**Proposed change:** add “Ethics Committees” between investigators and regulatory authorities

Line no.	Stakeholder no.	Comment and rationale; proposed changes
27	13	**Comment:** if "patients" are mentioned throughout the document does it then mean "trial subjects" in general (hence including healthy volunteers)? Does it deliberately distinguish between the patients and human- or study-subjects (as referred to in line 29 and/or line 36)? **Proposed change**: if this text should be revised to "subjects" or "study subjects" or "healthy volunteer or patient subjects" where appropriate **Comment:** IRB/IECs are not considered here as important players. **Proposed change:** "…from the perspective of sponsors, investigators, regulatory authorities, patients and IRB/IEC…"
27	33	**Proposed change:** Please consider including further stakeholders, e.g. health policy makers, public funding bodies
27	36	Page 1, line 27. Add "health technology bodies and healthcare professionals" to the list of stakeholders.
31	30	**Proposed change:** refer to a study of *one or more medicinal products*
31-32	5	**Comment:** Why restrict ICH to medicinal products ? Harmoniation of the design of clinical studies would also be highly relevant for medical devices, and even other interventions.
31-32	9	**Comment:** Although ICH E8 focusses of clinical trials relevant for the approval of medicinal products, the general principles outline are valid

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		for other purposes, too. **Proposed change:** Add: Nevertheless, general principles are valid for clinical trials irrespective of interventions investigated.
31-34	2	**Comment:** it should be clarified if this document also applies to integrated medicinal products with a device components and/or medical device clinical investigations. **Proposed change:** as applicable according to the clarification
32	12	**Comment:** guidance covers medicinal products and might be enlarged to combination which fall in definition of clinical trials **Proposed change:** enlarge the definition of scope to CT accordingly
32-33	13	**Comment:** Please clarify if the term "drug" or "medicinal product" in this guidance includes not only vaccines and biological products, but also regenerative medical products etc. and nucleic acid drugs.
32-33	16	*The term "drug" should be considered synonymous with "medicinal product," including vaccines and biological products* **Comment:** To clarify whether this also includes herbal medicinal products, pharmacy preparation (magistral formula), advanced therapies, or food supplements sold with health claims/benefits
34	8	**Comment:** The term "**drug approval**" refers to obtaining marketing authorization for the *drug*.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: Please add a second major aim of clinical research, i.e. the development of accurate evidence-based clinical practice guidelines. The term "**clinical practice guideline**" refers to developing and using guidelines for the optimal management - including diagnosis and (pharmacological and non-pharmacological) treatment - of patients with the disease of interest in clinical practice.
35-85	34	**Comment:** This contains a very helpful new wording on the importance of Quality by Design (section 2.2) and it is good to see that the role views of patients into study design is recognised (section 2.3) This section (and others in the document) fail to articulate the need to take an approach that is proportionate to the additional risks (relative to usual care and practice) that a particular trial poses. MHRA guidance on risk-adapted approaches to the management of clinical trials[1] articulates this quite nicely and would provide a reasonable basis for the revised E8 guidance.
37-40	32	**Comment:** **37** Important principles of ethical conduct of clinical studies and the protection of subjects E2A (clinical safety data management), E3 (clinical study reporting), E5 Ethnic Factors, E8 (general considerations for clinical trials), E9 (statistical principles) E12 Clinical Evaluation by therapeutic Category E19 Safety data collection **38** including special populations, are stated in other ICH guidelines (ICH E6 Good Clinical **39** Practice, ICH E7 Clinical Trials in Geriatric Populations, ICH E11 Clinical Trials in the **40** Pediatric Population, and ICH E15 Definitions in Pharmacogenetics / Pharmacogenomics, E16 Qualification of Genomic Biomarkers ICH E18 Genomic Sampling).
42-43	26	**Comment:** Investigator (or treating physician), Sponsor and Ethical Committee have indeed each their set of responsibilities in a clinical

[1] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/343677/Risk-adapted_approaches_to_the_management_of_clinical_trials_of_investigational_medicinal_products.pdf

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		investigation and specifically protection of human subjects. However, EORTC believes these responsibilities are quite distinct to the extent that it may not be really shared as per se. **Proposed change:** EORTC would suggest to use the following wording instead: "The investigator and sponsor collaborate and ensure they assume their respective responsibilities in order to guarantee the adequate protection of study subjects in compliance with recommendations of and through the dialogue with the Institutional Review Board / Independent Ethics Committee (IRB/EC)."
42-44	12	**Comment:** In the EU, the Regulatory Authorities is also a player in the protection of study subjects (according to directive 2001/20/EC and Regulation EU No 536/2014). **Proposed change:** Suggestion to add Health Authorities
42-44	20	**Comment:** Addition of some wording quoting E6 as a reference is suggested since the responsibility for the protection of subjects is complementary but does not overlap between PI, Sponsor and IRB. This phrase may be understood as if the responsibility to protect subjects is implemented in the same way or accountable equally to PI Sponsor and IRB. **Proposed change:** "**As further described in E6 guideline**, Investigator and Sponsor **have responsibilities to protect** study subjects together with the Institutional review Board/Independent Ethics Committee."
42 - 44	24	**Comment:** "Investigator and sponsor share responsibility for the protection of study subjects together with the Institutional Review Board/Independent Ethics Committee" This is not clear. Responsibility should not be shared. According to Declaration of Helsinki, Principle #4: It is the duty of the

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty. And Principle #9: It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent. This ICH E8 (R1) guideline should make very clear that the responsibility for life, health, well-being, dignity, privacy, confidentiality and right to self-determination of the study participant resides with the investigator. Due to his/her responsibility he/she should not accept to participate in a study that negatively impacts those rights of a study participant. The sponsor is responsible for proposing a study protocol and regulatory/quality environment that support the investigator in fulfilling his/her obligation towards the study participant. The IRB/IEC advises the investigator whether the study is ethically acceptable or not or under which conditions. The competent authorities give approval to the protocol and application dossier only when the benefit-risk balance is acceptable, but the responsibility for the study participants resides with the physician. **Proposed change:** The investigator *has responsibility* for the protection of study subjects *and is supported* by the sponsor, Institutional Review Board/Independent Ethics Committee *and competent authorities*
43	21	*"The investigator and sponsor share responsibility for the protection of study subjects ~~together with~~ supported by the Institutional Review Board/Independent Ethics Committee".* **Comment:** From a legal point of view, the sponsor and the investigator are responsible for the wellbeing of study subjects, not the IRB/IEC.
45	29	**Comment:** The protection of patient data is important, both for privacy reasons and also connected to paragraph 6.1.3 "data management ". Data protection should be carried out in accordance with GDPR.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
45-46	16	*"The confidentiality of information that could identify subjects should be protected in accordance with the applicable regulatory and legal requirement(s)"* **Comment:** Often the difficulty is to identify which legal requirements apply: the legal requirements where the sponsor is registered? The principal investigator? The local investigator? What about patients who need to travel to a different country to participate in the study? Legal requirements of the clinical trial site? Of country of residence? As a general rule, maybe to propose the legal requirements in country where trial subject resides **Proposed change:** The confidentiality of information that could identify subjects should be protected in accordance with the applicable regulatory and legal requirement(s) in study subject' country of residence.
47	24	**Comment:** It is mandatory that information is not only available but also systematically compiled, evaluated and understood. **Proposed change:** Before initiating a clinical study, sufficient information should be available, *compiled, evaluated and understood* to ensure that the safety *of a drug is within acceptable limits* for the planned study in humans.
47	37	"Before initiating a clinical study, sufficient information should be available to ensure that the" **Comment:** sufficient is too vague; should be more specific
47-48	2	**Comment:** In case of applicability also for integrated products (drug-device combinations), there should also be sufficient information available prior to the study on the acceptability of the device part. See also draft guidance EMA/CHMP/QWP/BWP/259165/2019

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: **....** for the planned study in humans. Emerging clinical and non-clinical data should be reviewed and evaluated, as they become available, by qualified experts to assess the potential implications for the safety of study subjects. **In case of drug-device combinations or stand-alone devices, the device component should be as advanced as possible, given the potential impact on safety and efficacy in terms of administration of the drug, and clinical and non-clinical data on this part should be considered in the evaluation.**
47-48	15	**Comment:** The terms "sufficient" and "acceptably" are too vague. Patients involved in clinical trials and clinicians performing such trials need to be safe and protected by a text that uses scientific vocabulary rather than general terms that cannot be evaluated.
47-48	25	**Comment:** "Before initiating a clinical study, sufficient information should be available to ensure….". Having the information is not enough. Recent disasters in exploratory phase studies were not caused by a lack of information but because the available information was not understood. **Proposed change:** "Before initiating a clinical study, sufficient information should be available *and understood* to ensure….".
48	3	**Comment:** Before initiating a clinical study, sufficient information should be available to ensure that the drug is acceptably safe **Proposed change:** "acceptably safe to humans"; Besides, "acceptably safe" is unspecific. Maybe a referral to standard/regulations on pre-clinical studies could help.
48	12	**Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		emerging clinical,non clinical and quality data should be…
48	24	**Comment:** It is not only the drug but also the administered dose that need to be safe. **Proposed change:** …to ensure that *the administration of the* drug….
48-50	15	**Comment:** Nowadays, this sometimes results in all SAE's being sent to ALL investigators using a drug in a trial. A better definition of "qualified experts" would be helpful. **Proposed change:** Emerging clinical and non-clinical data should be reviewed and evaluated, as they become available, **by the study sponsor** to assess the potential implications for the safety of study subjects. **The study protocol should describe the procedure.**
49	12	**Comment:** include a reference to competency here, just because someone is qualified does not mean that they are competent **Proposed change:** Emerging clinical and non-clinical data should be reviewed and evaluated, as they become available, by qualified and competent experts to assess the potential implications for the safety of study subjects
49	13	**Comment:** unclear what the guideline considers a "qualified expert" in this context. **Proposed change:** "Emerging clinical and non-clinical data should be reviewed and evaluated. As they become available by the sponsor to assess the potential implications for the safety of study subjects."

Line no.	Stakeholder no.	Comment and rationale; proposed changes
49	35	**Comment:** include a reference to competency here, just because someone is qualified does not mean that they are competent **Proposed change:** Emerging clinical and non-clinical data should be reviewed and evaluated, as they become available, by qualified and competent experts to assess the potential implications for the safety of study subjects
50-52	32	**Comment:** 50 Ongoing and future studies should 51 be appropriately adjusted and approved as needed, to take new knowledge into consideration and to protect 52 study subjects
51	20	**Comment:** The term "knowledge" is broad and open to interpretations. **Proposed change:** "…to take new **knowledge regarding the drug** into consideration…" or "…to take new **data** into consideration…" or "…to take new **available information** into consideration…"
54-55	16	*"Clinical studies should be designed, conducted, and analysed according to sound scientific principles to achieve their objectives, and should be reported appropriately"* **Comment:** To clarify what can be considered as "appropriate reporting" **Proposed change:** Clinical studies should be designed, conducted, and analysed according to sound scientific principles to achieve their objectives,

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		and should be reported appropriately to regulatory authorities and/or to scientific journals, whether results are positive or negative.
54-55	26	**Comment:** "Sound scientific principles" is vague and may vary from the point of view of regulator, MAH, IRB/EC, investigator or scientific expert. EORTC believes that clinical studies require independent peer review, requested/organised by the sponsor, provided it could justify the independency and expertise. **Proposed change:** EORTC suggest amending the wording as follows: "… according to sound scientific principles to achieve their objectives, reviewed preferably by and independent peer review committee, and should be reported appropriately."
54-55	31	"Clinical studies should be designed, conducted, and analysed according to sound scientific principles to achieve their objectives, and should be reported appropriately." **Comment:** "appropriately" should be specified. **Proposed change:** " … principles to achieve their objectives, and should be reported ~~*appropriately*~~ *fully and accurately*."
54-56	36	**Comment:** Pages 2, lines 54-56. The expressions "sound scientific principles" and "important questions" are too vague.
55	25	**Comment:** "Clinical studies should be designed, conducted, and analysed according to sound scientific principles to achieve their objectives,

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		and should be reported appropriately". In order to protect subjects, reporting should not only be appropriate, but also in a timely matter. **Proposed change:** … and should be reported ~~*appropriately*~~ *timely and comprehensively*
56	13	**Comment:** point out that scientific questions are asked. **Proposed change:** "…clinical research is to ask important and relevant scientific questions …".
56-57	31	"The primary objective of any study should be clear and explicitly stated." **Comment:** It is not only the primary objectives (but all objectives) that should be clear and explicitly stated **Proposed change:** '~~The~~ *All* ~~primary~~ objectives of any study should be clear and explicitly stated'
56-61	26	**Comment:** Terms "important questions" and "key questions" used in lines 56 & 59 do not provide clarity in who's opinion. Experience shows that views of regulators, payers, patients and sponsors may significantly vary in the consideration of importance of research question. **Proposed change:** EORTC would suggest adding between lines 61 & 61 a clarification: "To be considered as important or key, the relevance of any questions shall be independently validated by the representatives of the patient community and expert clinicians, unless

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		questions are directly designed by them.
57	12	**Comments:** 1. add the primary endpoint should not be changed during the lifetime of the trial – reference CTFGs Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials, section 4.2; 2. Many studies now have a lot of secondary endpoints should these also be covered?; 3 How endpoints are measured should also be explicitly stated **Proposed change:** 1. add 'the primary endpoint should not be changed during the lifetime of the trial'
57	21	*"primary objectives,"* **Comment:** Many studies have more than one objective, and more than one primary endpoint (e.g. as one endpoint does not appropriately represent the relevant treatment effects, e.g. in Alzheimer's disease).
57	21	*"{...} and explicitly stated. Results of a terminated study should to be publicly made available within reasonable time, e.g. 12 months after the last study related patient visit."* **Comment:** Clarification of the requirement for transparency.
57	24	**Comment:** From the outset it should be made clear that clear objectives and robust endpoints are jointly indispensable **Proposed change:** … The primary objective *and related primary endpoint* should be clear and explicitly stated.
57	35	**Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Many studies now have a lot of secondary endpoints should these also be covered?
57	35	**Comment:** How endpoints are measured should also be explicitly stated
58	31	"Quality of a clinical study is considered in this document as fitness for purpose. " **Comment:** would not hurt to remind the reader what quality is in the context of clinical studies. **Proposed change:** "Quality in this document is considered as fitness for purpose, not violating protection of trial/study participants and robustness and reliability of trial/study data."
58-61	32	**Comment:** 58 Quality of a clinical study is considered in this document as fitness for purpose. The purpose 59 of a clinical study is to generate reliable information to answer key questions and support 60 decision making while protecting study subjects. The quality of the information generated 61 should therefore be sufficient to support good decision making. The CTTI has characterized quality as "the ability to effectively answer the intended question about the benefits and risks of a medical product (therapeutic or diagnostic) or procedure, while assuring protection of human subjects" [9]. 9. Clinical Trials Transformation Initiative. Scope statement. http:// www.trialstransformation.org/scope. Accessed 4 December 2009.
59	20	**Comment:** "…generate reliable information…" is broad and can be clarified. **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		"…generate reliable **clinical data**…"
60	12	**Comment:** quality processes should also be considered **Proposed Change:** The quality of the information generated should therefore be sufficient to support good decision making <u>whilst knowing that the processes used for the generation of the data underpin the presented outcomes.</u>
60	35	**Comment:** quality processes should also be considered **Proposed Change:** The quality of the information generated should therefore be sufficient to support good decision making <u>whilst knowing that the processes used for the generation of the data underpin the presented outcomes.</u>
60	36	**Comment:** Page 3, line 60. "decision making" should be defined and include regulatory decisions (i.e. marketing authorisation) and reimbursement decisions, when applicable.
62	11	**Comment:** This sentence is unclear and misleading. Simplifying is needed. **Proposed change:** ~~Quality by design~~ **Designing quality** in**to** clinical research ~~sets out to ensure that the quality of a study is driven proactively by designing quality into the study protocol and processes. This~~ involves the use of a prospective, multidisciplinary approach to promote the quality of protocol and process 6design, and clear communication of how this will be achieved.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
62-65	32	**Comment:** 62 Quality by design in clinical research sets out to ensure that the quality of a study is driven 63 proactively by designing quality into the study protocol and processes. This involves the use 64 of a prospective, multidisciplinary approach to promote the quality of protocol and process 65 design, and clear communication of how this will be achieved. Avoiding errors, collecting data that is fit-for-purpose, and reducing patient burden are just a few of the many benefits of applying Quality by Design (QbD)—an approach that focuses resources on the errors that matter to decision making during a trial, such as primary endpoints and patient safety. CTTI has built a suite of resources—including recommendations for monitoring, recommendations for QbD, a principles document and a QbD toolkit—that outline how to apply QbD principals in clinical trials. We are also working on new case studies, models, and other assets that will give sites the tools and confidence they need to effectively implement QbD at their organization.
63-65	20	**Comment:** This sentence appears to be potentially confusing. **Proposed change:** "**To accomplish this, a prospective, multidisciplinary approach is used, promoting both quality in the study protocol and process design as well as clear communication on how this will be achieved.**"
63 - 65	24	**Comment:** Quality by design should not only focus on study protocol and processes but needs to include the appropriateness of the human factor, the persons involved in any aspect of the clinical study. **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		… proactively by designing quality into the study protocol, processes *and study team*. This involves … to promote the quality of protocol, process design *and staff*, and clear….
66	12	**Comment:** Studies can also be conducted outside the development plan - i.e. not connected with the MAH - for example academic studies. The Lifecycle can include the use of a product in real life (e.g. off-label) so encompassing all academic research as well. The product lifecycle does not apply in the same way to non-commercial studies.
66	24	**Comment:** To be inclusive with non-regulatory/non-submission directed clinical research it should be said: **Proposed change:** Across the *research and* product lifecycle, ~~different~~ *various* types of studies….
66	35	**Comment:** Studies can also be conducted outside the development plan - i.e. not connected with the MAH - for example academic studies. The Lifecycle can include the use of a product in real life (e.g. off-label) so encompassing all academic research as well. The product lifecycle does not apply in the same way to non-commercial studies.
66-67	20	**Comment:** "…different types of studies…" : Considering Annex 1 refers to "clinical studies", suggestion to add the term clinical for consistency. **Proposed change:** "…different types of **clinical** studies…" / "…position of the **clinical** study…"
66-68	2	**Comment:** In case of applicability also for integrated products (drug-device combinations), add a reference to device-specific investigations.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: Across the product lifecycle, different types of studies, **including assessments on the medical device part, if applicable,** will be conducted with different objectives and designs.....
68-70	13	**Comment:** Suggestion to remove reference to "non-clinical" development as this guideline's scope is "clinical" development. **Proposed change:** "For purposes of this guideline, the clinical development plan is considered to cover clinical and post-approval studies (Section 4).
69	30	**Comment:** The development plan also covers the manufacturing of the product. Either include this here or state that this is not considered as part of this GL but dealt with in specific ones. See also line 218 where it is clearly included
69-70	26	**Comment:** Linked to the comment to lines 1-20. Text considered that the development plan covers the entire product lifecycle. However, development plan is developed (including in collaboration with other stakeholders) by the MAH and does not considers studies that may be done other sponsors (specifically academic sponsor, but sometimes even by healthcare systems) independently of the MAH or outside the MAH development plan. Thus, MAH development plan cannot cover the entire product lifecycle. Further in the document (section 4.3.4), some of investigations typically performed by sponsors different from MAH, are named "additional developments". This supports the view that MAH development plan does not cover the entire product lifecycle. **Proposed change:** EORTC suggests adding at the end of the sentence starting at the line 68 and ending at the line 70: "…and post-approval studies conducted by MAH". EORTC also suggests deleting reference to the section 4 in the line 70 as direct link between development

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		plan and clinical trials (which may be conducted aside the development plan) is misleading and potentially detrimental to independent academic research.
70	12	**Comment:** Non-commercial trials must be included in Annex 1 as part of the Lifecycle – or create a separate annex to address this issue
70	35	**Comment:** Non-commercial trials must be included in Annex 1 as part of the Lifecycle – or create a separate annex to address this issue
72	35	**Comments:** link to principle of transparency here https://www.ich.org/page/transparency
72	10	The cardinal logic behind serially conducted studies is that the results of prior studies should inform the plan of later studies. Some studies aim for an extension of the conducted study and seamless inclusion of subjects from one study to the other without (final) results being known, taking into account the required time for submission and approval.
72	12	**Comments**: link to principle of transparency here https://www.ich.org/about/transparency.html
72, 245, 550, 728 vs 725, 732, 736, 742	31	**Comment:** Throughout the document the terms "clinical trials" and "clinical studies" are used, e.g. the latter in lines 245, 550, 728 and former in lines 725, 732, 736, 742. **Proposed change:** explain when the term "trial" and the term "study" is used.
72-73	13	**Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		"…the results of prior studies should be consulted to modify the plan of later studies".
72-75	16	*"The cardinal logic behind serially conducted studies is that the results of prior studies should inform the plan of later studies. Emerging data will frequently prompt a modification of the development strategy. For example, results of a confirmatory study may suggest a need for additional human pharmacology studies"* **Comment:** Not all studies are sequential. Within a study, preliminary results might inform the conduct of the study, or information gained in a study might be of relevance to a second study conducted in parallel to the first one **Proposed change:** The cardinal logic behind serially conducted studies is that the results of prior studies should inform the plan of later studies. The results of one study might also inform the conduct of studies conducted in parallel. Emerging data will frequently prompt a modification of the development strategy. For example, results of a confirmatory study may suggest a need for additional human pharmacology studies.
72-73	31	"The cardinal logic behind serially conducted studies is that the results of prior studies should inform the plan of later studies." **Comment:** Early phase trials are often not "serially conducted", innovative study designs include adaptive integrated designs where predefined minimum data requirements trigger new parts of trials which are often conducted in parallel, rather than serially. **Proposed change:** include adaptive, integrated study designs, don't limit to serially conducted studies.
72-75	24	**Comment:** Common current development practice to conduct adaptive studies may result in a more dynamic decision-making situation. **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		We suggest adding some text acknowledging potentially dynamic/responsive situations for certain trial designs - development within a study is not always sequentially dependent on prior studies, but can be within the design of the ongoing study too
74	30	**Proposed change:** development strategy *and potentially of the product requirement profile.*
75	13	**Comment:** As serially conducted studies are one approach, it is suggested to add approaches more frequently used which include combining study phases (adaptive design) and overlapping study phases. **Proposed change:** Addition of sentence: Another approach is to combine studies within the different study phases by use of adaptive design based on the emerging evidence during the study conduct. In addition, overlapping study phases is an approach which is frequently used.
76	22	**Comment:** Unlike in section number 3.3.3, this section is only about involving patients or patient organizations. However, it is deemed even more necessary to involve the treating physicians and/or clinical investigators as outlined in section 3.3.3. Putting the emphasis solely on the patients in section 2.3 might lead to a wrong picture. **Proposed change:** 2.3 Patient and Physician Input into Study Design …with appropriate additions in the following text. Alternatively, a separate section 2.4 should address the importance to request the input of treating physicians and/or clinical investigators.
76	31	"Patient Input into Study Design"

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Comment: Patient input into study design might not always be realistic, e.g. some FIH, some healthy volunteer (HV) studies. Justified exceptions should be possible.
76	36	**Proposed change:** Page 3 line 76. The heading should be rephrased "Stakeholders input into study design", and an additional paragraph added recognising the importance of consulting other stakeholders, including HTA bodies and regulatory authorities, during the clinical development process, particularly in the design of pivotal trials.
76–85 Section 2.3	13	**Comment:** This section could include examples of how patients' input could be gathered/shared. **Comment:** This section is redundant with Section 3.3.3. which addresses a broader group of stakeholders, including treating physicians and clinical investigators. It will be helpful to identify "stakeholders" at the beginning of the document. Caregivers are stakeholders too, but they will not always be included in feedback sessions. Generally, patient involvement should not be linked to operational questions only: patients' and caregivers' input will facilitate to develop drugs which are ultimately taken and adhered to by the patient, leading to improved health outcomes. **Proposed change:** Remove redundancy between 2.3 and 3.3.3 sections by largely referring to the other.
76-85	16	*2.3 Patient Input into Study Design* **Comment:** Excellent, cannot agree more with paragraph

Line no.	Stakeholder no.	Comment and rationale; proposed changes
76-85	17	**Comment:** Section 2.3 provides guidance on patient input into study design. This is further referred to in Section 3.3, 3.3.3 and 4.4. Whilst we understand that patient engagement can be beneficial in some cases, we are seeking clarification around how the ICH Assembly would envisage this working in practice, including consideration of the following: Expectations around how patient engagement would be documented, including whether recommendations were taken on board and rationale for when recommendation were not/could not be incorporated. (For example, it may not be considered appropriate or recommendations may be conflicting with other stakeholders, or conflicting input from patients depending on regional standards of care)? In terms of transparency, how should patient input be communicated/provided as feedback to stakeholders such as the Research Ethics Committees, Competent Authorities, Investigators and the patient groups themselves. If it is a multi-centre trial, would the expectation be that a number of patients in each country are consulted? The number of patients/patient groups which may be considered appropriate, including consideration of trials in Rare and Orphan indication. **Proposed change:** We suggest that this section be clarified to make it clear it may not always be appropriate. Furthermore, on occasions where it is considered appropriate, it should be expanded to include practical recommendations and expectations in relation to the above points.
76-85	18	**Comment:** ACRO fully endorses the concept and value of consulting with potential study subjects and/or patient organisations in the design, planning and conduct of clinical studies. However, such consultation is not limited to patients and is equally valuable when undertaken with healthy volunteers during the design of healthy volunteer studies. **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Change relevant references to "patients" in this section to "subjects" and add text to make clear that this may include healthy volunteers in relation to appropriate studies.
76-85	20	**Comment:** Despite its high level of pertinence, development of a direct relationship between sponsors and patient organizations raise questions about transparency, influence and conflicts of interests. This is currently a highly discussed topic and development of a specific Guideline for Best Practices in the matter to promote honest dialogue and transparency may be a need. The proposed change below would be an additional sentence to be implemented in line 85. **Proposed change:** "**When opening communication channels with patients and patient organizations, Sponsors should take careful consideration not to influence patients opinion about the investigational product or study participation opportunity.**"
76-85	20	**Comment:** Involvement of patients / patient's organizations in design, planning and conduct of studies shall take into account additional factors, such as health literacy, potential subjectivity of patient's view, populations/disease targeting third world countries and illiterate patients. Geopolitical considerations should also be taken into consideration on international trials when access to treatments and/or information may differ because of local health policies and impact the potential comparators. However, we strongly support this approach.
76-85 / 83	20	**Comment:** Reference to Patient-Reported Outcomes would be appropriate in this section. **Proposed change:** "…duration of the study, **appropriateness and pertinence of Patient-Reported Outcomes and associated tools**, and use of…"

Line no.	Stakeholder no.	Comment and rationale; proposed changes
76 to 85	29	**Comment:** In paragraph 2.3 it needs to be clarified how patients are consulted to receive an input for the study design. If this part is not clear, there is the risk for the study.
76 (entire section 2.3.)	26	**Comment:** EORTC welcomes the consideration of patient input (in this section, but also present in the entire document). However, this only recommendation may not be enough to meet the goal without the possibility for sponsors (whatever nature) to have access to a critical mass of individuals and/or organisations capable providing timely and independent input. Important initiatives such as EUPATI has been funded within EU to achieve this critical mass and despite this efforts several sponsors of different kinds, including EORTC, report the difficulty to get such a timely input, specifically in rare and heavy conditions. Shall ICH wish to mandate such involvement, it shall consider (through participating regions / countries) constructing infrastructure supporting independent patient input that can be used by sponsors, considering funding and/or complimentary access for non-for profit sponsors. **Proposed change:** EORTC would suggest having separate text with considerations detailing advantages, possible limitations and elements to be considered to have a valuable, relevant and independent patient input.
76-85 2.3	27	**Comment:** 76 2.3 Patient Input into Study Design 77 Consulting with patients and/or patient organisations in the design, planning and conduct of 78 clinical studies helps to ensure that all perspectives are captured. Patients' views can be 79 requested on all phases of drug development. Involving patients at the early stage of study 80 design is likely to increase trust in the study, facilitate recruitment, and promote adherence, 81 which should continue throughout the duration of the study. Patients also provide their

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		82 perspective of living with a condition, which contributes to the determination of endpoints that 83 are meaningful to patients, selection of the right population, duration of the study, and use of 84 the right comparators. This ultimately supports the development of medicines that are better 85 tailored to patients' needs. **Proposed Change:** 76 2.3 Patient Input into Study Design 77 Consulting with patients and/or patient organisations in the design, planning and conduct of 78 clinical studies helps to ensure that all perspectives are captured. Patients' views must be 79 systematically included on all phases of drug development. Involving patients at the early stage of study 80 design will increase trust in the study, facilitate recruitment, and promote adherence, 81 which must continue throughout the duration of the study. Patients also provide their 82 perspective of living with a condition, which must determine new primary patient outcomes and endpoints that 83 are meaningful to patients, selection of the right population, duration of the study, and use of 84 the right comparators. This ultimately supports the development 84 of medicines that are better 85 tailored to patients' needs.
77-78	13	**Comment:** Usually, only relevant stakeholder perspectives should be captured when designing a study. **Proposed Change:** "Consulting with patients and/or patient organizations in the design, planning and conduct of clinical studies helps to ensure that

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		all relevant perspectives are considered and captured".
77-85	23	**Comment:** Section 2.3 Patient Input to Study Design: Great care should be applied when writing "Patients' views can be requested on all phases of drug development". Patients with the disease condition in question do always have a bias, this might be an ethical problem: for example the demand to achieve therapeutic progress may expedite inadequately early phase trials without balanced assessment of risk-benefit for the participating subjects. Therefore a re-wording with reduced importance in early phase healthy subject trials is recommended.
77-83	4	**Comment:** The use of COS in clinical trials will ensure that outcomes important to patients, trialists and healthcare professionals are considered when research is planned. This is a more robust approach to generating patient-relevant evidence than involving just a few selected patients at the design stage of a trial. **Proposed change:** Recommend checking the COMET database (www.comet-initiative.org/studies/search) for any relevant COS and that minimum standards for development should specify that patients, healthcare professionals and those who will use the COS in their research should be involved in its development (journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002447). If a COS does not exist or has not been well developed, consideration should be given to whether this could be done during the study design stage.
78-79	22	**Comment:** It should be recognized that talking to patients/patient organizations does not fit to all clinical studies or indications. **Proposed change:** Patients' views can be requested on all phases of drug development, whereas it is recognized that this is dependent on the indication, the stage of development and whether this would be relevant for the patients.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
79	37	"Involving patients at the early stage of study.." **Comment:** This is not be applicable for early phase studies, like first in patient studies. Such comments should be regarded as tips & tricks. The risk of mentioning this in an ICH guideline is that is can lead to legislation.
79-80	12	**Comment:** It needs to be clear whose trust: Involving patients at the early stage of study design is likely to increase **patient** trust in the study
79-80	35	**Comment:** It needs to be clear whose trust: Involving patients at the early stage of study design is likely to increase **patient** trust in the study
79-81	16	*"Involving patients at the early stage of study design is likely to increase trust in the study, facilitate recruitment, and promote adherence, which should continue throughout the duration of the study"* **Comment:** most important: to increase the quality of the study and chances that it can conclude with relevant results **Proposed change:** Involving patients at the early stage of study design is likely to increase quality of the study, trust in the study, facilitate recruitment, promote adherence, which should continue throughout the duration of the study and increase chances that the study could conclude.
81-84	13	**Comment:** add wording as stated below.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: "Patients also provide their perspective of living with a condition, which contributes to the determination of endpoints that are meaningful to patients, selection of the right population, insights into benefit-risk perception from a patient perspective, duration of the study, perspective on drug administration and formulation, and use of the appropriate comparators."
84	12	**Comments:** include wording to ensure data also supports how already marketed drugs are prescribed. **Proposed change:** This ultimately supports the development **and use of** medicines
84	35	**Comments;** include wording to ensure data also supports how already marketed drugs are prescribed. **Proposed change:** This ultimately supports the development **and use of** medicines
85	9	**Comment:** The section lacks information about the challenges the selection of patient representatives may have. **Proposed change:** Add: When selecting patients representatives, their representativeness and independence need to be ensured.
85	13	**Comment:** add wording **Proposed change:** "This ultimately supports the development of medicines that are better tailored to patients' needs and potentially increase

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		patient's long-term adherence to treatment and therapy.”
86 (entire section 3)	26	**Comment:** EORTC welcomes the high consideration given to the good study design and execution (rather than formalistic compliance with documentation requirements). EORTC also strongly supports the flexibility introduced through the risk-based approach to requirements in general. EORTC strongly supports considerations of the section 3, specifically concepts expressed in its subsections 3.1, 3.3.1, 3.3.2. and 3.3.3. EORTC suggest to further building on these key considerations that would synergistically be much more efficient to ensure patient safety, data quality, relevance and robustness of results focusing limited resources on what really matters. **Proposed change:** Please, do not change these important concepts.
86 (Section 3)	34	**Comment:** In general this section is good. For example, it is encouraging to see it stated that, “Quality should rely on good design and its execution rather than overreliance on retrospective document checking, monitoring, auditing or inspection.” However, the document should be much clearer that QbD is not an additional requirement being layered on top of all the usual activities but should obviate the need for many of those retrospective activities (with monitoring and other checks only focussed on issues that matter – i.e. Critical To Quality factors) One significant weakness of this section, and the document as a whole, is a failure to recognise the unique value of properly conducted randomized trials (including allocation concealment, appropriate follow-up, and intention-to-treat analysis). There is lots of focus individual data points, but without consideration of the impact of errors (missing data, inaccurate data, etc) on the reliability of the results and the well-being of participants. Not every data point matters and not every data point needs to be traceable back to some source, and not every source will be fixed or reproducible (e.g. not only do symptoms vary over time but so too does their recollection). There is no recognition that there can be interactions between different CTQ factors. For example, study power is influenced by number of participants, risk of developing event of interest (or variability in continuous measurement), adherence to therapy,

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		and duration of follow-up. Each of these may be considered CTQ and assumptions about each will be embedded in the protocol and design. However, lower than expected performance in one (e.g. event rate) may be more than compensated for by over-performance in another (e.g. adherence to treatment). By contrast, smaller errors in several (e.g. number of participants, adherence to therapy) may have an important impact on overall study power. This multi-dimensional subtlety is missing in the current one-dimensional wording.
87	11	**Comment:** The wording "The quality by design approach to clinical research .." is misleading. **Proposed change:** "The **designing of quality approach** to clinical research (section 3.1) involves focusing on critical to quality factors …" or ""The **quality focussed approach** to clinical research (section 3.1) involves focusing on critical to quality factors …"
87	13	**Comment:** This section should cross-reference to ICH E6(R2) section 5.0
87	18	**Comment:** In section 3 of the current document, and in the ICH E6 (R2) guideline, a risk-proportionate approach to ensure the quality of clinical studies is discussed. For clarity and consistency, we recommend that this approach is also referenced here. **Proposed change:** Replace "….involves focusing on critical to quality factors…." with "….involves a risk-proportionate approach focusing on critical to quality factors…."
89	19	**Comment:** "… generation of meaningful results, …" **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		e.g. generation of meaningful answers to questions set in the study protocol
89-91	31	"The approach is supported by the establishment of an appropriate framework for the identification and review of critical to quality factors (section 3.3)." **Comment:** A reference to E6 section 5.0 is necessary as section 3 of this guideline and section 5.0 of E6 overlap to great extent (see also general comments).
92	9	**Comment:** Section 3.1 outlines some very important general principles that are explicitly supported.
92	11	**Comment:** The term "quality by design of clinical studies" is unclear and misleading. **Proposed change:** There are more possibilities, for example: 3.1 Quality ~~by Design~~ of Clinical Studies 3.1 Quality **Designing** Clinical Studies 3.1 Quality **Focussed** Clinical Studies
93	11	**Comment:** The term "quality" is not fully clear. **Proposed change:** Quality **of gained data** is a primary consideration in the design, planning, conduct and analysis of clinical 94 studies and a necessary component of clinical development programmes.
93	30	**Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		design, planning, conduct~~, *and*~~ analysis *and reporting*
94-98	24	**Comment:** In line with the comment relating to pages 63-65 the human factor should not be ignored. **Proposed change:** …of all components of the study protocol, procedures, operational plans, *and the competence of the executing staff*
96	7	**Proposed change:** add "Ethics Committees" between decision makers and patients
96	19	**Comment:** meaning of an "important error"? **Proposed change:** delete "while preventing important errors"; the first part of the sentence includes this aspect (questions are answered in reliable manner)
99	11	**Comment:** The term "quality" could be clarified. **Proposed change:** Quality **of the study** should rely on good design ….
99	31	"Quality should rely on good design and its execution rather than overreliance on retrospective document checking, monitoring, auditing or inspection." **Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		"Design" is not sufficient. **Proposed change:** "Quality should rely on good design, planning and preparation (including training) as well as compliant execution rather than overreliance on retrospective document checking, monitoring, auditing or inspection."
99–101	13	**Comment:** Monitoring is a quality control activity and not quality assurance activity. As such, the text should be amended to reflect this. Proposed change to 101 is to enhance clarity of the sentence **Proposed change:** "Quality should rely on good design and its execution rather than overreliance on retrospective document checking, monitoring, auditing or inspection. The latter activities are an important part of quality control and quality assurance processes but are not sufficient to ensure quality of a clinical study."
99-101	15	**Comment:** Sponsors and/or CROs worry that, if their work is audited, it may seem that they did not do enough. Therefore, they tend to become defensive and check all documents and files again and again. They should be warned against excessive document checking. **Proposed change:** Add the following sentence at the end of the paragraph: "Excessive document checking can be detrimental to quality assurance and should be avoided."
99-101	18	**Comment:** The current text does not reflect adequately the advantages of real-time risk-based monitoring in identifying quality issues at a point at which corrective action is feasible.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: Replace the sentence "These activities are an important part of a quality assurance process but are not sufficient to ensure quality of a clinical study" with "While traditional approaches to monitoring will be appropriate under specific circumstances, in general risk-based monitoring as described in ICH E6(R2) represents a best practice to allow sponsors to identify and address issues during the conduct of clinical investigations at a point at which corrective action is feasible."
99-101	20	**Comment:** Attention should be raised on the fact that study design is in a majority of cases not perform by the same persons who are executing a study. Quality assurance processes should also take into account the use of sponsor's representatives (CROs) that may lead to duplication of quality processes not especially fitted for a specific study, leading to a duplication of procedures, possibly leading to over-quality or under-quality objectives, and possible loss of focus on essential aspects of a protocol. A complementary Guideline on Best Practices would be appropriate.
99-101	24	**Comment:** We appreciate the strong statement on the relevance of a prospective quality strategy but this is inevitably supported by training of staff, quality control and quality assurance performed early in the trial. **Proposed change:** Quality should rely on ~~good~~ suitable design, *sophisticated processes and skilled, trained personnel in* its execution. *Quality Control and Assurance foster and improve these efforts by stating the need of corrective and preventive actions prior and during a study. Retrospective auditing and inspection* are not sufficient to….
99-101	37	Quality should rely on good design and its execution rather than overreliance on retrospective document checking, monitoring, auditing or inspection. These activities are an important part of a quality assurance process but are not sufficient to ensure quality of a clinical study. **Comment:** These two sentences contain contrasting information that hamper their practical implementation. The first sentence allows fit for purpose monitoring while the second one can be used to justify to opposite, namely rigorous monitoring and auditing.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
101	31	"… quality assurance … " **Comment:** "quality management" would be the better term and in line with E6 section 5.0. Quality management comprises QC and QA and the examples given (document checking, monitoring, auditing or inspection) are covering QC as well as QA.
107	26	**Comment:** Selection of appropriate subjects is relative to the context; as discussed later in the document selection shall neither be too large, nor too restrictive, but adequate to the study design and the place in the product lifecycle. **Proposed change:** EORTC suggests adding at the end of the line 108: "selection shall not be discriminative to any age, gender, health condition or specific characteristic, unless medically or legally justified"
107-108	16	*"selection of appropriate subjects that have the disease, condition, or molecular/genetic profile that is being studied"* **Comment:** Question of histology-independent studies in oncology **Proposed change:** selection of appropriate subjects that have the disease(s), condition(s), or molecular/genetic profile(s) that are being studied
107-108	21	*{...} selection of appropriate subjects that have the disease {...}, and ethical means of recruitment with adequate recruiting procedures;* **Comment:** An extra emphasis is needed in particular for the recruitment of vulnerable patients.
107-108	25	**Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		This bullet does not include the profile of healthy subjects in early phase trials. **Proposed change:** Selection of subjects that have the *required health or disease conditions*, or….
109-110	24	**Comment:** Unclear what is meant with "confounding" **Proposed change:** *…confounding factors.*
110	19	**Comment:** "… control of confounding;" **Proposed change:** "… control of confounding **factors**;"
111	25	**Comment:** "endpoints that are well-defined and measurable". We would like to suggest adding that they should be clinically meaningful whenever possible. **Proposed change:** "*clinically relevant* endpoints that are well-defined and measurable, ….
111	26	**Comment:** EORTC believes that endpoints shall be clinically meaningful and relevant to patients. **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		EORTC proposes to add within the sentence: "endpoints that are well-defined, measurable, clinically meaningful and relevant to patients, and methods…."
111	31	"endpoints that are well-defined and measurable, …" **Comment:** An endpoint has to be relevant in relation to the study objective(s). **Proposed change:** "endpoints that are relevant, well-defined and measurable, …"
111-113	13	**Comment:** "minimal" reporting be a limitation. **Proposed change:** "… to be implemented with reasonable reporting or …"
111-113	16	*"endpoints that are well-defined and measurable, and methods of assessment of those endpoints that are accurate and able to be implemented with minimal reporting or measurement bias"* **Comment:** Adequate study duration is another important factor. There is a balance between the desire of the developer to shorten the duration of the R&D phase, and the need for appropriate study duration to measure an effect. This is particularly needed for slowly evolving diseases or conditions such as Duchenne muscular dystrophy where efficacy results are sometimes controversial due to inappropriate study duration (fewer events than initially estimated) **Proposed change:** Endpoints that are well-defined and measurable, methods of assessment of those endpoints that are accurate and able to be implemented with minimal reporting or measurement bias, and adequate study duration

Line no.	Stakeholder no.	Comment and rationale; proposed changes
111-113	31	"• endpoints that are well-defined and measurable, and methods of assessment of those endpoints that are accurate and able to be implemented with minimal reporting or measurement bias. " **Comment:** There should be more openness for exploratory endpoints to encourage adaptive trial designs and flexibility within an approved adaptive "design space", limited by clear approved boundaries.
113	25	**Comment:** We recommend adding a bullet on the relevance of appropriate data collection and management, sample size and statistical analysis to come to interpretable, reliable results **Proposed change:** *use of validated data collection and management systems, statistically justified sample size and pre-planned data analysis.*
114	12	**Comments:** operational criteria should also include the competence of all the people involved in delivering the trial, both at the sponsor/CRO/vendor as well as the investigator site Resources should also be considered here Suitable methods of data collection and data transfer should also be considered in relation to data Integrity
114	35	**Comments:** operational criteria should also include the competence of all the people involved in delivering the trial, both at the sponsor/CRO/vendor as well as the investigator site Resources should also be considered here Suitable methods of data collection and data transfer should also be considered in relation to data Integrity

Line no.	Stakeholder no.	Comment and rationale; proposed changes
114-116	12	**Comment:** Communication is important operational criteria that adds to safety and well being of participants **Proposed change:** add communication to the list
114-116	13	**Comment:** The need to include only site staff who are qualified/trained may be implied by reference to "suitable investigator sites". However, for clarification it is recommended that a reference to "staff being qualified/trained" is included. **Comment:** The current draft does not specifically mention Critical to Quality (CTQ) factors that might be appropriate to consider when utilizing CROs, vendors or other third-parties. This may be implied by reference to "other parties" and "external sources" within the document. Given the prevalence/use of third parties in the conduct of clinical trials it would be helpful to call this out. **Proposed Change:** "Operational criteria are also important, such as ensuring a clear understanding of the feasibility of the study, selection of suitable investigator sites including qualified/trained staff, suitability and qualification of third-party service vendors, quality of specialized analytical and testing facilities and procedures, and processes that ensure data integrity."
114 - 116	23	**Comment:** thorough discussion of patient population at planning and feasibility stage is vital **Proposed change:** add in line 115 - " thorough discussion of patient population with investigators and/or pre-screening during feasibility.
114-116	24	**Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Also here the human factor is missing. **Proposed change:** Operational criteria are also important, such as ensuring a clear understanding of the feasibility of the study, selection of investigator sites, quality of specialised analytical and testing facilities and procedures, *competence of involved staff,* and processes that…..
117	13	**Comment:** ICH E6(R2) Section 5.0 describes the identification of data and processes that "are critical to ensure human subject protection and the reliability of trial results" (data) as being a critical step in the quality management process. Introducing a new term which seemingly has the same purpose is likely confusing. This needs to be aligned during the planned update to ICH E6.
117-153 (Section 3.2)	31	**Comment:** This section is focused on later phase trials (lines 125-129) and whilst going into detail about uncertainties for these later phase trials it ignores the uncertainties about PK/PD encountered in early phase trials.
118	12	**Comment:** These factors are equally important to the running of the ongoing study and the decisions made to support it (e.g. dose escalation, futility, safety etc) as to future uses of the data. So it is not just applicable to the results at the end of the trial
118	22	**Comment:** Even though ICH E6 (R2) section 5.0.1 clearly states that critical processes and data should be identified as early as during protocol development many sponsors actually start their risk-based quality management based on an already finalized protocol and, thus, fail to implement quality on the design level. It may therefore be helpful to emphasize that critical to quality factors need to be identified prior to and/or during protocol development. **Proposed change:** A basic set of factors relevant to ensuring quality should be identified for each study prior to or at the latest during the early

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		pagestages of protocol development.
118	35	**Comment:** These factors are equally important to the running of the ongoing study and the decisions made to support it (e.g. dose escalation, futility, safety etc) as to future uses of the data. So it is not just applicable to the results at the end of the trial
119	12	**Comment:** This is a very clumsy sentence that is hard to understand: These ~~critical to quality~~ factors **which are critical to quality** are attributes of a study ~~whose integrity is~~ **that are** fundamental to the protection of study subjects
119	35	**Comment:** This is a very clumsy sentence that is hard to understand: These ~~critical to quality~~ factors **which are critical to quality** are attributes of a study ~~whose integrity~~ **that are** fundamental to the protection of study subjects
124	30	**Comment:** To cover the IVD/assay dimension I suggest adding relevant text here or in another section: *As an example, these quality considerations also need to cover all evaluations of subjects' biological samples*
125	31	"The design of a clinical study should reflect the <u>state</u> of knowledge …" **Comment:** unclear what 'state of knowledge' means as this cannot be easily quantified **Proposed change:** **…**reflect the ~~state~~ **level** of knowledge …
127	16	*"and the population for which the drug is intended"* **Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Local context matters, even if the population for which the drug is intended can be defined globally, standard of care and other parameters can vary substantially among different regions. **Proposed change:** and the population for which the drug is intended, considering the local context
127-129	9	**Comment:** Although a reduction of uncertainties by research progress is generally expected, this depends on the quality of those studies. Therefore, this postulate needs to be rephrased. **Proposed change:** Change sentence: As research progresses, knowledge increases and uncertainties about the safety and efficacy of a drug are expected to decrease.
130	31	"The design of a clinical study should reflect the state of knowledge …" **Comment:** unclear what 'state of knowledge' means as this cannot be easily quantified **Proposed change:**… reflect the level of knowledge …
130	31	"This state of knowledge has a clear influence on the regulatory and ethical controls …" **Comment:** unclear what Ethics 'controls' refers to, suggest to replace with 'conditions'.. **Proposed change:** "...regulatory and ethical **conditions** …"

Line no.	Stakeholder no.	Comment and rationale; proposed changes
130-133	5	**Comment:** Knowledge of the target patient population and of their characterization through biomarker profiling are also essential when testing 'personalized' treatments. **Proposed change:** add the sentence above on line 133
131	9	**Comment:** When investigational active substances are used in clinical trials, there is generally an information asymmetry between its developer and ethical or regulatory committees regarding the characteristics of the product. This might affect decision making. **Proposed change:** Add: Therefore, it is important to ensure that regulatory and ethical authorities have comprehensive information on the characteristics of an experimental drug.
131	31	"The design of a clinical study should reflect the state of knowledge …" **Comment:** unclear what 'state of knowledge' means as this cannot be easily quantified **Proposed change:** **…**reflect the level of knowledge …
132-133	31	"…will therefore inform the identification of critical to quality factors and control processes used to manage them." **Comment:** Suggest minor rewording **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		"…will therefore ~~inform~~ **determine** the identification of critical to quality factors and control **the** processes used to manage them."
133	24	**Comment:** For emphasis on the relevance of the primary endpoint in this context. **Proposed change:** … will therefore inform the identification of critical to quality factors*, primary endpoint* and control processes …
134	12	**Comment:** It would be useful to give some example of what is meant by 'other parties' For example access to professionals outside the sponsor may assist in the 'real world' delivery aspects and risks of the trial
134	20	**Comment:** A reference to paragraph 3.3.3 would highlight the importance of involving relevant stakeholders (such as Investigators, Study Coordinators, Patients Representatives…) in this process. **Proposed change:** "The sponsor and other parties, **as described in 3.3.3**, designing quality into a clinical study should identify the critical to quality factors".
134	25	**Comment:** Quality needs to be designed into the study by more parties than the sponsor. It is also a duty for the executing parties. **Proposed change:** The sponsor and other parties designing *and executing* quality into a clinical study should identify….
134	35	**Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		It would be useful to give some example of what is meant by 'other parties' For example access to professionals outside the sponsor may assist in the 'real world' delivery aspects and risks of the trial
134-135	13	**Comment:** The term "other parties" is too generic and therefore it might be helpful to provide examples. **Proposed change:** "The sponsor and other stakeholders (such as CROs, other vendors, patient representative groups) designing quality into a clinical study should identify the critical to quality factors."
134-136	26	**Comment:** EORTC welcomes ICH puts the primary responsibility of designing quality into clinical studies and defining quality factors. Terms "and other parties" are however less clear. Indeed, it is not clear if these terms refer to "broad range of stakeholders" to be involved in the design (line 190) or regulators, authorities or IRB/ECs that may review the study design/protocol. **Proposed change:** EORTC suggest including the clarification that "broad range of stakeholders" (ref. line 190) shall not only be included in study design, but also in the confirmation of quality factors defined by the sponsor.
134-140	13	**Comments:** The process to identify and prioritize risks to quality described here is not consistent with that recently introduced in ICH E6(R2). Therefore, this needs to be aligned during the planned update to ICH E6.
134-140	18	**Comment:** Risk language in this section is not aligned in terminology with ICH E6 R2. E.g. refers to risk identification and probability, but omits reference to detectability. **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Align language in this section with terminology utilized in section 5 of ICH E6R2
134-140	24	**Comment:** We recommend to cross-reference to ICH *Q9*
135-137	13	**Proposed Change:** "Having identified those factors, it is important to identify the associated risks against existing risk controls by considering the likelihood of errors occurring, the extent to which such errors would be detectable, the impact of such errors on human subject protection and reliability of trial results."
136	28	**Comment:** While 'probability' and 'impact' are mentioned, 'detectability' is not. This does not match the guidance in E6 where it includes "The extent to which such errors would be detectable". This additional aspect is already becoming part of common methodology for quality risk management in clinical trials. **Proposed change:** Add "the extent to which such errors would be detectable" to line 136.
136	31	"… the probability and impact of those risks…" **Comment:** The guidance given here should be in line with ICH E6, section 5.0.3. Detectability is missing here. In addition, E6 should be referenced. **Proposed change:** "…the probability, detectability and impact of those risks (see ICH E6) …"
140	24	**Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		We recommend to cross-reference to ICH-E6(R2)
141-143	13	**Comment:** It is considered appropriate that critical to quality factors be predefined. **Proposed change:** "Proactive communication of the predefined critical to quality factors and risk mitigation activities will …"
143	12	**Comment:** Broad training is rather vague, training needs to be relevant to the role, so detailed where required and including a competency assessment if applicable
143	24	**Comment:** The examples provided in the bracket are not clear. What is meant by "…description in the protocol or case report form"? Description of what? Of the training content? Of the critical to quality factors? How to do this in a CRF?
143	35	**Comment:** Broad training is rather vague, training needs to be relevant to the role, so detailed where required and including a competency assessment if applicable
143-145	31	"Proactive support (e.g., broad training to all relevant site staff and description in the protocol or in the case report form) will enhance correct implementation of study protocol, procedures, and associated operational plans and process design." **Comment:** Precision of text suggested **Proposed change:** "Proactive support (e.g., broad as well as study specific training to all relevant site staff and description in the protocol, operational plans and/or in the case report form) will enhance the implementation of study procedures in compliance with the

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		study protocol.
144	24	**Comment:** Training in GCP should be mentioned **Proposed change:** (…protocol or in the case report form) *and GCP* will enhance…
146-147	9	**Comment:** Although it is acknowledged that perfection is rarely achievable, this sentence is unnecessary in the context of this passage of the guideline. In addition, it is not part of the guideline in force**.** **Proposed change:** Delete sentence.
146-147	13	**Comment:** It is considered that reference to "perfection" is not appropriate for this guideline. **Proposed change:** "The quality factors should be prioritized to identify those that are critical to the study at the time of the study design, and study procedures should be proportionate to the risks inherent in the study and the importance of the information collected."
146-147	15	**Comment:** We strongly support this statement. It would be useful, however, to define what "resources that are out of proportion" refers to, as it is a major issue that has to be addressed in the present revised version. "Out of proportion" should be defined for each of the actors involved in clinical research.
146-147	26	**Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		EORTC strongly supports this statement. Indeed, in our experience the incremental stimulation by GCP inspectors to do always better for every item on the checklist has led to dramatic complexification of requirements and consequent increase of costs, but also human errors without any prove of the direct benefit to the quality of research or patient safety. Therefore, EORTC strongly supports the recommendation to focus resources available to ensure critical quality factors are met. **Proposed change:** EORTC believes this is an important statement, please do not change.
147	12	**Comment:** It is not clear on the intent here. Have made some suggestions: The quality factors should be prioritized to identify those that are critical to the study~~,~~ at the time of the study design~~., and~~ sStudy procedures should be proportionate to the~~ risks inherent in the study and the~~ importance of the information collected and the risks …….. *Not sure what inherent study risks are being referred to here in relation to study procedures so have suggested moving to end of sentence but think it will need additional clarification.*
147	35	**Comment:** It is not clear on the intent here. Have made some suggestions: The quality factors should be prioritized to identify those that are critical to the study~~,~~ at the time of the study design.~~, and~~ ~~s~~Study procedures should be proportionate to the ~~risks inherent in the study and the~~ importance of the information collected and the risks …….. *Not sure what inherent study risks are being referred to here in relation to study procedures so have suggested moving to end of sentence but think it will need additional clarification.*
147-150	18	**Comment:** ICH E8R1 The quality factors should be prioritized to identify those that are critical to the study, at the time of the study design, and study procedures should be proportionate to the risks inherent in the study and the importance of the information collected. **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Recommend to also include reference to the fact that the monitoring strategy should also be proportionate to the critical data /processes and risks.
149-150	31	"… study procedures should be proportionate to the risks inherent in the study and the importance of the information collected. " **Comment:** Suggest to replace importance of the information collected' with 'relevance of the data collected' as this is the scope of the document **Proposed change:** …' and the ~~importance~~ **relevance** of the ~~information~~ **data** collected…'
150	24	**Comment:** We suggest including text to emphasise the importance of database design and data collection tools as those are frequently underfunded in academic studies.
150-153	13	**Comment:** CTQ factors are not an outcome. Is the purpose here to suggest that the study should be designed to avoid unnecessary complexity such that it is clear what is critical to quality in the study? What does proper protection mean? For subjects the safety and well-being, for study objectives however? Can include alpha protection e. g., but what else is meant? **Proposed change:** "The study should be designed to avoid unnecessary complexity and should be clear and not be cluttered with minor issues (e.g., due to extensive secondary objectives or processes/data collection not linked to the protection of the study subjects and/or primary study objectives) so that it is clear what is critical to quality in the study."
151	13	**Comment:** "extensive" secondary objectives – how is that understood? It may be subjective or a case-by-case assessment. In selected instances eg in case of qualification of a novel endpoint it may be valuable to include a number of secondaries, not to clutter but

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		to better inform validation
151	31	"…(e.g., due to extensive secondary objectives or processes/data …" **Comment:** suggest to replace 'extensive' with 'inappropriate' as this is more of the issue here **Proposed change:** "…due to ~~extensive~~ **inappropriate** secondary objectives…"
154 (3.3)	37	3.3 Approach to Identifying the Critical to Quality Factors **Comment:** More guideline on the practical implementation of these advices would improve this section.
154-211	13	**Comment:** It would be helpful to provide examples of critical to quality factors
156	13	**Comment:** ICH E9(R1), the estimand addendum, could be referenced here. It provides a framework to clearly articulate a study objective and derive an estimand from it. **Comment:** Engagement of regulators is only mentioned regarding novel elements in a study; however, a general recommendation of early engagement with regulators on quality aspects of clinical trials may be more advantageous
156	20	**Comment:** "…to meet the need…" : Plural to be considered, there may be several needs.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: "…to meet the **needs**…"
157-158	31	"…and whether the study hypotheses are specific, timely and scientifically valid." **Comment:** Not clear what timely refers to, is this regarding developmental program?
158	20	**Comment:** "The approach..." - Clarification **Proposed change:** "The **quality** approach…"
160	13	**Comment:** Sentence needs to be added to clarify that "avoid unnecessary complexity" does not exclude the conduct of studies which use modern approaches to trial design, such as adaptive designs, master protocols etc. **Proposed change**: add sentence behind "Study designs should be operationally feasible and avoid unnecessary complexity and unnecessary data collection. The use of modern approaches to trial design such as adaptive designs, master protocols and other innovative design approaches which can benefit patients are not to be considered as unnecessary complexity."
161	13	**Comment:** This wording is not clear – do we imply the expectation that patients are systematically consulted on the study design (e.g. including ph1 studies)?
161	18	**Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		As noted above in our comment on lines 76-85, consultation should not be restricted to patients but may also involve healthy volunteers. **Proposed change:** Replace the word "Patient" with "Subject".
161-162	13	**Comment:** Suggest addressing other important stakeholders as referenced in section 3.3.3 **Proposed change:** "Input from a broad range of stakeholders, including patient consultation and Investigator site early in the study design process contributes to these factors and would be likely to result in fewer protocol amendments. Patient consultation shall reflect the global requirements and shall not be limited to selected countries/regions." **Comment:** is "patient" consultation interchangeable with "subject" consultation?
161-162	16	*"Patient consultation early in the study design process contributes to these factors and would be likely to result in fewer protocol amendments"* **Comment:** Excellent, cannot agree more
161-162	17	**Comment:** Section 2.3 provides guidance on patient input into study design. This is further referred to in Section 3.3, 3.3.3 and 4.4. Whilst we understand that patient engagement can be beneficial in some cases, we are seeking clarification around how the ICH Assembly would envisage this working in practice, including consideration of the following: Expectations around how patient engagement would be documented, including whether recommendations were taken on board

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		and rationale for when recommendation were not/could not be incorporated. (For example, it may not be considered appropriate or recommendations may be conflicting with other stakeholders, or conflicting input from patients depending on regional standards of care)? In terms of transparency, how should patient input be communicated/provided as feedback to stakeholders such as the Research Ethics Committees, Competent Authorities, Investigators and the patient groups themselves. If it is a multi-centre trial, would the expectation be that a number of patients in each country are consulted? The number of patients/patient groups which may be considered appropriate, including consideration of trials in Rare and Orphan indication. **Proposed change:** We suggest that this section be clarified to make it clear it may not always be appropriate. Furthermore, on occasions where it is considered appropriate, it should be expanded to include practical recommendations and expectations in relation to the above points.
161-162	19	**Comment:** In addition to patient consultation early in the study design, very important is to consult physicians and experts treating patients with a certain condition (in different regions); they are also best to evaluate study complexity of the design. Not sure if one should mention protocol amendments here. **Proposed change:** delete sentence - topics are also addressed in section 3.3.3 and 4.4
162	28	**Comment:** The text mentions that the number of protocol amendments would be reduced but it is valuable to point out that the number of protocol violations should be reduced too. **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Change the phrase to "would be likely to result in fewer protocol violations and amendments".
162-163	13	**Proposed change:** "Clearly written study protocols and case report forms/data collection methods should enable the study to be conducted as designed."
164-165	13	**Proposed change:** "Identification of critical to quality factors and continuous oversight of risk management activities will be enhanced by approaches that include the following elements:"
166-168	37	*Create a culture that values and rewards critical thinking and open dialogue about quality and that goes beyond sole reliance on tools and checklists* **Comment:** This is very true, but how to do this? In places where critical thinking and open dialogue are not valued, this is probably not recognized as being the case.
166-180	13	**Comment:** This subsection is part of Section 3.3 "Approach to Identifying the Critical to Quality Factors". It is not considered that the reference to the sponsor organizational culture is appropriate for this guideline or relevant to Section 3.3. **Proposed change:** consider deleting this section 3.3.1 "Establishing a Culture that Supports Open Dialogue"
166-180	25	**Comment:** We think that the creation of such a culture also requires reliable and comprehensive information between all parties **Proposed change:** Create a culture that values and rewards critical thinking, *reliable and comprehensive information flow,* and open dialogue *amongst all involved parties* about quality……..
166-180	31	**Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
(section 3.3.1)		This section states the obvious and is non-specific management coaching that could be applied for any business. **Proposed change:** Add more clinical study specific content
167	12	**Comment:** Would also be useful to add here about creating a culture that is open to identifying errors without blame, a key value for DI
167	13	**Proposed change:** "Introduce a global culture approach that values and rewards critical thinking and open dialogue about quality and that goes beyond sole reliance on tools and checklists."
167	35	**Comment:** Would also be useful to add here about creating a culture that is open to identifying errors without blame, a key value for DI
167-168	9	**Comment:** Tools and checklists are important for a standardised quality assessment in clinical trials. Their use should not be discouraged and they should not be discredited. Nevertheless, sole reliance on those without taking into account the concrete study is problematic. **Proposed change:** Add to sentence: ,as important they are for quality assurance
169-172	13	**Comment:** Can't see how this example is related to the sentence in line 169. The example is a rather general description. **Proposed change:** Delete example

Line no.	Stakeholder no.	Comment and rationale; proposed changes
169-172	18	**Comment:** We welcome the emphasis in line 169-172 on reducing the focus on time to First Patient Enrolled. **Proposed change:** It would be helpful to provide some guidance on suitable types of quality measures and performance indicators, maybe in an additional appendix
169-172	20	**Comment:** Concerns are expressed on the feasibility and capacity of alignment of quality measures and performance indicators, especially when a Sponsor, who may define indicators for a whole programme on a product, will assign the performance of a specific study to a CRO who may implement additional and possibly contradictory quality measures and performance indicators.
169-175	20	**Comment:** As written, this sentence seems to focus on time optimization rather than quality through open communication. **Proposed change:** "Choose quality measures and performance indicators that are aligned with a proactive approach to design. **Outlining these critical quality objectives and encouraging open dialogue to meet study and program needs, further promotes the development of innovative methods for ensuring quality. This should not be jeopardized by other influences**"
170-172	37	*For example, an overemphasis on minimising the time to first patient enrolled may result in devoting too little time to identifying and preventing errors that matter through careful design.* **Comment:** This is obvious, but the force to minimize the time to first patient enrolled is almost always very strong, and a sponsor will usually think that they have performed careful design in balance with this force. But this is often not the case. How to assure this?

Line no.	Stakeholder no.	Comment and rationale; proposed changes
173-175	13	**Comment:** Is this sentence dealing with risk mitigation plan? Add practical examples of situations and stakeholders to be involved to create a culture that values and rewards critical thinking and open dialogue about quality or introduce risk mitigation. **Proposed change:** "Encourage proactive dialogue between … about what is critical to quality and establish a risk mitigation plan."
173-175	37	*Encourage proactive dialogue about what is critical to quality for a particular study or development programme and, when needed, the development of innovative methods for ensuring quality.* **Comment:** True but vague.
176-177	9	**Comment:** Blind use of inflexible approaches is discouraged. However, one should outline that standardisation in planning and conduct of clinical trials when adequate is necessary to ensure comparability and reduce the risk of bias. **Proposed change:** Add: Nevertheless, justification of all deviations from established standards of study conduct, e.g. regarding the definition of endpoints or training of investigators is needed.
176-177	15	**Comment:** We completely agree with this statement. However, if it applies to all stakeholders (including CROs), it should be mentioned in the manuscript that all teams involved in clinical trials should not only have expertise in clinical trials monitoring or design, but also some knowledge about the research topic. To avoid the "one size fits all" effect, training about the disease under study should be mandatory, as the monitoring process or safety management cannot be the same for all diseases. Specific processes should be customized based on the study design instead of following an internal process that is replicated from trial to trial without discernment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
176-177	18	**Comment:** There are circumstances in which a "one size fits all" approach may be desirable and should not be discouraged, e.g. to ensure the reliability of study results and conclusions, the use of consistent methodology for the measurement and assessment of critical endpoint variables in a clinical study may be necessary. **Proposed change:** Replace the current sentence with "To ensure the reliability of study results and conclusions, it may be necessary to use consistent methodology, for example, for the measurement and assessment of critical endpoint variables. However, inappropriate inflexible "one size fits all" approaches that undermine the creation of specific strategies and actions intended to effectively and efficiently support quality in a given study should be discouraged."
176-177	37	*Discourage inflexible "one size fits all" approaches that undermine creation of specific strategies and actions intended to effectively and efficiently support quality in a given study.* **Comment:** True but vague.
178	13	**Proposed change:** "Gather and synthesize evidence in a transparent manner, acknowledge gaps in data and conflicting data where present and known, and anticipate the possible emergence of such gaps or conflicts and communicate them clearly to all involved stakeholders upon awareness."
178	31	"Gather and synthesise evidence in a transparent manner …" **Comment:** Evidence should not be synthesised! Suggest to remove 'synthesised' **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		"Gather evidence in a transparent manner,…"
178-179	20	**Comment:** "…acknowledge gaps in data and conflicting data where present and known…" : Clarification. **Proposed change:** "…**acknowledge gaps in data as well as conflicting data when present**…"
178-180	20	**Comment:** Concerns are raised on how such evidence on gaps and conflicting data, as well as anticipation of such gaps, will be documented.
181-187	28	**Comment:** Despite the strong emphasis on patient input (Section 2.3), considering the impact of planned trial procedures on subjects could be discussed in more depth. Also, given the proposed expansion of the E6 guidance into non-traditional study types, more guidance on focussing on critical-to-quality factors in those scenarios would help. **Proposed change:** **-** Give more emphasis on minimising activities that are non-essential to the study but could be burdensome or discomforting to subjects. - Add more detail on determining critical-to-quality factors in non-traditional study types
181-187 (232-234)	28	**Comment:** Attention should be drawn to any relevant regulatory guidance regarding the design and conduct of particular types of trial or particular disease areas (examples would be those issued by the European Medicines Agency or the US Federal Drug Administration. **Proposed change:** Add sentence at Line 183: "Refer to available regulatory guidance on requirements for the type of study or for studies in the

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		particular disease type." Alternatively/additionally, this could be addressed in lines 232-234.
181-188 (section 3.3.2)	31	**Comments:** This section seems to express an opinion rather than guidance. Whilst it may be valid for many trials to focus on essential activities, there needs to be space for exploration of other research objectives within the given and well defined scope of the trial, in particular in early phase research. This section stifles innovation and exploration. Early phases and later phases of trials should be distinguished.
182-183	20	**Comment:** "…meaningfulness of study outcomes for patients…" : it has to be highlighted that due to cultural, social, geopolitical or medical environment differences, what a patient may consider meaningful for an improve disease management may dramatically differs from one region to another and would be highly subjective.
183-185	31	"Consider whether non-essential activities may be eliminated from the study to simplify the conduct, improve study efficiency and target resources to critical areas." **Proposed change:** Add a sentence as below to clarify: Add: "Especially for higher phases trials, discourage unnecessary complexity, procedures and data collection that fall in the category "nice to have" but are not absolutely necessary to answer the study question(s)."
184-185	26	**Comment:** EORTC does agree non-essential activities may be eliminated. However, based on our experience, translational research and collection of biological material for further research on the backbone of a study may be considered by some stakeholders as non-essential activities. EORTC would like to emphasise, the importance of these side activities. **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		EORTC suggests adding at the end of the line 185: "translational research, collection of biological material for further research on the backbone of a study or other ways to gather further knowledge about drug or the disease studied shall not be considered as nonessential, specifically when its resources and/or results are planned to benefit a larger research community through, for example, data sharing platforms."
186-187	24	**Comment:** There should be considerations for the relevance of good data management practices to support integrity of the data and the need for their adequate resources and funding, and also precaution for the burden of (un-used) data collection **Proposed change:** Rigorously evaluate the study design to verify that planned activities, choice of *really relevant* data to be collected *and reliably managed* are essential.
188	13	**Comment:** It is suggested that the phrase "errors that matter" be clarified and put into context and to consider referencing that resources/effort should be applied in a manner that is proportionate to risk to quality. **Proposed change:** "Deploy resources to identify and prevent or control errors deemed to be important within the context of the study and apply those resources in a manner that is proportionate to risk to quality."
188	18	**Comment:** ACRO recommends the following change. **Proposed change:** Add at the end of the sentence "…..at a time at which corrective action is feasible."
188	20	**Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		"Deploy resources to identify and prevent or control errors that matter" : This sentence is highly open to interpretation. Consider defining or providing examples to clarify.
188	24	**Comment:** This is a valid but very demanding request and means emphasising the need for timely or even real-time data evaluation for proactive responses. Data collection devices that may track subject response are good at collecting large amounts of data, but if they are not evaluated alerts and trends of significance may be of little value to the individual or patient group **Proposed change:** ..or control errors that matter. *This requires diligent real-time monitoring of data to detect error trends before trial-level data are impacted.*
188	31	"Deploy resources to identify and prevent or control errors that matter." **Comment:** Suggest rewording **Proposed change:** "Deploy resources to identify risks and implement mitigation as necessary in order to prevent errors that jeopardize the quality of the study."
189	8	**Comment:** It could be useful to underline the importance of building a scientific / steering committee made of experts from diverse origins representative of the ultimate end-users.
189	13	**Comment:** Remove redundancy between sections 2.3 and 3.3.3 by largely referring to the other section.
189-190	26	**Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		EORTC welcomes the requirement to include "broad range of stakeholders" in study design. However, section 3.3.3. is part of the section 3.3. "Approach to identifying the critical to quality factors" and not part of 3.1."Quality of design". This may be confusing in order to understand the scope of the involvement. In EORTC view it shall be both, design and quality factors. **Proposed change:** EORTC suggest wording of section 3.1. and 3.3. is made more consistent in order to ensure "broad range of stakeholders" are involved in both, design and quality factor confirmation.
189-201	17	**Comment:** Section 2.3 provides guidance on patient input into study design. This is further referred to in Section 3.3, 3.3.3 and 4.4. Whilst we understand that patient engagement can be beneficial in some cases, we are seeking clarification around how the ICH Assembly would envisage this working in practice, including consideration of the following: Expectations around how patient engagement would be documented, including whether recommendations were taken on board and rationale for when recommendation were not/could not be incorporated. (For example, it may not be considered appropriate or recommendations may be conflicting with other stakeholders, or conflicting input from patients depending on regional standards of care)? In terms of transparency, how should patient input be communicated/provided as feedback to stakeholders such as the Research Ethics Committees, Competent Authorities, Investigators and the patient groups themselves. If it is a multi-centre trial, would the expectation be that a number of patients in each country are consulted? The number of patients/patient groups which may be considered appropriate, including consideration of trials in Rare and Orphan indication. **Proposed change:** We suggest that this section be clarified to make it clear it may not always be appropriate. Furthermore, on occasions where it is considered appropriate, it should be expanded to include practical recommendations and expectations in relation to the above

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		points.
189-204	16	***3.3.3 Engaging Stakeholders in Study Design*** *Clinical study design is best informed by input from a broad range of stakeholders, including patients and treating physicians* **Comment:** Patients and their representatives, and other healthcare professionals than treating physicians (dieticians, research nurses, physiotherapists…) **Proposed change:** Clinical study design is best informed by input from a broad range of stakeholders, including patients, their representatives, treating physicians and other healthcare professionals
189-204	36	**Proposed change:** Page 7 section 3.3.3. "Engaging with stakeholders in study design". The first sentence line 190 should be changed as follows: "Clinical study design is best informed by input from a broad range of stakeholders, including HTA bodies, patients, treating physicians and informed by certified clinical guidelines (from HTA agencies and learned societies)."
190-191	13	**Comment:** It should be clarified that the proposed stakeholder list is not exhaustive. In addition, normal practice would be that the patients' perspective is provided by representative(s) of patient organization(s). It is also suggested that the broader term "health care professional" be used in place of "physician". **Proposed change:** "Clinical study design is best informed by input from a broad range of stakeholders, such as patients' organizations (s) and health care professionals. "
190-191	20	**Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		"…including patients and treating physicians.": Treating physicians may be considered broad and may possibly exclude expected investigators and other site personnel, such as Clinical Research Coordinators, who may provide key inputs on the feasibility of a study design. Additionally, some concerns are expressed on the willingness from industrial sponsors to be open to suggestions from outside stakeholders, as it may not have been historically been the case. **Proposed change:** "…including **but not limited to** patients, physicians, **whether they are treating or expected investigators, and key sites personnel, such as research coordinators or nurses**."
190-191	24	**Comment:** The intention here is to say that input from the site is relevant. However, valuable input can be provided from other members of the site team. **Proposed change:** … including patients and ~~*treating physicians*~~ *healthcare providers*.
190-191	31	"Clinical study design is best informed by input from a broad range of stakeholders, including patients and treating physicians " **Comment:** Too focused on patient studies. Clarify that this needs to be checked for applicability for trials in healthy volunteers or early proof of concept trials in patients (i.e. all trials with no therapeutic intent)
191	7	**Proposed change:** add "Ethics Committees" between patients and treating physicians
191	26	**Comment:** EORTC believes the independence of stakeholder is important. **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		EORTC suggests to amend the following wording: "… open to challenge by subject matter experts and stakeholders from outside, in an independent way, as well as within…"
193-195	18	**Comment:** This section makes reference to clinical investigators, site staff and patients/patient organizations but does not reference CROs or other vendors who may be involved in the conduct of the study, and who may have a lot of valuable insight and experience to share **Proposed change:** Add CROs and vendors to list of groups to consult with during the study design phase
193-201	13	**Comment:** This paragraph could also acknowledge the benefit of fostering early patient engagement which can enhance recruitment and retention and thereby improve the collection of data. **Proposed change:** Add statement after Line 201: "This early patient engagement can also enhance recruitment and retention and improve the collection of data."
196	12	**Comment:** it would be useful to detail some of the more niche staff e.g. laboratories, pharmacy, imaging etc particularly where it may help with the real world delivery of the study e.g. lab staff may be able to advise on standard panels of tests so as to remove the need for bespoke trial panels; imaging on acquisition, review and transfer of images etc in addition to how important or not the sample handling and process is or image parameters are etc.
196	35	**Comment:** it would be useful to detail some of the more niche staff e.g. laboratories, pharmacy, imaging etc particularly where it may help with the real world delivery of the study e.g. lab staff may be able to advise on standard panels of tests so as to remove the

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		need for bespoke trial panels; imaging on acquisition, review and transfer of images etc in addition to how important or not the sample handling and process is or image parameters are etc.
196-199	16	"potential study subjects have valuable insights into the feasibility of enrolling subjects who meet proposed eligibility criteria, whether scheduled study visits and procedures may be overly burdensome and lead to early dropouts, and the general relevance of study endpoints and study settings to the targeted patient population" **Comment:** A bit restrictive. **Proposed change:** potential study subjects have valuable insights into the overall development plan, the target population and eligibility criteria, the feasibility of enrolling subjects who meet proposed eligibility criteria, whether scheduled study visits and procedures may be overly burdensome and lead to early dropouts, and the general relevance of study endpoints and study settings to the targeted patient population
201	9	**Comment:** A comment should be added that a thorough characterisation of the target patient population regarding its size and the natural course of disease is deemed necessary. Experience shows that this is underestimated, especially in orphan diseases. **Proposed change:** Add: A thorough characterisation of the target population regarding its size and the natural course of disease is fundamental.
201	24	**Comment:** It is suggested to add a precautionary note regarding the burden of data collection, poor CRF design, etc. in terms of resource during collection and subsequent review, revision/correction etc. to highlight the risk of poor CRF design as well as benefit of good design
202-204	13	**Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Should also reflect the need to discuss novel designs with regulatory authorities and other stakeholders e.g. ethics review boards. **Comment:** As noted in Section 4, early engagement with regulatory authorities should be considered for efficient drug development. Recommend revising statement to encourage early engagement with regulatory authorities to agree on study elements critical to quality, and not only when a study has novel elements. **Proposed change:** "When a study has novel elements considered critical to quality (e.g., defining patient populations, procedures, or endpoints), or uses a novel design approach (e.g. adaptive design, master protocols etc.), early engagement with regulatory authorities and possible other stakeholders, such as ethical review boards should also be considered." Early engagement with regulators should also be considered for seeking agreement on study elements critical to quality.
202-204	21	*" ..,e.g. defining patient populations, procedures, endpoints or logistical issues like the use of 'flying nurses or remote trial visits by TC or WebConferences (Skype) {...} regulatory authorities and the competent IRBs/IECs should also be considered."* **Comment:** As the IRBs/IECs play a major role in the authorization procedure they should be explicitly mentioned here too. We would like to emphasize that the involvement of investigators located in different locations (even in different EU Member States) for one trial subject in the setting of very rare diseases, the involvement of so called-flying study nurses, remote trial visits by TC or WebConferences e.g. via Skype, performed by staff, which is not directly connected with an investigator site etc. can generate relevant ethical issues too.
203	12	**Comment:** Maybe add study design in the brackets? (is mentioned in line 217) **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Suggestion to add study design in the brackets.
204	36	**Proposed change:** Page 8, line 204. The following sentence should be added: "The technology value proposition should be devised early in the clinical development process. Evidence aimed at informing reimbursement decisions should be integrated early in the clinical development, and companies should consider engaging with HTA bodies to realise this."
206	12	**Comment:** Mention documentation to support ongoing review and risk adaptation as this supports sponsor oversight and use of the risk adaptive approach.
206	35	**Comment:** Mention documentation to support ongoing review and risk adaptation as this supports sponsor oversight and use of the risk adaptive approach.
206-208	13	**Comment:** Based on this description, the need is to review risks that have been identified in order to validate that risk control measures have been sufficiently effective. **Proposed change:** "Build on accumulated experience and knowledge with periodic review of critical to quality factors to determine whether adjustments to risk control mechanisms are needed to account for new risks that were not previously identified, since new or unanticipated issues may arise once the study has begun and account."
208	24	**Comment:** There should be a recommendation on a holistic approach to data integrity as well as critical to quality factors through a regular general data quality review (e.g., completeness of records, issues in CRF completion, GCP corrections) to support change where repeated issues arise.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
209	31	"Pay special attention to studies designed to include adaptations …" **Comment:** Suggest to replace 'adaptations' with 'adaptive features' **Proposed change:** designed to include ~~adaptations~~ **adaptive features**…
209 - 211	23	**Comment:** should be added: "To this end, criteria for such adaptations and/or interim decisions, the involved parties to make such decisions, and the need to approval by authorities and/or Institutional Review Board/Ethics Committees should be actively addressed.
209-211	32	**Comment:** **209** Pay special attention to studies designed to include adaptations and/or interim decision points **210** during the study. These will require proactive planning and ongoing review and adjustment of **211** critical to quality factors, and risk management. https://www.ctti-clinicaltrials.org/toolkit/qbd/introduce-qbd/qbd-principles/explore-ctq-factors
210-211	24	**Comment:** We recommend to cross-reference to ICH E9 Statistical Principles for Clinical Trials
212	12	**Comment:** There needs to be some overview here about academic trials - where focus is on improving treatment regimes, not necessarily developing a new product for the market
212 ff	24	**Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		The strict division of the development process in phases I-IV is vanishing more and more. We have Phase 1/2 and 2/3 trials, phase 3b trials that cover in fact phase 4-relevant topics. And we assume that this is an increasing trend as more and more innovative study designs are developed. This guideline should support this development and give guidance on how to handle the classification of innovative studies and treatment development strategies.
212	35	**Comment:** There needs to be some overview here about academic trials - where focus is on improving treatment regimes, not necessarily developing a new product for the market
212 to 429	29	**Comment:** In Chapter 4 it is important to highlight that the hospital pharmacist should be consulted for the drug development planning. Involvement of the hospital pharmacist should be included to improve the quality of the study.
212 to 429 (section 4)	34	**Proposed change:** <u>This section could be removed.</u> Sections 4.1-4.3 are not particularly informative. They catalogue various types of study that can be done but provide little guidance about when or why a particular design might be preferable. It is not clear that these sections add anything to the sort of information that is available in a standard clinical pharmacology textbook or webpage. Section 4.4 about feasibility is useful but could be moved to section 3.3 (Quality). The feasibility assessment should be proportionate, e.g. for some trials the combination of design, operational methods, research group, etc. may mean that this is "business as usual" with no new issues - in which case a minimal feasibility assessment would be fine. Other trials are closely aligned with routine clinical practices and care pathways. But others require particular equipment, patient groups or skills. The word "detailed" (line 410) is an invitation to produce mounds of unnecessary documentation and a new industry of people who create, check and double-check it!
215	7	**Proposed change:** consider the idea to add “Ethics Committees” after regulatory authorities

Line no.	Stakeholder no.	Comment and rationale; proposed changes
215	36	**Proposed change:** Page 4 line 215. After "with regulatory authorities" add "and other relevant stakeholders (e.g. health technology assessment bodies)."
216	9	**Comment:** The closer the interaction between developers and regulatory authorities, the higher the risk of conflicts of interest. Regulatory authorities need to be aware of these risks and implement appropriate measures. **Proposed change:** Add sentence: regulatory authorities need to implement appropriate measures to reduce the risk of conflicts of interests arising thereby.
217	13	**Comment:** Consider adding reference to interactions with HTAs as this is becoming more and more important. **Proposed change:** "This is particularly important for multiregional studies to ensure the study design is aligned with regional regulatory requirements as well as requirements to ensure subsequent market access where appropriate."
217	24	**Comment:** It is important that such a global development strategy fulfils the regulatory requirements of all the regions of interest. **Proposed change:** …is aligned with *all* reginal regulatory requirements
218-219	18	**Comment:** The sentence refers to the target product profile, and ACRO recommends that the text should be strengthened to promote the concept of the target product profile (TPP) as an aid to drug development planning. In a TPP, the sponsor specifies the

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		labeling/prescribing information concepts that are the goals of the drug development program, documents the specific studies intended to support these concepts (thus focusing the aim of each study, facilitating the ability to build quality into study design), and uses the TPP to facilitate dialogue with regulatory agencies. **Proposed change:** Include further detail on the target product profile as an aid to drug development planning.
218-219	19	**Comment:** Section 4 Drug development planning - There may be legacy development plans, combinations of (co-development) plans etc. E.g. early drug development is sometimes performed in specialized companies which then collaborate or sell their development program to larger pharma. They would not necessarily have a drug development plan from the target product profile through post-approval activities.
218-226	31	**Comment:** The list of potential studies should either be shorter, or if it is intended to be comprehensive, then several types should be added, such as PK/PD, ADME, formulation, tolerability. **Proposed change:** see above (line 190-191).
219	24	**Comment:** A drug development is always prepared prospectively. **Proposed change:** The plan is ~~*usually*~~ prepared prospectively…..
220-226	2	**Comment:** In case of applicability also for integrated products (drug-device combinations), add a reference to device-specific investigations.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: The plan generally includes characterisation of formulation development, non-clinical studies required to support the evaluation of the product in human clinical studies and to support product approval, clinical studies designed to support the demonstration of efficacy and safety in the relevant patient population, **including aspects of device handling, if not covered in separate usability studies, as applicable,** studies in special populations .....
220-226	13	**Comment:** Suggest also listing the use of registries here. **Proposed change:** "The plan generally includes characterization of formulation development, non-clinical studies required to support the evaluation of the product in human clinical studies and to support product approval, clinical studies designed to support the demonstration of efficacy and safety in the relevant patient population, studies in special populations as well as any proposed registries and any other relevant sources of real world data (e.g., pediatric populations), regional considerations for product commercialization (e.g., health technology assessments), and post-approval studies.
225	9	**Comment:** Health technology assessments' importance is not limited to commercialisation of drugs, HTA also informs policy decisions. **Proposed change:** Change to: regional considerations for policy decisions on reimbursement and pricing (e.g., health technology assessments)
225	12	**Comment:** important that HTA is mentioned.
226	30	**Comment:** It might also include additional considerations due to the fact that the product is a GMO or due to the incorporation of an

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		integral or non-integral medical device.
227	13	**Comment:** unclear what the guideline means by "priorities of stakeholders" **Proposed change:** clarify or give example.
227	31	"It is important to ensure that the experiences, perspectives, needs, and priorities of stakeholders…" **Comment:** … priorities of stakeholders may conflict with patient safety which is unethical
228	21	*{...} are captured and transparently as well as meaningfully incorporated into the development programme."* **Comment:** Transparency is essential for obvious reasons.
232	10	**Proposed change:** Early engagement with regulatory authorities to understand local/regional requirements and legislation is encouraged and will facilitate the ability to design quality into the study protocol.
232	12	**Comment:** Consideration of regional guidance and other relevant material by regulatory authorities may also assist in defining acceptable ways of working and regulatory expectations
232	13	**Comment:** This draft document and ICH E17 "Multiregional Clinical Trials" cited do not have much guidance in how to tackle challenges among different data privacy, protection, and compliance regulations from EU (GDPR), US (HIPAA), Japan (APPI) etc.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
232	35	**Comment:** Consideration of regional guidance and other relevant material by regulatory authorities may also assist in defining acceptable ways of working and regulatory expectations
232-234 (181-187)	28	**Comment:** Attention should be drawn to any relevant regulatory guidance regarding the design and conduct of particular types of trial or particular disease areas (examples would be those issued by the European Medicines Agency or the US Federal Drug Administration. **Proposed change:** Add sentence at Line 183: "Refer to available regulatory guidance on requirements for the type of study or for studies in the particular disease type." Alternatively/additionally, this could be addressed in lines 232-234.
234	12	**Comment:** results may also be used to change prescribing practice or tailor post-licensing regimes (unless there is a separate section covering academic trials)
234	24	Question: Is there also action for authorities to ensure guidance readily available, accessible & transparent when changed. **Comment:** It can be difficult to locate current local regulatory guidance (for some countries)
234	35	**Comment:** results may also be used to change prescribing practice or tailor post-licensing regimes (unless there is a separate section covering academic trials)
234 - 236	2	**Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		We do not support the correlation between the study design and regulatory acceptability. Studies may not be conducted in the region where the submission is planned. Study design is dictated primarily by scientific objective, and study execution can happen anywhere in the world, provided the set-up is acceptable for the future regulatory body to approve the marketing authorization. Selection of geographical location of the study may be governed by ethnic population, indication (important for recruitment), availability of comparator treatment, but we do not see a direct connection to the region where it will be submitted. **Proposed change**: The results of a study are often used in regulatory submissions in multiple regions. ~~and~~ The study design should ~~also~~ **therefore** consider ~~the relevance fo the study results for regions other than the one(e) in which the study is conducted~~ **acceptability of the chosen population, indication, parameters, etc. according to regulatory submission plan**.
234-236	13	**Comment:** a global approach is also needed for patients' consultations/input. **Proposed change:** "The results of a study are often used in regulatory submissions in multiple regions, and the design should also consider the relevance of the study results for regions other than the one(s) in which the study is conducted. A global approach to patient consultation and input should also be considered."
237-239	18	**Comment:** ACRO agrees with this sentence, that drug trials may include aspects of co-development with other products, but is not clear on the intent of the statement within this guideline. Consequently, we recommend the inclusion of additional text as indicated below. **Proposed change:** Add text to clarify general points that should be taken into account in the design of co-development studies.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
237-239	26	**Comment:** EORTC welcomes the encouragement of co-development and recognition of studies that not only aim to register drugs, but also address questions relevant to devised, diagnostic testing, biomarkers etc… This further emphasise our previous comment (on lines 1-20) that currently this guidelines is drug centred and will not address those complex studies in an adequate way. **Proposed change:** EORTC suggests more consideration is given to cross-modality studies in this or a separate document.
239	30	**Comment:** See comment above – the assays/IVDs are critical for the data quality of the study and this should be made explicit without going into detail
242	10	**Comment:** 4.1 Non-Clinical Studies A description of the animals used is missing, were parameters to be tested are outlined.
242	31	"Non-clinical Studies" **Comment:** it appears that the list of potential non-clinical studies is incomplete. If the intention is to have a complete list, please add relevant other studies. **Proposed change:** see above (line 190-191).
242-255	18	**Comment:** The paragraph does not make clear that the recommended timing of non-clinical studies in relation to clinical trials is described in ICH guideline M3(R2).

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: Include appropriate clarification.
242-258	13	**Comment:** Suggestion to delete the entire section 4.1 as this discusses non-clinical studies which are out of scope of this guideline. The reference to ICH S guidelines and ICH M3 guideline has been suggested instead. **Proposed change:** Delete entire section 4.1, Non-Clinical Studies.
243 - 246	23	**Comment:** Safety pharmacology is missing, core battery of safety pharmacology studies generally should be conducted before human exposure.
244	23	**Comment:** please add immunogenicity
245	31	**"**pharmacology, and pharmacokinetics …" **Comment:** pharmacokinetics is part of pharmacology **Proposed change:** "pharmacology (e.g. pharmacodynamics (PD) and pharmacokinetics (PK)) …"
246	32	**Proposed change:** and M3 Nonclinical Safety Studies). ICH M3 (R2)

Line no.	Stakeholder no.	Comment and rationale; proposed changes
248- 250	13	**Comment:** In the current text, both drug type (small molecule) as well as modalities (biologic/cellular/gene therapy) are listed as examples of the drug's chemical or molecular properties. It is therefore recommended that the text be amended accordingly. In addition, clarification is requested regarding the meaning of the term "complex drug." **Proposed change:** "These characteristics are determined by the drug's chemical or molecular properties when given as, for example, a small or large molecule, or as a cellular/gene therapy product, complex drug, or vaccine); …"
248-253	25	**Comment:** We recommend adding to the list of required investigations the need for in-vitro drug-interaction test at different levels (transporters, enzymes) **Proposed change:** … duration of action; *in-vitro drug-interaction tests at different levels;* and indication
251	3	**Proposed change:** adding: "for antimicrobials, potential for inducing antimicrobial resistance"
256	3	**Comment:** "Before proceeding to studies in humans, there should be sufficient information [etc]": I would consider explicit mention of animal studies (I realize it might not be appropriate)
256	12	**Comments:** The information must also be of sufficient quality. For example we have seen examples of IBs with draft or incorrect data submitted as part of the application. It would be helpful to have the ability to trace the GLP studies used to support a trial, so quality can be checked if required. Currently IBs do not provide information on the study number that allows traceability to a

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		GLP facility.
256	35	**Comments:** The information must also be of sufficient quality. For example we have seen examples of IBs with draft or incorrect data submitted as part of the application. It would be helpful to have the ability to trace the GLP studies used to support a trial, so quality can be checked if required. Currently IBs do not provide information on the study number that allows traceability to a GLP facility.
256-258	18	**Comment:** Given the importance for subject safety of selecting the initial human dose, and the different methods available for calculating this, we recommend again that a specific reference on this subject is made to ICH M3(R2). **Proposed change:** Refer to ICH M3(R2) for methodology on determining the initial dose for human exposure.
256-258	25	**Comment:** We consider it relevant to request creation of more safety information in the non-clinical study phase **Proposed change:** … selection of the initial human dose, *the maximum safety human exposure, initial frequency of administration* and safety duration of exposure, and to….
256-258	37	*Before proceeding to studies in humans, there should be sufficient information to support selection of the initial human dose and safe duration of exposure, and to provide a preliminary assessment of physiological and toxicological effects of the drug.* **Comment:** Please refer to the EMA guideline from 2017: Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
257	12	**Comment:** selection of initial human dose is supported/based on expected/estimated human exposure **Proposed change:** selection of the initial human **exposure and** dose **as well as** safe duration of exposure
258	12	**Comment:** While it is generally understood by default that pharmacological effects expected in clinical studies should be justified by non-clinical data, it is important to mention this in the guideline as well to ensure stronger regulatory reference. **Proposed change:** Suggestion to add the following sentence after the existing wording in Line 258: "Primary pharmacological effects relevant for the intended studies in humans should be confirmed using appropriate in vitro and in vivo models."
258	23	**Comment:** Non-clinical safety information should be adequate to assess potential risk for participants of human trials
258	24	**Comment:** We support the statements in this section, however, there should also be encouragement to limit animal studies to the minimally required extent taking into consideration modern technologies in in-vitro testing and modelling & simulation, but also the uniqueness of the human immune system.
260	12	**Comment:** it would be useful to add in the IMP section about having appropriate comparators and placebos available to support the trial. We have seen plenty of examples of trials which were affected by differences which ultimately meant that the double blind trial could not be claimed as such e.g. differences in appearance, taste, labelling and packaging as well as ineffective blinding processes.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
260	35	**Comment**: it would be useful to add in the IMP section about having appropriate comparators and placebos available to support the trial. We have seen plenty of examples of trials which were affected by differences which ultimately meant that the double blind trial could not be claimed as such e.g. differences in appearance, taste, labelling and packaging as well as ineffective blinding processes.
262-263	2	**Comment:** should there be a cross-reference to GMP and device quality requirements? **Proposed change:** Of particular importance in transitioning from non-clinical to clinical studies is the quality of the product formulation (according to GMP requirements) **as well as the development status of the device part** to be taken into clinical development.
267-268	31	"Links between formulations, established by bioequivalence studies or other means, …" **Comment:** Formulations are often assessed by bioavailability, rather than bioequivalence studies. **Proposed change:** re-word
269	12	**Comment:** Other populations should be considered here and elderly or vulnerable populations (may be adults but the disease/disability may inhibit ability to administer dose **Proposed change:** Age-appropriate formulation development is a consideration when clinical studies are anticipated in paediatric and other vulnerable populations

Line no.	Stakeholder no.	Comment and rationale; proposed changes
269	30	**Comment:** Switching to integral device formulations later in development is frequent and deserves a mention here.
269	35	**Comment:** Other populations should be considered here and elderly or vulnerable populations (may be adults but the disease/disability may inhibit ability to administer dose **Proposed change:** Age-appropriate formulation development is a consideration when clinical studies are anticipated in paediatric and other vulnerable populations
269-270	23	**Comment:** Section 4.2 addresses Quality and Formulations of Investigational Medicinal Products. The reference to age-appropriate formulations only mentions paediatric populations. It is suggested to include age-appropriate formulations in elderly populations as well. **Proposed change:** Age-appropriate formulation development is a consideration when clinical studies are anticipated in paediatric populations (ICH E11) and in the elderly (ICH E7).
269-270	24	**Comment:** Age-appropriate formulations are not only relevant for paediatric but also geriatric populations. **Proposed change:** … when clinical studies are anticipated in paediatric formulations (ICH E11) *and geriatric populations (ICH E7)*.
270	31	"…in paediatric populations (ICH E11)."

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Comment: This could also be a valid point for the geriatric population. **Proposed change:** "…in paediatric or geriatric populations (ICH E11, ICH E7)."
271 (entire section 4.3) and Annex I	26	**Comment:** EORTC recognises efforts made to account for changes in the classical triangular model of drug development (phase I to phase IV, starting from smaller, going to larger trials). However, this model is not anymore the dominant one. EORTC has published its vision with the "diablo shaped model" it may be that further level of evidence involves less participants as it aims to refine the population that may benefit the most from the drug. **Proposed change:** EORTC suggests referring to the ongoing change in the drug development and refer to alternative drug development models, including patient centred and not product (drug or device) centred models.
273	19	**Comment**: "…knowledge accumulated from previous studies": note that one should evaluate knowledge quite widely and not just within development plan of one's own product , e.g. studies by other sponsors on compounds of the same method of action/ drug class
274, 4.3.1	31	**Comment:** The terms Phase 1-4 should be explained using a "more modern" approach as, for example, in the "Appendix on disclosure rules to the "Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014" Phase I: Clinical trials in healthy volunteers or patients, that are carried out to test whether a treatment is safe for people to take, rather than to try to treat, prevent or diagnose a condition (i.e. "without therapeutic, prophylactic or diagnostic intent"), and to study pharmacokinetics and pharmacodynamics (where possible). These trials are usually

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		very small, (typically around 30 people), and usually involve healthy volunteers or sometimes patients. Phase 2 and 3: Trials which are being carried out for treatment, prevention or diagnosis in the patients included in a clinical trial. Phase 4: For treatment, prevention or diagnosis in patients included in a clinical trial using an authorised IMP. EUCROF suggests to use the above approach to explain the trial phases.
276	1	**Comment:** ”categorized” **Proposed change:** “categorised”
276	13	**Comment:** Introduce the concept of pre-proof of concept and post-proof of concept studies.
277-279	22	**Comment:** The statement that temporal phases to not imply a fixed order is misleading. It should be clarified that there are logical and regulatory restrictions to the temporal arrangement of study phases. **Proposed change:** It is also important to realise that the temporal phases do not always imply a fixed order of studies. It should be noted though that legal requirements have to be adhered to, i.e. in some instances one study can only be started when another study has been completed.
278-279	13	**Comment:** The text states “...ideally a logical, step-wise process...”. However, almost all drug development is actually an orchestration of

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		multiple, parallel studies and processes. The text should acknowledge this parallel nature of clinical development. **Proposed change:** "Drug development usually follows a logical, step-wise process in which information from small early studies is used to support and plan later larger, more definitive studies. However, modern exploratory clinical research studies may expand and extend multiple times."
279	24	**Comment:** As it is not always possible to perform larger studies (e.g., rare diseases) we recommend deleting "larger".
281	31	"…in the early stages of development and to plan an appropriate development based on this profile." **Comment:** add 'programme' **Proposed change:** …an appropriate development **programme**…
282-284	25	**Comment:** "Initial studies for….. exploratory studies is confusing. **Proposed change:** ~~*Initial*~~ *Phase 1* studies provide an early evaluation of…
288	12	**Comment:** In academic trials new data / studies conducted by others or change sin prescribing practice may also have a significant impact
288	13	**Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Consider also referencing the use of real-world evidence here. **Proposed change:** "Throughout development, new data may suggest the need for additional studies or use of real-world data to support the use of the product."
288	35	**Comment:** In academic trials new data / studies conducted by others or change sin prescribing practice may also have a significant impact
290	12	**Comment:** Phase 0 (microdosing) has also been used in terminology, so it would be helpful to mention it here
290	35	**Comment:** Phase 0 (microdosing) has also been used in terminology, so it would be helpful to mention it here
290-377	28	**Comment:** The risks to subjects taking part in early-phase trials, especially First-in-Human trials, are not discussed. Several changes to local regulations and guidelines and increased regulatory scrutiny have been implemented by EU member states or the EMA since the previous version of E8. **Proposed change:** Use this section to include that safety risks very as a treatment progresses through stages of development. It could both highlight key elements of trial design to enhance safety of subjects and indicate how they such considerations may feature in risk management and critical-to-quality factors, such as dose escalation decisions, dosing strategies or stopping criteria. A reference(s) to where further guidance can be found would be useful.
290-360 (sections 4.3.1-	31	**Comments:** These sections explain basic clinical pharmacology for traditional oral medicines in lay terms to a lay audience. Some of the

Line no.	Stakeholder no.	Comment and rationale; proposed changes
4.3.2)		content is not correct (such as drug-drug interaction studies being conducted at later phases of drug development (line 318-319)). Some of the content is additionally too prescriptive and rigid (such as activity and potential therapeutic benefit being explored as a secondary objective and being explored in later phases) and not reflect current knowledge or practice to sufficient extent. **Proposed change:** Please refer back to our general comments and previous specific comments about audience purpose and content of the guidance.
295	24	**Comment:** This draft guidance does not encourage early development planning of the paediatric development as, e.g., legally required in Europe. **Proposed change:** Please add: *Results from Phase 1 studies should be suitable for informing the drug's paediatric drug development plan.*
296	37	*Studies typically address one or a combination of the following aspects:* **Comment:** Please refer to the EMA guideline from 2017: Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products.
297 and also 361	16	***4.3.1.1 Estimation of Initial Safety and Tolerability*** ***4.3.3 Post Approval Studies (usually referred to as Phase 4)*** **Comment:** These paragraphs focus very much on chemical entities, and do not address the whole range of advanced medicinal products (gene therapy, somatic cell therapy, tissue-engineered products, nucleic acids based therapies, novel vaccine-based approaches (e.g. Oncolytic Viruses as therapeutic vaccines), gene editing ex-vivo/in-vivo). These products raise series of new scientific

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		challenges (novel mechanisms of action, On target and on target/off tissue associated risks, bio-distribution, pre-clinical safety evaluation with species specificity and predictability, FIH typically not in healthy volunteers, dose determination and PK assessment, often one dose and can't adjust or "stop" dosing, clinical trials often in limited numbers of patients, immunogenicity/stimulation of adaptive immune response, many modulate immune system -(opportunistic infections, malignancies, adverse neurological effects), potential transmission, extended safety monitoring due to longer half-lives and longer term effects, persistence of advanced therapy drug product…) Even if these guidelines are for general considerations and are not specific to some medicines or others, there should be more detailed guidelines for advanced therapies, or links to existing guidance such as: • Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (June 2015): ○ https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-design-early-phase-clinical-trials-cellular-and-gene-therapy-products • Gene Therapy Clinical Trials –Observing Subjects for Delayed Adverse Events (November 2006) ○ http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm078719.pdf • Guideline on Follow-Up of Patients administered with Gene Therapy Medicinal Products (May 2010) ○ http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/11/WC500013424.pdf • Guideline on Safety and Efficacy Follow-up -Risk Management of Advanced Therapy Medicinal Products (December 2008) ○ http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500006326.pdf
297-299	25	**Comment**: The initial and subsequent administration of an IMP in Phase 1 is usually intended to determine the IMP's tolerability in a broader than the expected dose range in patients. **Proposed change:** …the tolerability of *at least* the dosage range expected….
298	12	**Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		add in this section the dose escalation aspect – ie single and multiple doses could be single or multiple ascending doses
298	35	**Comment:** add in this section the dose escalation aspect – ie single and multiple doses could be single or multiple ascending doses
298-300	13	**Comment:** not only the "tolerability" but also the "safety" will be assessed of "the dose range expected to be evaluated in later clinical studies" and above.
302-320	13	**Comment:** The section on pharmacokinetics is not applicable for vaccines. This should be acknowledged. **Proposed change:** Add the following paragraph at the end of section 4.3.1.2: Pharmacokinetic studies are usually not required for vaccines. However, such studies might be applicable when new delivery systems are employed or when the vaccine contains novel adjuvants or excipients. The need for pharmacokinetic studies and their design should be considered on a case by case basis and it is recommended to consult Regulatory Authorities.
303	24	**Proposed change:** Characterisation of the drug's absorption, ~~*distribution, metabolism, and excretion*~~ *ADME* continues throughout…
303-305	2	**Comment:** Cross-reference to device-specifics influencing the absorption is recommended. **Proposed change:** Characterisation of a drug's absorption **(in line with device characteristics influencing the absorption)**, distribution, metabolism and excretion continues throughout the development plan, but.....

Line no.	Stakeholder no.	Comment and rationale; proposed changes
303-312	25	**Comment:** Today, most Phase 1 programmes include Modelling & Simulation studies, especially in the area of drug-drug interaction and PK under certain pathopharmacological conditions or in population sub-groups. **Proposed change:** Obtaining pharmacokinetic information *generated by human studies and/or Modelling & Simulation techniques* in sub-populations such as….
308 - 309	23	**Comment:** Reference to food interaction studies should not focus on modified release formulations only. Instead food interaction studies are already needed at the early stage focusing on the drug compound properties. Later in clinical development when more sophisticated oral formulations are developed, formulation specific food interaction studies may also be needed. **Proposed change:** Food interaction needs to be adequately addressed already during early development. Extent of food interaction as well as in certain cases interaction with specific food components may be necessary. Furthermore, in case of modified release formulations intended for oral administration food interaction studies may become necessary which investigate robustness of the formulation when co-administered with food. In case of certain sensitive ingredients food-component related interaction studies may become necessary.
309	12	**Comment:** It is worth adding that PK in sub-populations is usually done in later phase trials.
309	35	**Comment:** It is worth adding that PK in sub-populations is usually done in later phase trials.
310	32	**Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		310 information in sub-populations such as patients with impaired elimination (renal or hepatic 311 impairment), https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-pharmacokinetics-medicinal-products-patients-impaired-hepatic-function_en.pdf https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-pharmacokinetics-medicinal-products-patients-decreased-renal-function_en.pdf
321	8	**Comment:** Under the PK/PD section, it may be worth noting that "inactive" metabolites of the drug may continue to be responsible for adverse effects, e.g. the time course of QTc prolongation after moxifloxacin differs considerably from what would be expected from PK data.
321-330	13	**Comment:** The section on pharmacodynamics does not address the vaccine specificity. For vaccines, pharmacodynamic studies consist of the assessment of immunogenicity. This should be acknowledged. **Proposed change:** Add the following paragraph in section 4.3.1.3: For vaccines, pharmacodynamic studies are essentially comprised of the immunogenicity studies that characterize the immune response to the vaccine.
321-330	16	***4.3.1.3 Pharmacodynamics & Early Measurement of Drug Activity*** **Comment:** The paragraph does not address recent developments of phase I open label trials with an important effect-size that could be measured, and then the trial evolved to a confirmatory trial (still uncontrolled due to high effect-size that could not be attributed to something else than the drug). • FDA - ~60% of the 28 approvals for anti-PD-(L)1 drugs have been accelerated approvals based on single arm studies (Objective Response Rate ORR)

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		• EMA - ~30% of the 19 approvals for anti-PD-(L)1 drugs have been based on single arm studies (ORR) Clearly, the guidelines is for general considerations, but this could be mentioned as a recent development.
321 - 330	23	**Comment:** role of biomarker should be added
322-326	13	**Comment:** Consider also referencing the use of modelling approaches here. **Proposed change:** "Depending on the drug and the endpoint studied, pharmacodynamic studies and studies relating drug levels to response (PK/PD studies) may be conducted in healthy volunteer subjects or in patients with the target disease. A PK/PD modelling approach can also be employed to reduce the extent of clinical studies where appropriate. If there is an appropriate measure, pharmacodynamic data can provide early estimates of activity and potential efficacy and may guide the dosage and dose regimen in later studies."
324-326	37	*If there is an appropriate measure, pharmacodynamic data can provide early estimates of activity and potential efficacy and may should guide the dosage and dose regimen in later studies.* **Comment:** And must be included; see the EMA guideline from 2017: Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products.
325	13	**Comment:** specify target engagement as well. **Proposed change:** "…. early estimates of activity, target engagement and potential efficacy…"

Line no.	Stakeholder no.	Comment and rationale; proposed changes
326	13	**Comment:** Introduce the concept of proof of mechanism. **Proposed change:** "… and dose regimen in later studies. These studies can support clinical proof of mechanism."
328-330	13	**Comment:** Given that certain medicinal products (e.g. monoclonal antibodies, drug-device combinations) may have long t1/2, consider revising this statement "with a short duration of drug exposure". **Proposed Change:** "… with limited dosing in patients at this early stage."
328-330	25	**Comment:** Preliminary studies of activity or potential therapeutic benefit can include healthy subjects as well, depending on the drug mechanism. **Proposed change:** … of drug exposure in patients *or healthy volunteers* at this early stage.
331	12	**Comment:** For section 4.3.2 it may be worth adding a comment about trials in small populations: the standard separation between exploratory and confirmatory trial may not be possible and the rules of typical clinical development might not necessarily apply.
331	35	**Comment:** For section 4.3.2 it may be worth adding a comment about trials in small populations: the standard separation between exploratory and confirmatory trial may not be possible and the rules of typical clinical development might not necessarily apply.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
331 onwards	13	**Comment:** We suggest to move away from the numbering of clinical trial phases as this can cause confusion with some international bodies as to what these phases really mean in this new era of innovative trial designs and phaseless development. **Comment:** We suggest to include a general comment that traditionally the phases were numbered 1-4, but we should now focus on the concept of totality of evidence which can come from exploratory and confirmatory designs. Flexibility here is important.
332	13	**Comment:** should not define that Exploratory studies are Phase 2 following new guideline concept. **Proposed Change:** "Exploratory studies (usually Phase 2) support clinical proof of concept…"
332-360	39	4.3.2 Exploratory and confirmatory studies **Comment:** We suggest introducing that some flexibility is possible for specific condition/disease such as orphan diseases where confirmatory studies in larger population are not feasible. Moreover, it could be mention at the end of this paragraph that the clinical program may be discussed during the drug development with the regulatory authorities at the occasion of scientific advice.
334-338	4	**Comment:** The draft states that explorary studies (phase 2) should include 'potential study endpoints for further study' in later phase trials. Development and uptake of COS will ensure that this is possible, for these early trials but also that relevant outcomes are present throughout the drug development lifecycle (studies phase 1-4). See podcast from SBU: www.youtube.com/watch?v=PGMhUkdoZag.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: Recommend checking the COMET database (www.comet-initiative.org/studies/search) for any relevant COS and that minimum standards for development should specify that patients, healthcare professionals and those who will use the COS in their research should be involved in its development (journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002447). If a COS does not exist or has not been well developed, consideration should be given to whether this could be done during the the study design stage.
336	13	**Comment:** unclear what the guideline says about "concomitant medication" here. **Proposed change:** suggest to clarify, is this combination therapy, or give example.
337	3	**Comment:** provide a more robust safety profile for the drug, […] **Proposed change:** "provide a more robust safety profile for the drug (including, for antimicrobials, an assessment of potential for selection of resistance), […]"
340	39	4.3.2 Exploratory and Confirmatory Studies (usually referred to as Phase 2 or Phase 3) **Comment:** Could you please clarify what should be the format of modelling and simulation data that could be used to predict clinical outcomes and/or inform study design of clinical trial? We also suggest adding the term simulation alongside modeling, such as: "Other studies may involve modelling and simulation early or intermediate outcome data to predict clinical…"

Line no.	Stakeholder no.	Comment and rationale; proposed changes
340-341	9	**Comment:** Modelling and early outcomes are an indispensable part of hypothesis generating trials, but are inherently not suitable to allow for confirmative results. **Proposed change:** Add: It is important to note that this is the sole purpose of modelling and early outcomes - to inform follow-on trial. Phase II trials are not designed to base regulatory decisions upon.
342	13	**Comment:** Should not define that Confirmatory studies are Phase 3 following new guideline concept. **Proposed Change:** "Confirmatory studies (usually Phase 3) are designed…"
344	9	**Comment:** Confirmative trials are designed to prove hypothesis generated in preliminary studies and, thereby, substantiate marketing authorisation applications. Thus, this is their predominant purpose. **Proposed change**: Delete "often"
345	23	**Comment:** please add: "as well adequate basis for benefit/risk assessment
347-350	13	**Comment:** The sentence seems to imply that a broader population is needed in the confirmatory trials. This is not necessarily the case but is subject to various aspects such as but not limited to trial design/feasibility, drug, disease. It is therefore suggested to add

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		"may". **Proposed change:** "These subjects may more accurately represent the population of patients who will receive the drug once approved and may include subgroups of patients with frequently occurring or potentially relevant co-morbidities (e.g. cardiovascular disease, diabetes, hepatic, and renal impairment) to characterize the safe and effective use of the drug in patients with these baseline conditions."
352	24	**Comment:** The presentation of the term "confirmatory" and the explanations provided is confusing: Confirmatory studies are supposed to "confirm", not to further "explore". If there is a need for further exploration of the dose-response relationship then this needs to be done in Phase 2b to ensure the exact characterisation of the intended dose, expected effect and proposed dose to be confirmed in the confirmatory studies. Studies performed after submission of the marketing dossier with the aim to investigate the drug's use in other stages of disease or the combination with other drugs occur in preparation of a future expansion of the label, have thus an exploratory character and are called "Phase 3b".
353	8	**Comment:** "Exploring the drug in different stages of disease" this should maybe also refer to subgroups / phenotypes, which may not be considered as "stages of disease".
357	3	**Comment:** "the duration of effect of the drug will usually guide the demand for understanding long-term effects and therefore the duration of follow-up in the study." **Proposed change:** add: "or, in communicable diseases, the assessment of transmission to other individuals"

Line no.	Stakeholder no.	Comment and rationale; proposed changes
358	35	**Comment:** adaptive trials are mentioned here, but without much detail, however this is an area where there is a real need for quality by design
358-359	31	**"**They may use complex adaptive or innovative designs to realize efficiencies or test assumptions as data accumulate during the study." **Comment**: Only in this context of confirmatory studies, adaptive designs are being mentioned (see general comments). Also, it would be desirable, the learn more about innovative designs. The mentioning here is very vague.
358-360	12	**Comments:** 1. adaptive trials are mentioned here, but without much detail, however this is an area where there is a real need for quality by design; 2. Confirmatory study may use adaptive design, while complex adaptive or innovative design is acceptable in exploratory CTs only!; 3. Comment: complex adaptive trials are not only seen in conformity (phase III) studies. Please consult recommendation paper on complex trials designs published by CTFG https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2019_02_CTFG_Recommendation_paper_on_Complex_Clinical_Trials.pdf section 5, where the following is stated: "Complex clinical trial designs are generally considered appropriate primarily for phase I/II exploratory clinical trials.". Our experience is also that the complex trial design is most common in Phase II. **Proposed change:** 2. Add complex design in line 339 and lines 331-341; 3. correct accordingly
359	1	**Comment:** "realize" **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		"realise"
359	13	**Comment:** Suggest to either delete "innovative" here or explain difference between innovative and adaptive. The key point is to use designs that have the potential to be efficient, such as group-sequential or adaptive designs. **Proposed Change:** "They may use complex adaptive or design to realize …"
360	5	**Comment:** also mention the multi-drug, multi-arm trials using a master protocol **Proposed change:** add : A particular example is the multi-arm 'integrated research platform' or 'platform trial' using a master protocol and a series of amendement to assess multiple drugs in a given disease, with a common control arm.
360	9	**Comment:** So called adaptive or innovative trial designs are not yet sufficiently established in the scientific community. Their use is associated with methodological challenges regarding the introduction of bias. Therefore, caution is warranted. **Proposed change:** Add: It needs to be ensured that the use of such trial designs does not introduce new sources of bias and is not detrimental for the quality of results in comparison with the conduct of separate randomised trials for each study question.
360	24	**Comment:** This guidance should also take a position on Long-term follow-up studies and the needs for long-term data collection as well as the issue of long-term follow-up of patients who in fact have recovered and are not willing to travel to the site anymore. The role of the patient's treating physician in collecting and providing the remaining information should be defined.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
360	30	**Comment:** With many products the discrimination between exploratory and confirmatory is not as clear cut, e.g. orphan setting, ATMPs etc. Recommendation to make reference to this by inserting text such as: **Proposed change:** *Where clinical trial phases are not as clear-cut due to indication (e.g. orphan setting) or nature of the product (e.g. gene therapy) the distinction should be made on the basis of whether the trial is designed to generate pivotal data for a marketing authorisation application (MAA).*
361	8	**Comment:** Regarding post-marketing surveillance, the manufacturers should be able to provide information on the likely number of doses used (e.g. concerns may be misjudged by anecdotal reports when the denominator taking the drug is large).
361 and also 297	16	***4.3.1.1 Estimation of Initial Safety and Tolerability*** ***4.3.3 Post Approval Studies (usually referred to as Phase 4)*** **Comment:** These paragraphs focus very much on chemical entities, and do not address the whole range of advanced medicinal products (gene therapy, somatic cell therapy, tissue-engineered products, nucleic acids based therapies, novel vaccine-based approaches (e.g. Oncolytic Viruses as therapeutic vaccines), gene editing ex-vivo/in-vivo). These products raise series of new scientific challenges (novel mechanisms of action, On target and on target/off tissue associated risks, bio-distribution, pre-clinical safety evaluation with species specificity and predictability, FIH typically not in healthy volunteers, dose determination and PK assessment, often one dose and can't adjust or "stop" dosing, clinical trials often in limited numbers of patients, immunogenicity/stimulation of adaptive immune response, many modulate immune system -(opportunistic infections, malignancies, adverse neurological effects), potential transmission, extended safety monitoring due to longer half-lives and longer term effects, persistence of advanced therapy drug product…) Even if these guidelines are for general considerations and are not specific to some medicines or others, there should be more

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		detailed guidelines for advanced therapies, or links to existing guidance such as: • Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (June 2015): o https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-design-early-phase-clinical-trials-cellular-and-gene-therapy-products • Gene Therapy Clinical Trials –Observing Subjects for Delayed Adverse Events (November 2006) o http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm078719.pdf • Guideline on Follow-Up of Patients administered with Gene Therapy Medicinal Products (May 2010) o http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/11/WC500013424.pdf • Guideline on Safety and Efficacy Follow-up -Risk Management of Advanced Therapy Medicinal Products (December 2008) o http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500006326.pdf
361 - 371	23	**Comment:** Non-interventional studies are not governed by ICH-GCP. It should be made clear in section 4.3.3 that post approval studies are only mentioned to complete the picture.
363	8	**Comment:** Post approval studies are critical to provide additional information on effectiveness of the drug, including real life effectiveness and comparative effectiveness. **Proposed change:** Please add effectiveness to the sentence (e.g. real life effectiveness and comparative effectiveness). Please refer to the glossary of key terms and definitions.
363	24	**Comment:** This guidance should not ignore the increasing need for providing Health Technology Assessment-relevant data, mostly generated in Phase 4.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: … including providing additional information on the efficacy, safety, *Health Technology Assessment-relevant topics,* and use of the drug.
364	21	*"{...} use of the drug, e.g. in reality/real life setting".* **Comment:** This type of study gets more important.
364-366	9	**Comment:** The approval of drugs based on preliminary results and surrogate endpoints shifts risks from pre- to post-authorisation. If this risk shift is deemed appropriate, it needs to be ensured that relevant data is generated in due time after approval. **Proposed change:** Change sentence #2: After such an approval, studies need to be conducted to reliably demonstrate effects on clinical endpoints meaningful to patients.
365-366	16	*"After such an approval, studies would be conducted to demonstrate effects on clinical endpoints"* **Comment:** Confirmation more than demonstration **Proposed change:** After such an approval, studies would be conducted to confirm effects on clinical endpoints
366	13	**Proposed change:** "… be conducted to demonstrate effects on clinical outcomes."
366-368	16	*Studies in special populations, such as paediatric and elderly populations, may be conducted to understand the drug effects in these populations*

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Comment: Ideally paediatric studies should be conducted in the pre-authorisation phase. This is the goal of different legislations. Here the text can give the impression that they typically are for the post-authorisation phase. **Proposed change:** Studies in special populations, such as paediatric and elderly populations, may be conducted to understand the drug effects in these populations when the evidence has not been generated prior to the authorisation already.
367	13	**Comment:** As elderly subjects are likely to be studied in Phase 3 or earlier, suggest the following edit: **Proposed Change:** "Studies in special populations, such as pediatric populations, may be conducted…."
367	24	**Comment:** Studies in special populations such as paediatric populations are supposed to occur during Phase 2 and 3 according to European legislation. Although this is a global guidance it should express the need for adherence to regional legalisation.
368	1	**Comment:** "authorization" **Proposed change:** "authorisation"
368-369	13	**Comment:** suggest to be more specific about "special patient groups". **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		"… potential risks or specific patient groups at risk."
369-370	16	*"Studies with long-term follow-up or with comparisons among authorized drugs may provide important information on safety and efficacy to the medical community"* **Comment:** Maybe to expand post-approval studies to comparisons with other treatments than authorised products (e.g. radiotherapy, surgery, life-style measures such as diet…) **Proposed change:** Studies with long-term follow-up or with comparisons among authorized drugs or other treatments may provide important information on safety and efficacy to the medical community
370-371	32	**Comment:** **370** may provide important information on safety and efficacy to the medical community. Post **371** approval studies encompass a range of designs and data sources (See Section 5). https://www.ema.europa.eu/en/scientific-guidance-post-authorisation-efficacy-studies
372	8	**Comment:** A mention should be made regarding drug combinations and trials consisting of standard regimens vs standard + 1 regimens (the history of improvements in leukaemia treatment and a significant role in MDR-TB). These sorts of trials, especially if they involve drugs of known safety and efficacy when used for other conditions, should be subject to less strict requirements compared to new drugs.
372	12	**Comment:** this section would be a good place to mention investigator led studies and how this data can be used to support extensions of a licence or future directions for investigation. Allows another link to academic research whilst allowing for the mention of data and information exchange

Line no.	Stakeholder no.	Comment and rationale; proposed changes
372	35	**Comment**: this section would be a good place to mention investigator led studies and how this data can be used to support extensions of a licence or future directions for investigation. Allows another link to academic research whilst allowing for the mention of data and information exchange
373-375	24	**Comment:** Co-administration of drugs or new delivery devices should be mentioned as well. **Proposed change:** …new routes of administration, *combination of drugs or new drug delivery device,* or additional patient populations….
373-377	12	**Comment**: New nonclinical or human pharmacology studies / data may be needed also in case of off label/new or additional indication as well as different population. while previous studies and clinical expertise can inform such programme , however not the only source of information **Proposed change:** please change accordingly
376-377	31	"Data from previous studies or from clinical experience with the approved drug may inform these programmes. " **Proposed change:** "…may ~~inform~~ **influence** these programmes'.
378	8	**Comment:** Women as a whole may be special populations, in various domains PK/PD may differ by gender.
378	13	**Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		For special population, it is often difficult to conduct regular clinical trials, so how should we consider various trial designs as described in Section 5?
378ff	24	**Comment:** This guideline should contain a paragraph on patient information and informed consent, especially in vulnerable populations like children, elderly, incapacitated adults, pregnant women, etc. as only subjects who are properly informed, with the appropriate communication tools, understand their important role and contributions to the study. Although achieving optimal quality of a study in all aspects is the primary goal in clinical studies, the pre-requisite for all studies is the informed consent of the participants.
386	13	**Comment:** Although technically not a "special population", recommend that non-clinical (section 4.1) and clinical considerations for investigations in women of child-bearing potential are addressed in this guideline.
386 & 387	7	**Comment:** wouldn't it be better to start the § by stating that pregnant should never participate to a clinical trial except in trials where the medicinal product is intended for use during pregnancy?
386-391	16	4.3.5 Consideration in Special Populations • Investigations in pregnant women If a pregnant woman is enrolled in a clinical study, or a woman becomes pregnant while participating in a clinical study, evaluation of the pregnancy, foetus, and child, and reporting of all outcomes in the clinical study report, is often necessary. The same applies for clinical studies that include pregnant women, where the medicinal product is intended for use during pregnancy. **Comment:** This paragraph follows 4.3.3 on Post-approval studies, and one could deduce investigations in special populations to be conducted post-approval. Why to restrict the enrolment of pregnant women in post-approval studies? Depending on the nature

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		of the product, these studies could be envisaged during the pre-authorisation phase in a controlled way. Are the risks for women, their foetus and society greater when such well controlled research is conducted during the pre-authorisation phase, or when the product is released on the market with no or little information on the use during pregnancy, wishing for the best? **Proposed change:** To move 4.3.5 before 4.3.3 and to add: Studies in special Populations can be done pre or post-approval.
386-395	32	**Comment:** **386** • Investigations in pregnant women **387** If a pregnant woman is enrolled in a clinical study, or a woman becomes pregnant while **388** participating in a clinical study, evaluation of the pregnancy, foetus, and child, and reporting **389** of all outcomes in the clinical study report, is often necessary. The same applies for clinical **390** studies that include pregnant women, where the medicinal product is intended for use during **391** pregnancy. **392** • Investigations in nursing women **393** Excretion of the drug or its metabolites into human milk should be examined where applicable **394** and feasible. When nursing mothers are enrolled in clinical studies their babies are usually also **395** monitored for the effects of the drug. https://www.ema.europa.eu/documents/scientific-guideline/guideline-risk-assessment-medicinal-products-human-reproduction-lactation-data-labelling_en.pdf
387-388	19	**Comment:** woman becomes pregnant while participating in a study herself, or her partner (male) is participating in the study?

Line no.	Stakeholder no.	Comment and rationale; proposed changes
389	9	**Comment:** The guideline in force insisted on the exclusion of women that become pregnant while participating in a clinical study. This may indeed not be necessary and appropriate in all cases. However, proper documentation of the effects the study drugs exerts is indispensable, since pregnancies on treatment will occur sooner or later. **Proposed change:** Delete "often"
389	13	**Comment:** outcome of the pregnancy may not be known at the time of the clinical study report finalization. **Proposed change:** suggest to add "or further reporting", or "if available at the time of the clinical study report".
389	24	**Comment:** As there is very limited information about the effect of drugs during pregnancy there is urgent need to collect all possible information, also on the outcome, however, flexibility should be enabled. **Proposed change:** Delete "often" and add *"except if stipulated differently in the protocol"*.
392 & 393	7	**Comment:** same consideration as above for nursing women.
394	9	**Comment**: As with pregnancies, drug exposure to women who are breast-feeding will occur. Therefore, it is important to gather data on possible effects and on the exposure, this means for the child. Feasibility of the analysis of metabolites excreted and monitoring

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		of babies who were exposed to the drug cannot be optional **Proposed change:** Delete "and feasible" and substitute "are usually" by "should be"
394	12	**Comment:** Inclusion of nursing mothers in a trial is extremely rare and this should be conveyed in additional wording.
394	35	**Comment:** Inclusion of nursing mothers in a trial is extremely rare and this should be conveyed in additional wording.
397-398	39	4.3.5 Consideration in special populations **Comment:** We suggest adding "the drug development in the paediatric population may be defined in a Paediatric Application Plan (PIP) approved by the regulatory authorities".
405	12	**Comment:** include here vulnerabilities for other populations such as healthy volunteer or patients with terminal illnesses who enter FIH trials
405	35	**Comment:** include here vulnerabilities for other populations such as healthy volunteer or patients with terminal illnesses who enter FIH trials
405-406	20	**Comment:** "Particular attention should be paid to the ethical considerations related to informed consent in vulnerable populations…" : Despite its importance and application to all subgroups detailed in paragraph 4.3.5, the location of this sentence at the end of the chapter may result in readability issues and reader may assume this global recommendation only applies to the last

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		subgroup detailed (renal and hepatic impaired population). **Proposed change:** Rise this sentence as written in line 386, prior to the description of specific population.
405 to 406	29	**Comment:** Further clarification in regard to the patient's informed consent is needed. Poor informed consent can be responsible for decreasing the quality of a clinical trial.
after 406	23	**Comment:** A new section 4.3.6 should be added here, such as: 4.3.6 Research-Driven Clinical Studies. Beyond studies conducted for the purposes of obtaining and maintaining marketing authorization by pharmaceutical companies, studies conducted by independent researchers are important to close initial and emerging knowledge gaps at later stages of the life cycle of a drug. These studies are often referred to as investigator-initiated trials (IIT). Objectives, design and conductance of such studies may differ considerably from those supported by the owners of the marketing authorization, also related to the limitation of respective resources and the need to provide information on drug effects in "real-world" patients. Peculiarities in study designs, including the process to obtain informed consent, should be justified by the relevance of the data to be acquired by such studies.
407	9	**Comment:** Feasibility of clinical trials is often discussed. In practice, feasibility seems not always be an objective value, but to depend on how much effort investigators are willing to invest when planning for endpoint assessment or inclusion of participants. Only in rare cases, trial designs itself are not feasible. Thus, the inclusion of a paragraph on feasibility bears the risk of promoting subpar trial designs due to insufficient efforts due to commercial considerations. This is often inappropriate, bearing in mind that uncertainties remaining due to insufficient studies are fought on the back of patients.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
407	13	**Comment:** The concept of obtaining input from the various parties that will play a role in performing high quality clinical studies is referenced in many different sections of the document. Could the document be simplified if that process is consolidated here in the feasibility section?
409-410	24	**Comment:** To link with proposed addition on good data and data management in line 410 **Proposed change:** **...**is a protocol that is ~~*both*~~ scientifically sound, operationally viable, *and enabling robust quality data*.
410 - 412	13	**Comment:** As enrichment strategies are becoming more widely used to ensure targeting of treatments to patients who can most benefit, it is suggested to mention enrichment strategies. **Proposed change:** **"**A detailed feasibility assessment includes consideration of study design (e.g. using enrichment strategies) and implementation elements that could impact the successful completion of a clinical development program or study from an operational perspective in a geographical region."
413-420	18	**Comment:** May wish to also include the following additional examples (subject to clarification of above point – lines 413-429): 1. 'Logistical' considerations for delivery of investigational product(s); such as shipping/handling, local import/export requirements, storage requirements, and local availability and/or acceptance of comparator drug(s), where applicable. 2. Competitive landscape/saturation of clinical trials which are ongoing and/or planned which may directly target the same patient population and in turn lessen the availability of potential subjects to enrol

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: Add appropriate text to identify need to ensure an evaluation of logistical considerations for delivery of the investigational product(s) to sites, and the ability of the site to dispense, handle, store and return or destroy the product(s) as required. Add text to identify the need to consider study plan in relation to clinical development space in indication. Suggest to also state the importance of collecting input from investigators and site staff when conducting the feasibility assessment.
413-420	20	**Comment:** This paragraph mostly describes site-related feasibility metrics. However, attention should be raised that sponsors also consider their own organization ability to ensure proper systems are in place for data integrity and patient safety monitoring**.**
413 - 429	18	**ICH E8(R1) TEXT:** Feasibility considerations include but are not limited to the availability of qualified investigators/site personnel with experience in conducting a clinical study; availability of equipment and facilities required to successfully conduct the clinical study; availability of the desired patient population; ability to enrol sufficient numbers of participants as determined by the study's power analysis analysis; the ethical and regulatory considerations, which include informed consent, parental/caregiver consent and patient assent for paediatric studies; and regional standards of care. An important aspect of study feasibility is understanding the view of potential study subjects about protocol elements that could impact their willingness to enrol or continue participation in the study (e.g., impact of study procedures, meaningfulness of the study objectives/outcomes). The retention of study subjects and the follow-up of subjects who have withdrawn from treatment are key critical to quality factors. **Comment:** These are quality factors that are limited to the conduct of clinical trials, not the conduct of all types of clinical studies. **Proposed change:** Revert to using the term "trial" and "clinical trial" throughout Revision 1 of ICH E8.
414	12	**Comment:** qualifications and experience do not always ensure competence. Quality by design should also consider how the competence is

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		assessed for all individuals involved in the conduct of clinical trials.
414	35	**Comment:** qualifications and experience do not always ensure competence. Quality by design should also consider how the competence is assessed for all individuals involved in the conduct of clinical trials.
414-420	13	**Comment:** The study's schedule of activities is also an important determinant of operational feasibility at the site. Also include reference that obtaining input from study site staff is important to assess and improve operational feasibility. **Proposed change:** "Feasibility considerations include but are not limited to the availability of qualified investigators/site personnel with experience in conducting a clinical study; availability of equipment and facilities required to successfully conduct the clinical study; operational feasibility at the site based on the study schedule of activities; availability of the desired patient population; ability to enroll sufficient numbers of participants as determined by the study's power analysis; the ethical and regulatory considerations, which include informed consent, parental/caregiver consent and patient assent for pediatric studies; and regional standards of care. Obtaining input from staff at the potential study site is important to assess and improve operational feasibility."
414-420	16	*"Feasibility considerations include but are not limited to the availability of qualified investigators/site personnel with experience in conducting a clinical study; availability of equipment and facilities required to successfully conduct the clinical study; availability of the desired patient population; ability to enrol sufficient numbers of participants as determined by the study's power analysis; the ethical and regulatory considerations, which include informed consent, parental/caregiver consent and patient assent for paediatric studies; and regional standards of care"* **Comment:** First of all the feasibility relies on the review of the clinical trial by an ethics committee. As explained in EMA "Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU Regulatory Authorities"

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		(https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/reflection-paper-ethical-good-clinical-practice-aspects-clinical-trials-medicinal-products-human-use/european-economic-area-submitted-marketing-autho_en.pdf), *"Research may only be undertaken if the research project has been approved by an EC (or other body authorised to review clinical research on human beings) with appropriate jurisdiction for the investigator sites and trial concerned, after independent examination of its scientific merit, including assessment of the importance of the aim of research, and multidisciplinary review of its ethical acceptability".* **Proposed change:** Feasibility considerations include but are not limited to the availability of an ethics committee, of qualified investigators/site personnel with experience in conducting a clinical study; availability of equipment and facilities required to successfully conduct the clinical study; availability of the desired patient population; ability to enrol sufficient numbers of participants as determined by the study's power analysis; the ethical and regulatory considerations, which include informed consent, parental/caregiver consent and patient assent for paediatric studies; and regional standards of care
418	13	**Comment:** For a study with a time-to-event endpoint (such as e.g. PFS or OS), the number of patients is not determined through the power analysis. Rather, the latter determines the number of events that need to be collected. The number of patients then "only" determines how long it takes to collect the prespecified number of events.
420	9	**Comment:** As already mentioned, feasibility almost always is not an objective measure, but relies on efforts taken in recruitement, study size, training of personnel, etc. Often, methodological challenges are used to hide commercial decisions. **Proposed change:** Add: If problems regarding feasibility are foreseen, quality measures to circumvent those should be implemented, such as appropriate training of investigators and site personnel, inclusion of additional study sites, better explanation of the trial rationale to patients

Line no.	Stakeholder no.	Comment and rationale; proposed changes
420	21	*{...} and patient assent for paediatric studies; and regional standards of care, as well as adequate recruitment methods."* **Comment:** see comment for line 107/108.
421-424	13	**Comment:** Duration of the study is an important factor here. **Proposed change:** "… (e.g., impact of study procedures, meaningfulness of the study objectives/outcomes, study duration). …"
421-429	16	*An important aspect of study feasibility is understanding the view of potential study subjects about protocol elements that could impact their willingness to enrol or continue participation in the study (e.g., impact of study procedures, meaningfulness of the study objectives/outcomes).* **Comment:** Practical aspects are equally important (length of study, amount of visits, amount of blood draws, amount of school / work missed for parent / child, etc.) **Proposed change:** An important aspect of study feasibility is understanding the view of potential study subjects about protocol elements that could impact their willingness to enrol or continue participation in the study (e.g., impact of study procedures, meaningfulness of the study objectives/outcomes, practical aspects).
421-429	17	**Comment:** Section 2.3 provides guidance on patient input into study design. This is further referred to in Section 3.3, 3.3.3 and 4.4. Whilst we understand that patient engagement can be beneficial in some cases, we are seeking clarification around how the ICH Assembly would envisage this working in practice, including consideration of the following:

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Expectations around how patient engagement would be documented, including whether recommendations were taken on board and rationale for when recommendation were not/could not be incorporated. (For example, it may not be considered appropriate or recommendations may be conflicting with other stakeholders, or conflicting input from patients depending on regional standards of care)? In terms of transparency, how should patient input be communicated/provided as feedback to stakeholders such as the Research Ethics Committees, Competent Authorities, Investigators and the patient groups themselves. If it is a multi-centre trial, would the expectation be that a number of patients in each country are consulted? The number of patients/patient groups which may be considered appropriate, including consideration of trials in Rare and Orphan indication. **Proposed change:** We suggest that this section be clarified to make it clear it may not always be appropriate. Furthermore, on occasions where it is considered appropriate, it should be expanded to include practical recommendations and expectations in relation to the above points.
423-424	20	**Comment:** "…meaningfulness of the study objectives/outcomes…": As mentioned in a previous comment, what can be meaningful for a patient may bring several levels of subjectivity. Sufficient weight in feasibility metrics shall be implemented to avoid omission of medical key factors (for example a change in a key lab value) that may not sound meaningful for a patient.
424-425	2	**Comment:** Subjects may withdraw and refuse follow-up discussions of any kind. **Proposed change:** In line with the principles in GCP, this should be considered to be nice to know and not need to know.
424-426	25	**Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		The statement on the relevance of patient consultation in the feasibility phase of the study also applies to healthy volunteers. **Proposed change:** … early consultation with ~~*patients*~~ *representatives of the intended study population* will have….
425	13	**Comment:** Whether patients who withdraw from treatment should remain in the study depends on the clinical objective and the estimand derived from it. A reference to ICH E9(R1) might be useful. Or, pertaining to quality factors, does the statement intend to say that patients should remain in the study for safety reasons primarily? Suggest to clarify this.
425-429	13	**Comment:** Meaning of bolded part of sentence not entire clear "It is important to not underestimate the value that appropriate and early consultation with patients will have on the feasibility of the study, adherence to the protocol, and, more essentially, relevance (or suitability) **for patients of the drug approval based on the accumulated knowledge and experience from the clinical studies.** " **Proposed Change:** "It is important to not underestimate the value that appropriate and early consultation with patients will have on the feasibility of the study, adherence to the protocol, and, more essentially, relevance (or suitability) of the drug approval for patients, based on the accumulated knowledge and experience from the clinical studies."
425-429	22	**Comment:** Once again, the need to consult patients is stressed, whereas the need to involve treating physicians / clinical investigators during feasibility is limited to ensuring sufficient qualification and resources. In reality, clinical investigators often complain that they have not been asked to give input on the feasibility of the study protocol and procedures from a physician's point of view. **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		It is important to not underestimate the value that appropriate and early consultation with patients and treating physicians and/or clinical investigators will have on the feasibility of the study, […].
430	13	**Comment:** Section 5 directly links the study objectives with the study design. Subject to its approval, the draft ICH E9(R1) Addendum to the guideline on statistical principles for clinical trials (on estimands and sensitivity analysis in clinical trials) specifies an intermediate step of defining relevant estimands for the study. Only after this intermediate step can the most appropriate study design be considered, which can address the defined estimands. In addition, terminology from the ICH E9(R1) Addendum seems to be present, for example the concept of "intercurrent events" is specified in lines 568-569. **Proposed change:** Please add cross reference to ICH E9(R1) Addendum and the notion of estimands, if approved at the time of publishing this guideline.
430 (section 5)	34	**Proposed change:** <u>This section could be removed.</u> If it is to remain, then it should be significantly improved to provide guidance about how these aspects influence the Quality of the trial. For example, simply stating, "The use of a cluster unit has implications for multiple design elements and quality factors (e.g., intervention, analysis, consent)" (lines 473-474) provides no insight into what these implications might be or how the might be handled in a QbD approach. There are many other similar examples of simple statements of fact with no analysis or guidance: e.g. lines 477-478; 499-505; 506-511; 512-514; 515-519; 520-523; 529-533; 633-638. In each of these cases, the text should either be deleted or there should be guidance as to what the implications might be for study quality (well-being of participants, reliability of results). The section on Intervention (section 5.1.2) should be about the nature of the intervention and the implications for study design (e.g. what additional checks are needed prior to enrolment or during the treatment phase), training & monitoring in order to ensure participant safety and reliable results (including ascertainment and assessment of potential safety issues). Similarly, simply stating, "Interventional studies often have the potential to control biases better than observational studies"

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		(line 484) is not particularly helpful and in any cases the potential for bias in an interventional study will be hugely influenced by whether it is randomized or not (yet randomization is not mentioned in this paragraph). The wording on pragmatic trials (lines 488-490) is both confused and confusing! First, a pragmatic trial may be randomized or not. A pragmatic randomized trial combines the key elements of randomization (including allocation concealment and intention-to-treat analysis) with collection of data from routine sources (e.g. electronic healthcare records). In other words, pragmatic relates to how the data are collected, the participants are enrolled, or the treatment is administered. Secondly, in all clinical trials, management of the participants' health remains the responsibility of their regular clinicians with the investigator being responsible only for those aspects that relate to the trial itself. In some trials the regular clinician and the investigator may in fact be the same person, in others they may not. For example, if a patient is enrolled in a trial of Parkinson's disease treatment by their neurologist, they would still seek care for their eczema from a dermatologist or primary care physician.
440	31	"Clear objectives will help to determine the study design …" **Comment:** suggest to replace 'the' with 'good' **Proposed change:**… help to determine ~~the~~ **good** study design…
442	24	**Comment:** Objectives may also need to be modified as new risks are revealed. When there are modifications it should be stressed that the modifications have to be handled in line with GECP and relevant legislation **Proposed change:** … modified as practical considerations, *risks* and limitations are revealed. *Changes should be made in accordance with GCP and relevant legislations concerning necessary regulatory and ethics approvals.*

Line no.	Stakeholder no.	Comment and rationale; proposed changes
442	25	**Comment:** Also unexpectedly arising risks can lead to a modification of objectives. **Proposed change:** … as practical considerations, *risks* and limitations…..
444-445	25	**Comment:** A very important element of a clinical study is the Time-and Events-Schedule. We recommend adding this. **Proposed change:** ...control group, *time-and-events-schedule,* response variable, …
445	12	**Comment:** include data capture and transfer **Proposed change:** The protocol brings these elements together with the study objectives, study type, data sources, data capture and data transfer
445	35	**Comment:** include data capture and transfer **Proposed change:** The protocol brings these elements together with the study objectives, study type, data sources, data capture and data transfer
447	24	**Comment:** The protocol needs to be completed before study approval to enable the respective study approval. **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		..should be finalised before start of the study *and approved according to the applicable legislation*
448	8	**Comment:** It should emphasize the importance of ensuring that study populations, as defined in the study objectives and detailed in inclusion/exclusion criteria, are concordant with the considered ultimate target populations.
448	24	**Comment:** This explanation is confusing as there is no "mix" of studies as the most stringent study requirements apply. The example provided here is an interventional trial with additional health management data collection. The example should explain that a combination of two types of data collection can be combined and that the more stringent legislation applies.
448-478 (section 5.1.1)	31	**Comment:** healthy volunteers are not mentioned at all. Other highly specific populations and trial types are mentioned without context or explanation. Statistical sample size calculations are not done for some types of trials (e.g., first-in-human or other early phase exploratory trials). **Proposed change:** Suggest to amend accordingly.
450-451	13	**Comment:** It is recommended that the term "available" be replaced by "eligible" as the latter is a more accurate description of the study population. **Proposed change:** "In practice, the study population is limited to subjects eligible to participate and for whom consent is available (see ICH E6)." **Comment:** This will be under the current ICH-E6, but the need for consent when using various data sources such as Real-World data will be

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		a future discussion. **Proposed Change:** "… the study population is limited to subjects available to participate and usually for whom consent is available."
450-451	16	*In practice, the study population is limited to subjects available to participate and for whom consent is available (see ICH E6).* **Comment:** Although I acknowledge that this is true in practice, the sentence as it is written undermine a bit the concept of clinical trials **Proposed change:** In practice, the study population is often limited to subjects available to participate and for whom consent is available (see ICH E6).
451	26	**Comment:** EORTC would like to recall that though consent is indeed mostly required, there is a limited number of situations that need special approach (e.i. emergency research) **Proposed change:** EORTC suggests wording is nuanced to allow for justified and currently already accepted exceptions.
454	24	**Comment:** We recommend to reference to ICH E9, Statistical Principles for Clinical Trials
455	1	**Comment:** "maximize" **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		"maximise"
455	29	**Comment:** The study population is a critical point. **Proposed change:** EAHP suggests to change "might" to "must" .
460	9	**Comment:** Choices on the broadness of study populations are indeed depending on the progress of development. However, to avoid inappropriate slicing of indications, more heterogeneous and broader populations should be enforced in pivotal trials **Proposed change:** Change "tend to be" to "should generally be"
461	37	*"for a precision medicine study, for example , may target the subgroup of diseased patients with"* **Comment:** This and the below mentioned examples do not add to a better understanding of study population selection. Besides enrichments study designs and cluster randomization, there are more issues to consider.
462	5	**Proposed change:** add : The stratification methods used to identify and to define the subgroups of diseased patients represent a critical to quality factor.
462	9	**Comment:** Enrichment designs create its own challenges: They presuppose an in depth knowledge of relevant patient criteria (such as biomarkers predictive for treatment response) and respective cut-offs in case of non-binary markers. Although this knowledge is a key element of quality by design, it has become clear in the past that preliminary data is often insufficient to draw firm

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		conclusions on these elements. Adaptive enrichment designs have been proposed as a solution to these problems, but are currently not fully established and discussed critically. Therefore, the guideline should mention challenges associated with enrichment designs and should not endorse adaptive enrichment designs as a solution to those problems. **Proposed change:** Add: Enrichment designs require in-depth knowledge of relevant criteria, which needs to be established a priori and critically assessed.
467	22	**Comment:** The term "pragmatic trial" is used without prior introduction of the concept of "pragmatic" versus "explanatory" trials. **Proposed change:** Add a definition for "pragmatic trials" (ideally together with one for "explanatory trials") at an appropriate spot within this guideline (e.g. in section 5.1.4). If such a definition is provided after the first use of the term add a reference.
470-471	16	*Because of the study objectives or because of feasibility or efficiency, there may be situations in which the population unit is not an individual but a group of subjects (known as a cluster)* **Comment:** With n-of-1 trials, the individual is actually the trial **Proposed change:** Because of the study objectives or because of feasibility or efficiency, there may be situations in which the population unit is not an individual but a group of subjects (known as a cluster, n of 1 trials notwithstanding)

Line no.	Stakeholder no.	Comment and rationale; proposed changes
472	37	*"For example, some vaccine studies make use of cluster randomisation to measure their"* **Comment:** See above (line 461) - This and the below mentioned examples do not add to a better understanding of study population selection. Besides enrichments study designs and cluster randomization, there are more issues to consider.
475	10	**Comment:** The study should plan to have a sufficient number of subjects (but no more than strictly necessary) to make statistical conclusions based on the findings either by obtaining a certain precision or by controlling the probabilities of making false conclusions
479-482	18	**ICH E8 (R1) TEXT:** An important distinction between studies is whether the choice of the study drug and the health management of the subjects are controlled by the study (with proper regard to human subject protection and regulatory requirements) or merely observed in the study. The former case is referred to as an interventional study and the latter case is referred to as an observational study. Interventional studies often have the potential to control biases better than observational studies (see Section 5.1.5). Factors such as study objectives, feasibility, data sources, and anticipated biases and uncertainty play a role in the choice between interventional and observational studies. Observational studies are usually conducted in the post-approval period. **Comment:** The text (lines 479 – 487) in the "intervention" section is confusing and problematic. It provides a vague 'inferred' meaning of 'intervention' that reads as 'intervention = patient's health management and study drug controlled by the study'. Whereas, according to the "objectives of this document" (refer to Section 1), "Clinical studies of medical interventions are conducted to provide information that can ultimately improve access to safe and effective drugs with meaningful impact on patients, while protecting those participating in the studies. This document focuses on designing quality into clinical studies, considering the diversity of clinical [TRIAL] designs and data sources used to support regulatory and other health policy decisions." In the context of the ICH E6(R2) definition of a "clinical trial" it is important to note that the 'inferred' meaning of 'intervention' is treatment intervention involving an investigational product. If there is no investigational product, then the clinical study

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		cannot, by definition, be a clinical trial. **ICH E6 (R2) Definition of Clinical Trial** = Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy (as per Section 1.12 of ICH E6 (R2)). **Proposed change:** In the absence of an agreed upon (by ICH partners and stakeholders) definition for "Intervention" and/or "Medical Intervention", we would recommend that these terms are avoided or presented in line with the definition of a clinical trial i.e., "Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s)…" meaning the trial protocol dictates the use of an investigational product, which is a treatment intervention.
480	13	**Comment:** For adapting the scope to broader study designs. **Proposed Change:** "An important distinction between studies is whether the choice of the drug and the health …"
480-482	9	**Comment:** The guideline fails to mention the most important feature of interventional studies, the a priori planned allocation of participants. Therefore, the sentence should be revised. **Proposed change:** Change sentence to: An important distinction between studies is whether allocation to intervention or control is planned (e.g. by randomisation) and whether the choice of the mode of administration of the study drug and the comparator as well as the health management of the subjects are controlled by the study (with proper regard to human subject protection and regulatory

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		requirements) or merely observed in the study.
480 - 483	18	**ICH E8 (R1) TEXT:** An important distinction between studies is whether the choice of the study drug and the health management of the subjects are controlled by the study (with proper regard to human subject protection and regulatory requirements) or merely observed in the study. The former case is referred to as an interventional study and the latter case is referred to as an observational study. **Comment:** The highlighted text above infers that observational studies are not conducted "with proper regard to human subject protection and regulatory requirements". This is not correct. Observational studies, non-interventional studies and registries must all comply with the applicable regulatory requirements. Implementation of the Declaration of Helsinki 2013, in local law emphasises that, "It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects" (as per Section 9 of the Declaration of Helsinki, 2013) and ensure that "Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information" (as per Section 24 of the Declaration of Helsinki, 2013). **Proposed change:** Delete lines 480 - 483
480-483	32	**Comment:** **480** An important distinction between studies is whether the choice of the study drug and the health **481** management of the subjects are controlled by the study (with proper regard to human subject **482** protection and regulatory requirements) or merely observed in the study. The former case is **483** referred to as an interventional study and the latter case is referred to as an observational study
483	12	**Comment:** "observational study" - there are other options for the naming of these studies

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: "observational, non-interventional or registry study"
484	9	**Comment:** According to the theory of science interventional studies do not only have a "potential" to control bias better than comparable observational studies. **Proposed change:** Substitute "often have the potential" by "are designed to"
485-487	9	**Comment:** The order of factors mentioned should be adjusted according to scientific priorities and their potential to influence the validity of trial results. **Proposed change:** Factors such as study objectives, anticipated biases and uncertainty, data sources, and feasibility play a role in the choice between interventional and observational studies.
487	13	**Comment:** "Observational studies are usually conducted in the post-approval period." **Proposed Change:** This is no longer true. Observational trials are also conducted pre-approval/registration, suggest to delete this sentence
487	18	**Comment:** The statement "Observational studies are usually conducted in the post-approval period" is confusing as observational studies observe patients in normal clinical settings and therefore, by definition, can be performed only when a product is available on

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		the market. The sentence should either be clarified or deleted. **Proposed change:** Clarify or delete the sentence.
487	24	**Comment:** Observational studies are also prospective epidemiological studies which are often performed before the start of the clinical development programme to gain insight into incidence, course of disease, treatment approaches, co-morbidities, etc., potentially also with the aim to generate data for an external comparator group. As this is an increasingly important type of observational studies we recommend to mention this here.
488	29	**Comment:** There is a need to better clarify the quality of the observational study (retrospective vs. prospective) related to the quality of the study.
488-489	31	"For example, a pragmatic trial is a mix of the two types in that the intervention is controlled by the study, but health management is controlled to a lesser degree than in other study types." **Comment:** From a regulatory point of view, pragmatic trials are interventional trials. This should be mentioned in order to avoid confusion. **Proposed change:** "For example, a pragmatic trial bears characteristics of the two types of studies in that the intervention is controlled by the trial (randomisation), but health management is being controlled by routine activities of health care professionals. It has to be mentioned, that, from a regulatory point of view, such trials are considered interventional."
488-490	8	**Comment:** A pragmatic trial is an interventional study (i.e. a randomized controlled trial), performed in unselected patients in real world settings (e.g. under the care of the usual physician of the patient) and using open label therapies (as opposed to double-blind

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		treatments in exploratory and confirmatory trials).
489-490	12	**Comments:** 1. observational studies are mentioned, but the example is a pragmatic trial – which is still an interventional trial not an observational study – this is not clear in the text; 2. Definition/example of a pragmatic trial is too vague; is it an introduction of 'registries' – the latter should be avoided!
488 - 490	18	**ICH E8 (R1) TEXT:** There is varying overlap between interventional and observational studies. For example, a pragmatic trial is a mix of the two types in that the intervention is controlled by the study, but health management is controlled to a lesser degree than in other study types. **Comment:** In the absence of ICH definitions for "interventional studies" and "observational studies" it is difficult to contextualise the 'overlap' between these two study types. **Proposed change:** Delete lines 488 – 490
489	35	**Comment:** observational studies are mentioned, but the example is a pragmatic trial – which is still an interventional trial not an observational study – this is not clear in the text**.**
490	13	**Comment:** What do you mean by saying that health management is controlled to a lesser degree? This statement is misleading as it could imply to the reader that safety monitoring of patients or rescue medication provision is relaxed as compared to other studies.
after 490	23	**Comment:** Minimal intervention studies

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: It should be added: Minimal interventional studies may be categorized as observational studies if both the intervention itself and related the risk and effort for participants in the study is minimal.
491–533	21	**Comment:** The description of the use of an external control group is in our opinion too positive and encouraging. Although disadvantages of an external over an internal control group are addressed, the description in the present guideline might be interpreted as if both types of control groups are valid options, with the external control being only slightly inferior. The usually unknown or unquantifiable problems in bias, confounding, data quality, consistency, comparability, etc. arising from the use of an external control group should be emphasized in more detail. Although the ICH E10 guidance document is referred to, some of its caveats could also be included into the ICH E8(R1). Otherwise, sponsors and investigators might believe that the high standards of an internal control group is a design feature that can be refrained from, resulting in only minor decrease in trial quality and validity. A clarification is essential that external control groups are only acceptable under very special circumstances (e.g. very rare diseases) and that the internal (randomly allocated) control group remains the state of the art.
492-498	16	"The drug effect of interest may be the effect relative to not receiving the drug or the effect relative to receiving other therapies. For example, comparisons may be made with placebo, no treatment, active controls or different doses of the drug under investigation. To derive these comparisons, information on a group of subjects not receiving the drug or receiving other therapies is usually needed. This group is known as the control group (see ICH E10). The choice of a control group may be influenced by the study objectives, ethical considerations, and study feasibility" **Comment:** In any case, study subjects should receive optimum care, or standard care, not losing a chance. **Proposed change:** To add: Whether receiving the interventional drug or other therapies, trial subjects are entitled to be treated with best-proven intervention and not lose chances of receiving adequate care.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
493	8	**Comment:** control arms often receive placebo + usual care (not only placebo).
493	10	**Comment:** Relative to receiving other therapies. Clarify "other therapies": not just any treatment, but treatment normally used in standard care for that specific condition of illness.
493 - 494	23	**Comment:** Standard of care should be highlighted, which can also be non-chemical treatment **Proposed change:** For example, comparisons may be made with placebo, no treatment, standard-of-care (with or without medication), active controls or different doses of the drug under investigation.
496-498	9	**Comment:** Regarding the choice of comparators, one essential criterion for ensuring the informative value of study results is missing and should be added. **Proposed change:** Add: The choice of comparator particularly needs to reflect current standard of care.
497	37	*"choice of a control group may be **influenced** by the study objectives, ethical considerations"* **Proposed change:** determined
497-498	2	**Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		The choice of a control group may be influenced also by the regulatory strategy. **Proposed change:** The choice of a control group may be influenced by the study objectives, ethical consideration, **regulatory strategy** and study feasibility.
498	37	*"**and** study feasibility"* **Proposed change:** and or
499	9	**Comment:** It should be explicitly mentioned that the choice of the comparator group influences the possibility for conclusions that can be drawn from results. **Proposed change:** Add: ", resulting respectively in direct or indirect comparisons between intervention and control. Indirect comparisons generally limit the possibility to draw valid conclusions from the results of the study.
499	23	**Comment:** It should be clearly emphasized that internal control is preferred compared to historical control
499-505, 524-533	12	**Comment:** historical control group seems to get to be accepted know, e.g. in combination with single arm study or complex trials; however suitability is to be justified
502	13	**Comment:** "…are due to the treatment they receive." That is only true if the control data is not only collected internally to the study, but

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		the treatment assignment is also randomized.
502-505	22	**Comment:** The difference between internal and external control group should be clearer and more comprehensive. Also, it should be more clear which kind of patient population the external control group could consist of. **Proposed change:** With use of an external control group, subjects are selected from an external source, such as <example to be named>, and the control group subjects may be treated at an earlier time (historical control group) or during the same time but in another setting than subjects in the study.
503 onwards	13	**Comment:** This section covers the possibility to use external data to build a control group. Given the increasing use of RWD and RWE in regulatory submissions and the possibility to build external controls using RWD we suggest to introduce this concept here. **Proposed change:** "With use of an external control group, subjects are selected from an external source (which could come from other clinical studies or from Real World Data (RWD) sources such as Electronic Health Records (EHRs), Insurance claims/billing data or registries) and the control group subjects may be treated at an earlier time (historical control group) or concurrently to the patients in the experimental arm (prospective control).
505	23	**Comment:** Internal control is defined by the protocol in the same way the test group is. The data generated is more robust than data obtained from external controls that are not defined by the same protocol. **Proposed change:** Add: Use of internal control is to be preferred to external control.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
506-511	22	**Comment:** Although the use of an external control group is discussed in detail in this section, potential requirements regarding obtaining consent from control group subjects for use of their data are not addressed. **Proposed change:** It should be stated that the use of data from an external control group may require consent by each of the control group subjects.
511	9	**Comment:** Further limitations to external controls should be mentioned: **Proposed change:** Add: Additional confounders may be unknown and therefore impossible to control.
512-514	9	**Comment:** It remains unclear, what additional information is to be expected from an additional indirect comparison, if a sufficiently informative direct comparison can be performed. If the direct comparison is insufficient, this results from problems in the quality of the study design and should be addressed appropriately. **Proposed change:** Delete lines.
512-514	18	**Comment:** We agree that it is possible for a single clinical study to use both internal and external control subjects. However, we recommend that text is added to advise that such a plan should be discussed with the relevant regulatory agencies. **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Add appropriate text.
517	12	**Comment**: for consistency use either non-interventional or observational. Both are used in this text to mean the same thing **Proposed change:** add a short definition or refer to other guidelines with definition
517	35	**Comment:** for consistency use either non-interventional or observational. Both are used in this text to mean the same thing
517 and 519	39	5.1.3 Control Group **Comment:** "… interventional and non-interventional studies…" **Proposed change:** We recommend using "… interventional and observational studies…" in consistency with wording exposed in section 5.1.2 (17/483) and used throughout the rest of the document.
519	9	**Comment:** Problems related to those study designs should be outlined. **Proposed change:** Add: However, these designs are limited e.g. by the information available on natural behaviour of a case or the natural course of disease.
520	37	*"There are critical to quality factors that **are associated with** the choice and use of the control"*

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: determine
524-528	9	**Comment:** Individual patient data are important for enabling the assessment of confounder control. Therefore, the paragraph on the possibility of using summary measures alone is far too optimistic. **Proposed change:** Add: This limits their usability for confirmative trials in contrast to trials for hypothesis generation.
524-533	12	**Comment:** historical control group seems to get to be accepted know, e.g. in combination with single arm study or complex trials; however suitability is to be justified
528	3	**Comment:** "the critical to quality factor of comparability between treatment groups is unable to be addressed through adjustment for subject-level covariates." **Proposed change:** add "and therefore is not suitable to confirmatory trials". Marginally, I would note that the whole field of "causal epidemiology" argues against this strict view, but I also feel that given the current state-of-the-art of clinical research, it would be dangerous to state that observational research can infer causality…
528	30	**Comment:** Where an external control group is used specific attention needs to be given to matching individuals
529-533	9	**Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Uncontrolled trials can only be informative, if the natural course of disease is deterministic and effects caused by the intervention are large. This is further limited, if patient relevancy of surrogate endpoints is not proven. **Proposed change:** Add: However, this is limited by the nature of the disease, effect sizes observed and the validity of endpoints.
534	8	**Comment:** It is important to define a priori what the clinically relevant thresholds will be and how they are defined.
534	13	**Comment:** Exploratory endpoints play an important role in some clinical research scenarios. Reference and guidance on their appropriate use should be provided in 5.1.4 Response Variables. **Comment:** In this section, perhaps the concept of 'estimand' should be introduced with appropriate reference to ICH E9(R1), when approved.
534-558 (section 5.1.4)	31	**Comment and proposed change:** consider and add exploratory objectives.
535	31	"A response variable is a subject-level attribute of interest that may be affected by the drug." **Proposed change:** "A response variable is a subject-level parameter of interest that may be affected by the drug."
536	19	**Comment:** do the listed response variables (e.g. efficacy) include quality of life variables?
538	24	**Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Response variables are increasingly frequently HTA-related variables. **Proposed change:** …that are chosen to assess drug effects *and/or HTA-related variables*
539-540	21	*"endpoints and variables" .* **Comment:** see line 57.
541-542	9	**Comment:** Patient relevancy of endpoints is not dependent from feasibility of their assessment. The non-consideration of relevant endpoints jeopardises the validity of a study. **Proposed change:** Delete sub-clause "taking into account feasibility considerations"
543-545	4	**Comment:** The choice of study outcomes should be meaningful to the intended population and take into account patients' views. **Proposed change:** Recommend checking the COMET database (www.comet-initiative.org/studies/search) for any relevant COS. If a COS does not exist or has not been well developed, consideration should be given to whether this could be done during the the study design stage, with full involvement of patients. Where an established COS exists, outcomes should be included amongst the list of outcomes to be measured in the study, unless there is good reason to do otherwise (which should be stated). Minimum standards for development now exist that can also be used to help users determine if a COS has been developed with adequate patient input (journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002447).
543-545	31	"The choice of endpoints should be meaningful for the intended population and take into account the views of patients."

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Comment: suggest to add 'where applicable' **Proposed change:** views of patients, **where applicable**.
544-545	16	"The choice of endpoints should be meaningful for the intended population and take into account the views of patients" **Comment:** Excellent, cannot agree more
548-549	28	**Comment:** This sentence mentions the attributes of robust study endpoints but does not caution regarding the use of patient reported outcomes for primary end points and the associated challenges in meeting the requirements for robust endpoint data. **Proposed change:** Add a caution regarding patient reported outcomes.
550	13	**Comment:** Are these then always pragmatic trials when they make use of existing data?
550-558	15	**Comment:** This is a complex issue: health data may be scarce on the one hand but, on the other hand, excessive collection of data for study purposes should be avoided. The extent of safety data must be tailored to avoid important signals getting lost in an overflow of information.
552	3	**Proposed change:** add: "careful consideration of any misclassification, under-ascertainment, loss to follow-up, or other types of bias (see 5.1.5)

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		should be made early, as they are critical to quality."
553	31	"The knowledge of the drug …" **Comment:** suggest to add 'The level of knowledge' **Proposed change:** "The **level of** knowledge of…"
554-555	13	**Comment:** Both short-term surrogates and clinical outcomes can be "objective". **Proposed change:** Remove the word "objective". "For example, a proof-of-concept study may employ short-term surrogates rather than clinical outcomes."
554-556	16	"a proof-of-concept study may employ short-term surrogates rather than objective clinical outcomes. Clinical outcomes would then be used to confirm a clinically meaningful effect in a large-scale confirmatory study" **Comment:** Discussions often arise about surrogate markers, less on the fact that they are measured short-term, more on the fact that they are not always validated. Real surrogate markers have been adequately "validated," that is, shown to predict the effect of the treatment on the clinical outcome of interest. Confirmation study would then only be useful if surrogate not properly validated. **Proposed change:** a proof-of-concept study may employ not-validated surrogates rather than objective clinical outcomes. Clinical outcomes would then be used to confirm a clinically meaningful effect in a large-scale confirmatory study

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Or a proof-of-concept study may employ short-term surrogates rather than objective clinical outcomes. Clinical outcomes would then be used to confirm long-term clinical effect in a large-scale confirmatory study (if there are ICH guidelines on surrogacy, to mention them here)
555-558	32	**Comment:** **555** Clinical outcomes would then be **556** used to confirm a clinically meaningful effect in a large-scale confirmatory study. In other **557** cases, for example, a post-approval study where the safety profile of the drug is well **558** characterised, the extent of safety data collection may be tailored to the objectives of the study. **Interventional study (clinical trial)** A type of clinical study in which participants are assigned to groups that receive one or more intervention/treatment (or no intervention) so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes. The assignments are determined by the study's protocol. Participants may receive diagnostic, therapeutic, or other types of interventions. **Observational study** A type of clinical study in which participants are identified as belonging to study groups and are assessed for biomedical or health outcomes. Participants may receive diagnostic, therapeutic, or other types of interventions, but the investigator does not assign participants to a specific interventions/treatment. A patient registry is a type of observational study. USA 1.12 Clinical Trial/Study Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		A post-authorisation safety study (PASS) is defined in Article 1(15) of Directive 2001/83/EC as "*any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures*". A PASS is non-interventional if: the medicine is prescribed in the usual way in accordance with the terms of the marketing authorisation; deciding how to treat the patient is based on current practice and not a trial protocol; the prescription of the medicine is clearly separated from the decision to include the patient in the study; patients do not undergo additional diagnostic or monitoring procedures; data analysis uses epidemiological methods[1] An EU competent authority may impose a non-interventional PASS, either as a condition of marketing authorisation (category 1) at the moment of granting the marketing authorisationor in the post-authorisation phase, or as a specific obligation in a conditional marketing authorisation or a marketing authorisation under exceptional circumstances (category 2). For more information, please refer to the good pharmacovigilance practices (GVP) Module VIII- Post-authorisation Safety Studies. https://www.ema.europa.eu/en/documents/other/guidance-format-content-protocol-non-interventional-post-authorisation-safety-studies_en.pdf https://www.ema.europa.eu/documents/regulatory-procedural-guideline/guidance-format-content-final-study-report-non-interventional-post-authorisation-safety-studies_en.pdf
556	3	**Comment:** Core Outcome Sets (COS, COMET initiative) are increasingly developed and used **Proposed change:** "Clinical outcomes would then be used to confirm a clinically meaningful effect in a large-scale confirmatory study"; whenever available, a Core Outcome Set should be collected, to facilitate comparison between studies and pooling of results in subsequent meta-analyses."
556	9	**Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		The purpose of confirmative studies should be reiterated. **Proposed change:** Add: Confirmative studies form the basis of marketing authorisation applications.
556	12	**Comment:** ref to E19 should be added
556	35	**Comment:** ref to E19 should be added
558	3	**Proposed change:** add "Another example would be the case where drug effects extend to more than the actual patients enrolled, as is the case with communicable diseases: in this case outcome measures of effects to this wider population should be also considered (e.g. incidence of infections with resistance to antimicrobials)"
558	13	**Proposed Change:** "…the extent of safety data collection may be tailored to the objectives of the study (See ICH E19)."
558	31	"…the extent of safety data collection may be tailored to the objectives of the study." **Proposed change:** "…the extent of safety data collection may be tailored to the objectives of the study (see ICH E19)."
559	24	**Comment:** This title is not suitable. **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		"Methods to control bias" or *"Methods to assess, avoid or reduce bias"*
559 (section 5.1.5)	34	Section 5.1.5, *"In conducting a controlled study, randomised allocation is the preferred means of assuring comparability of test groups, thereby minimising the possibility of bias in treatment assignment"* (lines 564-566), is helpful but does not go on to explain why randomization is so valuable and what the impact is on the reliability of the results, the need to ensure accuracy of individual data points, etc. In the current wording it sounds like a nice-to-have option. **Comment:** The section on "drop-outs" should be much more carefully worded (lines 569-574). Loss to follow-up, missing measurements or study visits, and stopping study treatment will each have different levels of importance depending on the study design and require different mitigations. The inclusion of observational studies in a broadened scope is not particularly helpful (see earlier comments). In particular whilst there is discussion of some of the challenges in controlling bias (lines 585-589), there is no discussion of what observational studies can reliably detect (large effects of treatment on rare outcomes) vs. what they can not (moderate effects on common outcomes – which is the situation for most treatments).
559	37	*Methods to Reduce or Assess Bias* **Comment:** This section aims to describe methods against bias reduction in 30 sentences. The section is vague and incomplete as much more can be said about this topic.
559-585	20	**Comment:** It has to be mentioned that ICH E17 also assess bias resulting from a cultural or physiological aspects of race and ethnic groups involved. Diversity should be guaranteed in a way that results are meaningful to the target population of patient. **Proposed change:** Additional reference to E17 for bias management.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
564	13	**Comment:** The potential for external controls is limited by the current wording; suggest to include broader wording to take future developments in the design of control groups into consideration
564-566	13	**Comment:** Clarification of the phrase "comparability of test groups" is requested e.g. balance in baseline characteristics across test groups. Also, the use of word "thereby" suggests that the randomization does not work directly towards minimizing the possibility of bias in treatment assignment, suggest deleting it. **Proposed change:** "In conducting a controlled study, randomized allocation is the preferred means of assuring comparability of test groups, minimizing the possibility of bias in treatment assignment."
566	9	**Comment:** The paragraph does not yet mention one important advantage of randomisation regarding confounder control. **Proposed change:** Add sub-clause: "and controlling for undetected confounders."
568-569	13	**Comment:** what is exactly meant with "events after randomization" (intercurrent events)?
569	13	**Comment:** The term "intercurrent events" is introduced in ICH E9(R1), might be good to add a reference.
569 - 574	13	**Comment:** Suggestion to have terminology which is consistent with other sections (4.4 line 424-425 and 6.2.2 line 709) on withdrawal. I.e.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		study subjects withdrawing either from the study or from treatment. **Proposed change:** "For example, there may be differences in the follow-up patterns between the groups, such as subjects in one group withdrawing from the study because of adverse events or lack of efficacy. Careful consideration of the potential impact of intercurrent events will help with the identification of critical to quality factors, such as preventing withdrawals, retrieving data for withdrawals, and definition of treatment effect in the presence of withdrawals."
577 - 579	13	**Comment:** Single-blind might mean the patient knows the assignment, but the investigator does not. It is not an inherently directional term. In addition, there can be studies where the patient is blinded to assignment, but only some of the study staff are blinded, such as only the investigator making efficacy assessments, but the investigator who evaluates adverse events and can make decisions on management of the patient during the study is not blinded or expected to become unblinded due to adverse events or laboratory values. This scenario does not fit either the two definitions the guideline describes. It is therefore recommended that the definition of "single blind" studies be expanded. **Proposed change:** " A study where only one party is blinded, (for example only the investigator or only the patient) to the treatment allocation is called a single blind study."
577-579	31	**"**A study where the treatment assignment is not known by the study participant is referred to as a single-blind study." **Comment:** It could be vice versa as well: The investigator is blinded/masked and the subject knows what he/she is receiving, when unpacking the neutrally packaged drug (for example aluminium blister). **Proposed change:** A study where the treatment assignment is not known either by the study participant or by the investigator (dependent on the

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		type of drug, packaging, or administration) is referred to as a single-blind study.
578	19	**Comment:** A single blind study is probably more often a study where the investigator (or person evaluating the response) is blinded
579-581	3	**Comment:** there could be triple blind, etc. Sometimes the patient is not blind, but the outcome assessor is. Rather than using "single-" or "double-" blind, "who" is blinded to "what" should be clearly stated **Proposed change:** rather than using "single-" or "double-" blind, "who" is blinded to "what" should be clearly stated
579-581	9	**Comment:** It is advantageous, if all personnel responsible for the analysis of data and evaluation of results is blinded. This should be clarified. **Proposed change:** Add “and evaluation of clinical results” after “subjects”
581	12	**Comment:** It should be essential (not just helpful) to do this in a double-blind trial
581	35	**Comment:** It should be essential (not just helpful) to do this in a double-blind trial
582	12	**Comment:** analysis consideration should also be added here

Line no.	Stakeholder no.	Comment and rationale; proposed changes
582	35	**Comment:** analysis consideration should also be added here
582-585	9	**Comment:** Unblinded studies in addition especially bear the risk of bias when assessing subjective endpoints. This should be added. **Proposed change:** Add: However, bias caused by the lack of blinding regarding subjective endpoints may still pose a problem
582-585	13	**Comment:** The use of pre-specified decision rules always reduces the consequences of lack of unblinding. However, as written, the text suggests that this may or may not occur. Furthermore, the use of response variables with objective measurements will also have this impact. It is therefore recommended that the text be amended to reflect these considerations. **Proposed change:** "In an open-label study (either single-arm or unblinded comparative), the consequences of the lack of blinding will be reduced through the use of response variables with objective measurements and pre-specified decision rules for aspects of study conduct, such as treatment assignment, subject management, safety reporting, and response variable ascertainment."
585	31	"…response variable ascertainment." **Comment:** an example would be beneficial for the reader. **Proposed change:** "…end-point assessment, for example, by blinded/masked independent raters."
586-590	23	**Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Steering of recruitment should be considered to avoid bias **Proposed change:** add "balanced recruitment between sites, regions and countries should be considered to avoid bias through over-recruiting investigational sites" to section
586-590	32	**Comment:** **586** Observational studies pose unique challenges to the control of bias. Multiple design elements **587** are often necessary to address these challenges, including methods to address biases associated **588** with the (1) selection of subjects, (2) differences in prognostic factors associated with the **589** choice of therapies (confounding), and (3) ascertainment of response variables and other **590** important study variables. Beginning in the planning stages of a study, measures should already be taken to defend against biases that may arise through selection, confounding, etc. Such measures could include, for example, participant matching (during sampling) or a limitation of the variability of potential confounders, or rather the collection of information required for control of confounding. Sensitivity analyses can be planned as extra investigations to estimate the impact of measurement errors on the results of the study. Recommendation 3.4 The concept of the minimization and control of potential selection biases due to non-participation and unavailability of data for selected study participants should be addressed in the study protocol. Such a concept implies a proband-oriented documentation of the reasons for nonparticipation or one's subsequent exclusion from the study. During the study, basic information should be obtained from non-participants as well. The objective in collecting such information is to estimate the direction and magnitude of a possible selection bias due to non-response. In order to document such non-participation, the various categories of non-participation must be defined in advance. To ensure a detailed response-analysis, successful as well as unsuccessful contact-attempts should be documented according to type, content, and date/time. In order to be able to better estimate possible biases due to selective nonparticipation and to better compare between studies, at least the following categories of probands should be included in the reporting of the results of an epidemiological study: Number of probands: • with complete participation • with incomplete participation • who refused participation • who were too sick to

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		participate • who were ineligible as a result of the study protocol, due to not fulfilling the inclusion criteria and/or fulfilling the exclusion criteria 12 • who were not reached (separated into those removed from the study and those who died during the study) A stratified analysis of the participants, for example by gender, may be necessary to prevent selection effects. When conducting cohort studies, reasons for the premature/early withdrawal from the study are to be recorded as well.
590	9	**Comment:** One key weakness of observational studies is that interpretation relies on the absence of uncontrolled confounding, which cannot be guaranteed. **Proposed change:** Add: The validity of those methods is strongly limited by undetected confounding.
591	13	**Comment:** In light of ICH E9(R1) we would consider it beneficial to add here that also an estimand, derived from the clinical objectives, needs to be stated in the protocol.
591-624	23	**Comment:** Section 5.1.6 mentions the elements required for a statistical analysis plan, including analysis populations (line 608). It is suggested to include a definition of the relevant analysis populations in this section, in the context of the quality aspect in clinical studies.
591-626 (Section 5.1.6)	34	**Comment:** In the section on statistical analysis (section 5.1.6) there is an implication that treatment discontinuations, use of rescue medication, or missed visits are protocol violations. This is not necessarily the case. Indeed, the protocol may anticipate or even mandate these. The fact that treatment is stopped does not mean that the protocol was not followed! The statement that, "Pre-specification is particularly important for studies that make use of existing data sources rather than primary data collection, not only for the statistical analysis planned for the study but also for any feasibility analysis to assess the applicability of the existing data" (lines 615-617) is confusing. It is unclear what the concerns are. For example, if during the

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		conduct of a trial, linkage to a dataset containing information on all cancers (with type and date) became possible, it would make perfect sense to take advantage of this additional information even though it wasn't pre-specified. The description of data types and their impact on quality of the results is confused, e.g.: *"The term primary data collection, refers to data collected for study purposes using processes that ensure a sufficient level of quality"* (lines 639-640). Primary data may be collected for study purposes but not of sufficient quality. Likewise, secondary data may be collected for other purposes but of sufficient quality. Thus data source and data quality are two different features of data. The key questions for QbD are: (a) Where are the data to be collected from (and is this feasible)?; and (b) Are the data of adequate quality to fulfil their function in the context of the clinical trial? (For example, a bedside test of liver function may be ideal to detect a potential safety issue (e.g. >3x ULN) but a central laboratory measurement may be needed to ensure adequately reliable information on mean changes in a novel biomarker.)
592-603	13	**Comment:** There is no reference to estimand, which is becoming the norm for statistical analysis. **Proposed change:** Include discussion of estimand around sensitivity analyses, intercurrent events, etc.…at least the concept may be introduced and cross-reference to ICH E9 as appropriate. **Comment:** It is proposed that consideration be given to specifying the possible scenario of using external data (e.g. results of newly completed studies or other emerging data such as real-world data) to facilitate decision making regarding modifying the design of an on-going study and amending the protocol and statistical analysis plan. **Proposed change:** After line 603: External data (e.g. results of newly completed studies or other emerging data, such as real-word data) may be used to facilitate decision making regarding modifying the design of an on-going study and amending the protocol and statistical analysis plan.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
592-626	39	5.1.6 Statistical analysis **Comment:** We suggest adding that statistical analysis can be limited specific condition/disease such as orphan diseases.
594	31	"The study protocol should include a statistical methods section that is appropriate for the objectives and study design (ICH E6 and E9)." **Comment:** Here, the guideline refers to ICH E6 in the context of study design, however in other paragraphs and especially in Annex 2, ICH E6 is only referenced as a guideline for the conduct and reporting of the study.
595 ff	21	**Comment:** We prefer to have the SAP ready before the first trial patient level follow-up data are collected. In particular, the analysis even of so-called blinded data which is currently permitted can allow relevant insights for the specifications of the SAP and introduce bias, e.g. the analysis of attrition-/dropout/follow-up-rates, adverse event/adverse drug reactions may often even allow the identification of treatment groups. Thus the text should be modified accordingly: see in particular line 601; analyses of so-called blinded study data needs either a very strict definition (e.g. no analyses for different groups even when formally still blinded), but we prefer to delete this option completely.
595-597	24	**Comment:** The timing for finalisation of protocol and Statistical Analysis Plan need to be clearly defined in this guidance. **Proposed change:** *While* the protocol ~~*should be*~~ is finalised before the conduct of the study, ~~*and*~~ the statistical analysis plan should be finalised before unblinding the study…. Clarification should be provided on the definition of "unblinding" as there are differences in European GCP and GMP definitions/expectations of blinding; GMP defines double-blind as subject/patient & investigator, monitor and in some cases data

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		analyst as unaware of treatment assignment, GMP Annex 13, 3 Feb 2010 Glossary, whereas GCP has expectations relating to the Sponsor and Clinical Operations.
595-598	2	**Comment:** "the statistical analysis plan should be finalised before the unblinding of study data, or in the case of an open-label study, before the conduct of the study". This represents an issue for practical reasons in many cases where a contract research organization is involved in the conduct of a bioequivalence study (short studies to perform). Furthermore, the PK endpoints can only be calculated when the bioanalysis has been performed so concluding the SAP before the bioanalysis starts should be enough to provide the necessary reassurance in the case of BE trials. **Proposed change:** In the case of BE studies, the statistical analysis plan should be ready before bioanalytical data analysis starts.
595-598	17	**Comment:** Section 5.1.6: We note the proposed requirement that the SAP "…should be finalised before the unblinding of study data, **or in the case of an open-label study, before the conduct of the study**". The requirement for a final SAP for open label studies before the conduct of a study has been a 'recommendation' previously but seems to be more strongly worded here. Practically, this could be of significant detriment to the start-up timelines for early phase trials (especially healthy volunteer trials) and therefore add a potentially unnecessary delay to the drug development process timelines. Typically, the Statistician would need a final protocol and CRF/eCRF to start work on the SAP and typically CRFs are finalised within a matter of days of the start of healthy volunteer trial conduct (start of screening). The SAP would generally take several weeks to finalise (minimum 4-5 weeks), so a requirement to finalise the SAP prior to study start for open label studies could add 4-6 weeks onto the clinical trial timeline. **Proposed change:** The approach to documenting statistical analysis/SAPs may need to be reconsidered to ensure competitive timelines e.g.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		• SAP finalisation could be a two-stage process (e.g. by splitting the text and shells and signing off an initial SAP with the text only). • SAPs could be split into two documents – one being the SAP describing the inferential stats and a second document only describing the TFL and derivations. • More rigor could be put into the protocol to describe how the primary and secondary endpoints should be analysed – thus avoiding the need for a final SAP before the conduct of open label studies. We also seek clarification on the definition of the "conduct of the study". Is this considered to be the start of screening?
595-598	22	**Comment:** It is questionable whether finalization of the statistical analysis plan prior to the conduct of a study can realistically be achieved in practice for an open-label study. **Proposed change:** The protocol should be finalised before the conduct of the study, and the statistical analysis plan should be finalised before the unblinding of study data, or in the case of an open-label study, before the conduct of the study, at least to that extent to cover the assumptions made in the protocol. An update before database lock would still be allowed. This would also apply to single-blind settings.
595 - 598	23	**Comment:** there are several cases where the SAP in a blinded study should be finalised earlier than the unblinding process (e.g. after 1/3 patients recruited) and for open studies it is not common to have the SAP finalised before the conduct of the trial **Proposed change:** The SAP should be finalised early enough to avoid inadequate interference with the study outcome
596-597	12	**Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		SAP finalized prior unblinding – however need to be specified in the protocol too
597	18	**Comment:** We recommend the text should note that, in addition to open-label studies, the statistical analysis plan for a single-blind study should also be available before the conduct of the study. **Proposed change:** Replace "an open -label study" with "an open-label or single-blind study"
598 - 600	13	**Comment:** The reason why the statistical analysis plan should be finalized before the unblinding of study data, or in the case of an open-label study, before the conduct of the study, is not only to "increase confidence that important aspects of analysis planning were not based on accumulating data in the study or inappropriate use of external data" but more to "avoid influence to the analysis planning by knowing unblinded data in the blinded study, and accumulating data in the open-label study". These steps will increase confidence that important aspects of analysis planning were not influenced by knowing unblinded group data in the blinded study, and accumulating data in the open-label study. For open label study, a key analysis plan included in the protocol might be sufficient but not a finalized statistical analysis plan.
600-603	13	**Comment:** The text does not seem to allow the for the possibility of resizing a study or revising the focus of a novel endpoint based on better estimates of the variability and/or performance of the endpoint from unblinded, interim data. **Proposed change:** Consider revising this text to less proscriptive.
601	30	**Proposed change:** the choice of analysis methods *or the primary endpoint* in a randomised clinical trial should not change after examining

Line no.	Stakeholder no.	Comment and rationale; proposed changes
604–606	21	**Comment:** The 'Statistical analyses of primary and secondary endpoints to achieve study objectives with respect to both efficacy and safety should be described, as well as interim analyses and/or planned design adaptations' in the trial protocol (not only in the Statistical Analysis Plan). The trial protocol should cover the exact definitions of the different patient analysis sets used, the statistical tests and procedures, whether statistical adjustments are used, as well as the procedures to handle missing values. If this information is missing, neither the assessors of the NCAs nor the members of ethics committees can decide about the quality and correctness of the planned statistical analyses, as typically the SAP is not part of the dossier for approval.
606-611	12	**Comment:** in case of predefined adaptation, and their criteria and impact should be taken up in the statistical analysis too.
606–611	21	**Comment:** The basics of the listed aspects of analysis (estimation/ tests of hypotheses, analysis populations, handling of intercurrent (e.g.competing) events, rescue medication, missed visits, protocol violations) should be described in the trial protocol, too.
608	3	**Comment:** to avoid alpha error inflation and spinning of results, multiplicity issues should be considered early in the planning stage. **Proposed change:** add: "any multiplicity issues,"
608	12	**Comment:** populations – there is usually more than one. More should be said about how the per protocol populations are decided without bias.
608	31	"…the analysis population…" **Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		the term "analysis sets" would be in line with ICH E9 **Proposed change:** "…the analysis sets (full analysis set, per protocol analysis set, safety analysis set) …"
608	35	**Comment:** populations – there is usually more than one. More should be said about how the per protocol populations are decided without bias.
610	25	**Comment:** While there is some explanation about the statistical approach to randomised clinical trials there is no mentioning of the general issues in early phase studies. We recommend adding a sentence. **Proposed change:** ...analysis strategy appropriate for the study design. *In early phase studies statistical analysis is often limited to descriptive statistics calculated for the primary and secondary endpoints.* The plan should address…
627	8	**Comment:** There should be a recommendation to stress test data transfer and fidelity between sites and data repository as data cleaning at end of study is much harder.
627	12	**Comment:** As the Clinical Trial Regulation (Regulation EU No 536/2014) focus on robust data, it should be mentioned in this chapter. **Proposed change:** Add robust data
628	3	**Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Collecting unnecessary data would add burden and possibly reduce the quality of NECESSARY data **Proposed change:** The study data should reliably contain **<u>ONLY</u>** the necessary information
628-629	13	**Comment:** The definition of the word "Study Data" is ambiguous. It may mean the data that is obtained by sponsor such as CRF. Is it correct? If yes, what does the sentence "necessary information to conduct the study" mean?" In addition, add "data review" as well as monitoring. Please delete the word ""conduct"" and add "review". **Proposed Change:** "The study data should reliably contain the necessary information to, monitor, review and analyze the study."
628-629	30	**Proposed change:** The study data should reliably contain the necessary information to conduct, monitor, ~~*and*~~ analyse *and audit* the study.
628-629	31	"The study data should reliably contain the necessary information to conduct, monitor, and analyse the study" **Comment:** It is not clear what is meant by the above sentence.
629	3	**Comment:** I would stress that data should correspond to the stated objectives, to avoid spinning of results, post-hoc analyses etc **Proposed change:** "to conduct, monitor, and analyse the study; this implies that they are closely and clearly linked to study objectives"
629 - 630	13	**Comment:** It is recommended that allowance be made for some quality checks, in relation to the paper-based capture, given the context of

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		quality by design. **Proposed change:** "The study data may be acquired through a variety of methods, including paper-based and electronic capture. Paper-based should include a quality check to ensure transcribed appropriately to electronic system for evaluation."
630-632	9	**Comment:** The sentence does not emphasise the necessity of quality assurance regarding the data used. **Proposed change:** Add "Quality assured" to the beginning of the sentence in front of "data".
630-631	18	**Comment:** The text refers to digital health tools. These may generate objective clinical data or more subjective data in the form of patient-reported outcomes (as may paper-based tools of patient-reported outcomes). Patient-reported outcomes (PROs) can play a significant role as study endpoints in the development and evaluation of new therapies, therefore we recommend that additional text is added specifically on the subject of PROs addressing, for example, the need to confirm that the chosen system is valid, reliable, and able to detect change, that the goals for collecting PROs have been aligned, that methods for administering, scoring, and reporting the questionnaire and its results are determined prospectively, and that strategies for responding to issues raised by the questionnaire and for reducing missing data are put in place. Additionally, many studies now incorporate some aspects of a virtual clinical study and we recommend that consideration of the unique issues associated with conducting study activities virtually are addressed in the final guideline. **Proposed change:** Add appropriate text.
630-631	31	"(e.g., digital health tools)" **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		"(e.g., digital health tools, e.g., wearables, ePROs, BYOD (bring your own device))"
632	12	**Comment**: add 'or changes in prescribing practise'
632	35	**Comment:** add 'or changes in prescribing practise'
635	12	**Comment:** this wording is getting the notion of the definition of a CRF in difficulty. This is the tool to transfer the trial data to the sponsor - and is usually transcribed from medical and other records. For electronic transfer, the specification of the system tool to extract it could be regarded as the CRF. Data from both types of data source can be combined in the database but do not comprise the clinical database
635	12	**Comment:** Use of electronic health records have other considerations too, such as inconsistencies across investigator sites and countries, different processes. Also access for monitors and inspectors.
635	35	**Comment:** this wording is is getting the notion of the definition of a CRF in difficulty. This is the tool to transfer the trial data to the sponsor - and is usually transcribed from medical and other records. For electronic transfer, the specification of the system tool to extract it could be regarded as the CRF. Data from both types of data source can be combined in the database but do not comprise the clinical database
635	35	**Comment:** Use of electronic health records have other considerations too, such as inconsistencies across investigator sites and countries, different processes. Also access for monitors and inspectors.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
637	13	**Comment:** Can" other mechanisms" be further clarified with examples (e.g.: ePRO?).
639-640	2	**Comment:** It appears confusing if primary data **collection** is compared to secondary data **use**. What about secondary data collection (is this term even existing?), and/or primary data use? Furthermore, in case of non-interventional studies with primary data collection/use, the data that is collected may also be part of the usual patient record, and is also used for the study. Therefore, the definition is not quite clear, and should be clarified further.
640	13	**Comment:** Clarify the definition of "secondary data use" (the sentence in line 640-641 is very misleading).? Presently it reads as if the study collects additional data that are not necessary for the primary objective but are just collected for some later use.
644	13	**Comment:** Secondary data could also be data coming from other RCTs / clinical trials – suggest to add **Proposed Change:** "Examples of secondary data sources that might be used in clinical studies include national death databases, disease and drug registries, claims data, medical and administrative records from routine medical practice, and other RCTs/clinical trials.
647	19	**Comment:** There may also be administrative considerations to determine whether the secondary use of data is allowed in the first place
647	21	*"With secondary data use, the appropriateness of the available data as well as the adequate legal basis for using this kind of data for the purpose of scientific research should be considered."* **Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		In many countries, the legal basis is an important issue.
647-650	9	**Comment:** It is generally not advisable to prioritize secondary data analyses over pre-specified analyses within clinical trials. **Proposed change:** Delete sentence.
647-652	39	5.2 Study Data **Comment:** Sources of secondary data and, when relevant, access timepoints should be prospectively planned and well-defined in the study protocol. Access to personal data recorded for another purpose than the clinical study can be an ethical issue with regards to locally applicable personal data protection framework and subject information and consent (ICH E6).
647-658	7	**Comment:** While this section rightly raises concerns on the appropriateness of secondary data, it fails to highlight the risks associated with a lack of validity of the systems where this data is kept. Doctors stress, basing on their knowledge from pharmaceutical studies, that the monitors have to check validity of every electronic health record, so this validity check would be appropriate in this document.
651-652	15	**Comments:** There is no data on the impact that additional confirmation of secondary data has on the results of clinical research. However, it makes processes cumbersome for the study sites and at times burdens patients with unnecessary investigations.
653	19	**Comment:** There may also be administrative considerations to determine whether the secondary use of data is allowed in the first place
653-662	39	5.2 Study Data

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Comment: The use of secondary data is mentioned for the purpose of collecting response variable data (Section 5.1.4, 20/550-551, and section 5.2, 23/639-658). They may also be used for evaluating whether a subject fulfils given eligibility criteria in screening step. We recommend to also refer to the evaluation of selection criteria fulfillment when mentioning measures to be put in place to assess the appropriateness of these data (23/647-650), and further when recommending the use of international data standards in order to address the comparability issue that may result from using data that have not be collected with methods designed for the purpose of the study (23/659-662).
659	13	**Comment:** Recommend to clarify what "data standards" are by adding examples.
661	3	**Comment:** International data standards exist for many sources **Proposed change:** International data standards AND ONTOLOGIES exist for many sources
661-662	2	**Comment:** We think it would be useful to list some of the international data standards, which are considered acceptable in all ICH regions. **Proposed change:** International data standards **(CDISC, XXY, etc)** exist for many sources of study data. Data standards should be developed for emerging sources of study data.
664-665	37	***Local regulation**s related to privacy of participants' data should be followed.* **Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Please refer to the General Data Protection Regulation (GDPR), this law is relevant for all EU and EEA countries, and data transfer to non-EU countries.
665	21	*"Local regulations related to privacy of participants´ data ~~should be~~ need to be followed.* **Comment:** Clarification.
666 (entire section 6)	26	**Comment:** EORTC believes this section is lacking flexibility that is not consistent with the proposed risk based and fit for purpose approach. For example, training needs are very limited when conducting pragmatic trials; intensive training may even introduce some bias. **Proposed change:** Please add in the introduction the statement that considerations of the section 6 shall be proportionate to the risk evaluation, study purpose and shall in general be fit for purpose.
666 (section 6)	34	**Proposed change:** <u>This section could be removed.</u> Much of this text is redundant and should be deleted to aid clarity and keep focus on Quality-by-Design. For example, the first paragraph of section 6.1 on study conduct (lines 667-672) repeats similar text in earlier sections.
668	11	**Comment:** The term "quality by design" is unclear and misleading. **Proposed change:** …, including those **designing quality**, …

Line no.	Stakeholder no.	Comment and rationale; proposed changes
668-670	20	**Comment:** Consider splitting into two sentences to improve readability. **Proposed change:** "The principles and approaches discussed in this guideline, including those of "quality-by-design", should be considered when planning the conduct and reporting of clinical trials. The proportionality of control measures employed to ensure the integrity of the critical-to-quality factors should also be appropriate for the clinical study's selected design."
669	2	**Comment:** typo **Proposed change:** The principles and approaches set out in this guideline, including those of quality by design, should inform **about** the approach taken to the conduct and reporting.....
670	28	**Comment:** Control measures employed to ensure the integrity of the critical to quality factors are mentioned but there is no reference to use of quality tolerance limits (QTLs), as mentioned in the E6 guideline. **Proposed change:** Add a reference to E6 section 5.0 and explain how the QTLs can be applied to the critical to quality factors and their associated risks.
670-671	24	**Comment:** Is "… integrity of critical to quality factors" meant or should we better say "…integrity of study data"?
671	13	**Comment:** Text implies that all mentioned Study types in text need to follow ICH E6 as Document refers to "Clinical Study" with a broad

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		scope as described in section 1 and following. However as per ICH GCP E(R2) the term Clinical Study is regarded as synonym to Clinical Trial associated with narrow scope. Further clarification is needed what embraces the term Clinical Study under the umbrella of ICH E8 and to differentiate to ICH E6.
673-677 (section 6.1.1)	31	**Comment:** There should be reference to adaptive trial designs where protocol adherence means operating within the limits of an adaptive design space where the boundaries are approved, but detailed steps might be flexible.
674	12	**Comment:** This includes any electronic systems used in the conduct of the study (IRT, eCRF, ePRO) which should be designed, configured and tested to be in accordance with the protocol requirements.
674	35	**Comment:** This includes any electronic systems used in the conduct of the study (IRT, eCRF, ePRO) which should be designed, configured and tested to be in accordance with the protocol requirements.
674-675	15	**Comment:** Protocols frequently do not reflect routine clinical approaches as they define very rigid rules. Whereas in some fields they may be helpful, in others, they do not add anything to the quality of the study and do not guide future use of the study drug. **Suggestion:** Adherence to the study protocol is essential. However, the protocol should mention where some flexibility is acceptable, without negative impact on study outcome or safety of the patient (e.g., flexibility on data collection dates that are not related to major statistical endpoints).
674-677	39	6.1.1 Protocol Adherence **Comment:** In addition to ensuring ethical and scientific integrity of the clinical study as well as regulatory compliance through modification

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		of the study protocol, an assurance system allowing the surveillance, traceability, primary and secondary prevention of protocol deviation, as well as reporting in accordance with applicable local framework, should also put in place. It may also be useful to refer more broadly to the adherence to the study documents. For instance, adherence to the Investigational Medicinal Product Dossier (IMPD) and pharmacy manual are also essential to guarantee the quality of the IMP and therefore the safety of the subjects as well as the reliability of the data generated.
675-677	15	**Comment:** Here, the term "necessary" is too vague and does not refer to a scientific concept. Please precise who is in charge of deciding what would (or would not) make it necessary (e.g., sponsor, PIs, patients). **Proposed change:** Add the following: "The amendment of the protocol should be decided by PIs and sponsors (this task should not be transferred to CROs) and accepted by patient reviewers. Especially a non-substantial amendment should be discouraged.
677	21	*"{...} a clear description of the rational for the modification and the impact on each part of the study as well as on each document (duration of insurance, patinfo, informed consent form, CRF, SAP etc.) should be provided in a protocol amendment (ICH E6) where the modifications are compared to the original documents, for transparency and traceability."* **Comment:** Clarification needed to facilitate the work of NCAs and of the members of IRBs/IECs.
677	24	**Comment:** Approval of modifications is essential. **Proposed change:** … should be provided in a protocol amendment (ICH E6) *with regulatory and ethics approval according to national legislation.*
678	12	**Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		this section could be expanded to include competence assessment as a combination of qualifications, training and experience appropriate to the role.
678	35	**Comment:** this section could be expanded to include competence assessment as a combination of qualifications, training and experience appropriate to the role.
678-684	20	**Comment:** It is agreed that training, along with training records and documentation, is a key element. However, to be efficient, a training shall be focused on pertinent aspects and evolutions observed during the course of the study, and it should be considered that multiple, redundant and non-pertinent training can have the opposite effect by causing a lack of confidence and sense of lost time. It would seem appropriate, considering the addition of third-party services training, to avoid a too broad approach of training and that it should be focused on each stakeholder activity/responsibility and impact of their respective role on the trial, or on a specific change or issue observed. This paragraph brings also room for interpretation on what would be the content of an updated training, why it would be done and when. **Proposed change:** "…should receive thorough training **fitted to their role and impact on a study** prior to enrolment…"…"Updated, **appropriate and focused** training should occur…"
678-684	23	**Comment:** Updated Training should also occur in case of new information or if a protocol amendment is available
678-684	32	***678 6.1.2 Training*** **Comment:** **679** Study stakeholders, such as sponsors; investigators, coordinators, and other local site staff; site **680** monitors; adjudicators and members of the data monitoring committee; and third-party service

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		681 providers (e.g., central laboratory or reading centre personnel) should receive thorough training **682** prior to enrolment of the first study subject. Updated training should occur during the conduct **683** of the study to reinforce the importance of adherence to study procedures and to address issues **684** related to critical to quality factors observed during the course of the study. Sponsors should have policies in place that approve the robustness of the good clinical practice training offered to research staff and that require periodic updating of all such training *When a clinical trial involves an investigational product, all key personnel should be knowledgeable of all applicable regulations, including those that pertain to human subject protections* Protocol training should also be documented and, especially for complex trials, periodically repeated. To ensure the adequacy of training procedures, testing of knowledge is highly recommended Protocol-specific SOPs, often called a Manual of Operations, can outline the protocol procedures in greater detail; it is imperative that the SOPs are critically reviewed to ensure consistency with the protocol. All staff should have documented SOP training. SOPs should be reviewed on a scheduled, periodic basis for potential updates However, quality-assurance programs at the investigator site are less frequently seen. Establishing such a program is not arduous and should be done promptly if none exists [22, 29, 30]. 22. Quality Assurance and Educational Standards for Clinical Trial Sites. J Oncol Practice 2008; 4(6):280–282. http://jop.ascopubs.org/content/ 4/6/280.full?sidpa9e414cd-8327-47cc-87aa-89959172e375. Accessed 21 June 2010. 29. FDA ORA Quality Manual. http://www.fda.gov/AboutFDA/ CentersOffices/ORA/UCM135836.htm. Accessed 21 June 2010. 30. Marinus A. Quality assurance in EORTC clinical trials. European Organisation for Research and Treatment of Cancer. Eur J Cancer 2002; 38(Suppl 4):S159–S161. There are 4 types of errors in randomized clinical trials: design, procedural, recording (both random and fraudulent) and analytical [32]. 32. Baigent C, Harrell FE, Buyse M, et al. Ensuring trial validity by data quality assurance and diversification of monitoring methods. Clin Trials 2008; 5:49–55. A quality system must address each of these. One solution for identified

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problems is adopting a Quality Management System approach that uses identified problems to make products safer and ensure data validity. After such a system is in place, it can achieve maximum customer satisfaction efficiently while improving the process. Among the most widely used tools for continuous improvement is a 4-step quality model—the plan-do-check-act cycle, also known as the Deming Cycle or Shewhart Cycle [33] 33. American Society for Quality. Project planning and implementing tools. http://www.asq.org/learn-about-quality/project-planning-tools/overview/pdca-cycle.html. Accessed 21 June 2010. (Table 2).

Table 2. The Plan-Do-Check-Act.

Step	Stage of cycle
Identify the error in the process and develop solutions	Cycle Plan: Who is authorized to consent subjects? Is there a pattern? How is the staff trained? Are there other factors involved? Develop a retraining plan
Apply the planned changes	Do: Retrain the identified staff
. Measure the results by monitoring and checking for any errors	Check: Directly observe staff performing the consent procedure; conduct an internal audit of the next 20 consent forms before the subjects leave the clinic
Implement the plan on a wider scale if all consent forms checked have been signed; if unsigned consent forms are still found, begin the cycle again	Act: If dates are still missing, have subjects date their consent forms, retrain staff or authorize another staff person to consent incoming subjects, correct any other factors that may be involved (eg, overburdened staff or distracted staff member)
NOTE. In the Plan-Do-Check-Act model, there is no end. In the example shown here, suppose that (hopefully found through systematic auditing) subjects are not dating consent forms in a clinical trial.	

Other widely used methods of continuous improvement are Six Sigma, Lean, and Total Quality Management.

Systems and standardization. Create systems that limit the opportunity for errors. Simplify protocols and outcomes assessed. Be realistic about the amount of data to be collected. Standardize systems and formats when possible. Use validated

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		instruments and definitions. Write down all procedures that need to be followed by clinical staff. Use checklists. Do not reinvent the wheel: there are many templates [27, 28], 27. Goldfarb NM. Something for everyone: standard operating procedure products for the investigative site. Journal of Clinical Research Best Practices 2005. http://firstclinical.com/journal/2005/0504_SOPReview .pdf. Accessed 21 June 2010. 28. Clinical Trials Networks Best Practices. SOPs. https://www.ctnbestpractices.org/sites/sops. Accessed 4 December 2009.forms, and case report forms that have already been developed and assessment instruments that have already been validated [34]. 34. PROMIS: Patient Reported Outcomes Measurement Information System. http://www.nihpromis.org/. Accessed 4 December 2009. Keep amendments to a minimum, and check case report forms and consent forms against each change The transfer of data from source documents to data collection forms and/or electronic data capture should be done systematically and as expeditiously as possible. In the rapidly changing clinical research environment, continuous vigilance is needed to ensure data integrity and human subject protections. The extra work in initial planning and preparation, in addition to continuous process improvement, will increase the quality and efficiency of clinical trials. Now, with the release of ICH-E6 R2, quality management is more connected with the clinical study report through risk control and risk reporting guidelines. Specifically, tolerance limits need to be established during the planning phase of a trial, and deviations from those tolerance limits require predefined policies to address what mitigations and actions will need to be taken. The benefits of defining, planning, documenting, managing, and reporting risk enables study teams to not only enhance subject protection and study data integrity, but also improve the risk management process.
678-684 (section 6.1.2)	34	**Comment:** The section on Training (section 6.1.2) is excessive and unhelpful. It invites over-interpretation and implementation. It goes well beyond what is stipulated (and sensible) in ICH E6, "Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s)." [ICH E6 R2 section 2.8] As currently worded, the need for "thorough training prior to enrolment of the first study subject" and for "updated training ..." without any sense of scope, purpose, or study role is excessive and would seriously impede or prevent many trials from happening. This is not in the interests of clinical care, public health, or patients. For example, why does an experienced phlebotomist need thorough training just because the patient they are taking blood from

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		is in a trial (when the very next patient they take blood from may have complex medical issues but happen to not be in a trial)? Similarly, in a study of treatments for acute MI, one needs large numbers of clinicians who are experienced in seeing patients with acute MI and to provide them with a small amount of training about the few aspects of the clinical trial that are relevant to them. They do not need extensive training in every nuance of the trial or in how to manage patients with acute MI (beyond the training they need to see such patients in routine practice). The need for updated training should be driven by the QbD principles: If nothing has changed (no relevant new information from within or outside the trial) and performance is good, why is it necessary to distract staff from a job they are doing well so that they spend time doing training they don't need? The current wording promotes the kind of approach that increases costs, reduces efficiency, harms quality (staff are too busy doing training to be paying attention to the actual work), and reduces enthusiasm and willingness of clinical staff to contribute to clinical trials. Stick with the principle set out in E6 (section 2.8) and with the QbD principles of focussing on what's important and plan-do-check-act, where ongoing / update training needs are informed by the "check" stage and can be a part of the "act" stage.
679	13	**Comment:** risk-based approach as per study needs also for training. **Proposed Change:** "Study stakeholders, such as sponsors, investigators, coordinators, and other local site staff, site monitors, adjudicators and members of the data monitoring committee, and third-party service providers (e.g., central laboratory or reading center personnel) should be qualified by training and experience prior to enrolment of the first study subject. Updated training should occur during the conduct of the study to reinforce the importance of adherence to study procedures and to address issues related to critical to quality factors observed during the study as required."
679-682	15	**Comment:** It should be specified that training must be relevant for those who are trained (e.g., the pharmacist should not be trained on

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		drug prescription or dose adjustments, whereas the PI should not be trained on the storage of the drug in the pharmacy). **Proposed change:** Study stakeholders, such as sponsors; investigators, coordinators, and other local site staff; site monitors; adjudicators and members of the data monitoring committee; and third-party service providers (e.g., central laboratory or reading centre personnel) should receive thorough **(and relevant)** training prior to enrolment of the first study subject.
680 - 682	2	**Comment:** include some specification on quality aspects **Proposed change:** and third-party service providers (e.g. central laboratory or reading centre personnel) should receive thorough training **on relevant aspects of study procedures, including the critical to quality factors,** prior to enrolment of the first study subject.
680-682	22	**Comment:** The requirement that all involved parties have to receive training prior to enrolment of the first study subject does not take into account that some parties may only become involved at a later stage of the study and therefore may be appointed only after enrolment of the first subject. **Proposed change:** […] should receive thorough training prior to ~~enrolment of the first study subject~~ their involvement in the study.
681	24	**Comment:** Training should include tools on how to implement the study into the site's clinical project management and quality management. The basis for such specific study-related training is the competence (demonstrated by evidence of qualification and experience) of the site and third-party staff per se. The frequent argument: we will first gain experience with a small number of enrolled subjects before we get to the agreed number of patients per months is not acceptable. No enrolled patient

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		should be "used" as a training exercise. Every enrolled patient should be optimally protected, and his/her data be optimally suitable for future treatment recommendation as of the first enrolled patient. Updated training, also including new staff members, during the study, should be part of the process. **Proposed change:** …. *should be competent in their respective function and* receive thorough *study-specific documented* training prior to the enrolment of the first study subject. Updated training *for the study team, including new staff,* should occur during the conduct….
681	25	**Comment:** Training of staff is not sufficient. There needs to be demonstrated qualification as a pre-requisite for taking over a certain responsibility in a study. **Proposed change:** …should *be qualified for the respective task, and* receive thorough *study-related* training before…
681	31	"e.g., central laboratory, …" **Comment:** One important type of third party are Contract Research Organisations. **Proposed change:** "e.g., Contract Research Organisations (CROs), central laboratory, …"
681	37	*providers (e.g., central laboratory or reading centre personnel) should receive ~~thorough~~ training* **Comment:** If "thorough" is added, then qualify it. Otherwise better to leave out.
682	21	*"{...} should receive thorough training prior to enrolment of the first subject and implement safety measures where needed*

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		(especially safety SOPs for sites conducting FIH or Phase I-studies).” **Comment:** For obvious reasons to protect the wellbeing of trial participants.
682-684	18	Section 6.1.2 Training Updated Training should occur during the conduct of the study to reinforce the importance of adherence to study procedures and to address issues related to critical to quality factors observed during the course of the study. **Comment:** It is unclear whether the expectation is that updated/repeated training is expected even in case of no updates to study requirements/documents or only in case of updates (e.g. re-training for protocol amendment). It is further unclear if there are any expectations regarding frequency of updated training.
685-690	28	**Comment**: The Data Management section does not mention the requirement for data provided to the Data Monitoring Committee to be cleaned ahead of the DMC meetings, to ensure decision are made based on complete and accurate information. **Proposed change:** Add a comment regarding data cleaning requirements of data provided to the DMC for review.
685-690 (section 6.1.3)	34	**Comment**: Data management (section 6.1.3) does not include anything about the need to consider carefully what data should be collected (collecting excessive data is a threat to quality).
686	12	**Comment:** There is no mention of source data, certified copies and transcribed data and who should control it etc. Use of "data" is a little simplistic.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		It would also be helpful to include something about the handling of study data once collected e.g. queries, changes to data, transmission between systems, reconciliation etc
686	35	**Comment:** There is no mention of source data, certified copies and transcribed data and who should control it etc. Use of "data" is a little simplistic. It would also be helpful to include something about the handling of study data once collected e.g. queries, changes to data, transmission between systems, reconciliation etc
686-687	28	**Comment:** This text seems to lack a reference E6 section 5.0.1; Critical process and data identification **Proposed change:** Add a suitable reference and ensure the two documents are aligned in the way critical processes and data are developed in line with the critical to quality factors.
687-689	28	**Comment:** Operational checks and statistical surveillance are mentioned, but this section fails to mention centralised monitoring, as stressed in ICH E6 5.18.3 & 5.18.6, for example. **Proposed change:** Add a comment on centralised monitoring. Also add comment regarding the selection of data/parameters for centralised review, operational checks and statistical surveillance and their ability to potentially bias or unblind the trial.
689-690	24	**Comment:** The need for proactive data management strategy and process planning, defined in a Data Management Plan, should be stressed

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: Line 690: Please add: *"The Data Management strategy and process should be described in a Data Management Plan that might also foresee the establishment of an "Endpoint/Adjunction Committee".*
691-695 (Section 6.1.4)	34	**Comment:** Access to interim data (section 6.1.4) should be clearer about what might impact study quality: It is not access to data per se that compromises study integrity, it is access to the aspects of the data that may introduce bias. In the context of randomized trials, this means access to information that relates to data that would result in unblinding of the treatment allocation. Those responsible for designing and overseeing the trial should have access to blinded interim data on recruitment, baseline characteristics, adherence to therapy, completeness of follow-up, number of clinical outcomes (efficacy and safety), etc.
692	12	**Comment:** Mention monitoring here specifically where access to unblinding such as a randomisation list or dosing record etc may mean that the monitor cannot be used for monitoring blinded data also.
692	20	**Comment:** Integrity could also be jeopardized in case of violation of local or other regulations and access to other types of data than the one collected for the trial. **Proposed change:** "Inappropriate access to study data **or other data type (e.g. patient data in medical records)** during the conduct…"
692	35	**Comment:** Mention monitoring here specifically where access to unblinding such as a randomisation list or dosing record etc may mean that the monitor cannot be used for monitoring blinded data also.
694	24	**Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		To highlight the need for good data and good data management it is recommended to add: **Proposed change:** …to avoid inappropriate access. *Consideration should also be given to the timing of validation of extraction and analysis programmes to assure the quality of the interim analysis.*
694-695	22	**Comment:** It should be more clearly outlined what is meant by "ongoing monitoring of data to avoid inappropriate access" for studies without interim analyses. **Proposed change:** Even in studies without planned interim analyses, special attention should be paid to any ongoing monitoring of data to avoid inappropriate access, for example <example to be named>.
695	9	**Comment:** The paragraph should emphasise the risk of unplanned interim analyses being guided by results and advise against their use. **Proposed change:** Add: Not pre-specified interim analyses bear a high risk of being guided by results and are generally advised against.
695	13	**Proposed change:** "… attention should be paid to any ongoing monitoring of data to avoid inadvertent unblinding."
695	20	**Comment:** Additional example or further explanation would increase the understandability of the section. **Proposed change:** In example, analysis on unvalidated data may lead to inaccurate interpretation of results or changes once data is later cleaned

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		and validated.
696-721	23	**Comment:** Section 6.2 addresses the need for clear criteria for stopping study treatment, and Section 6.3 the role of a DMC to determine whether to continue, modify, or terminate a study. Since studies may be terminated without involvement of a DMC, it is suggested to include a reference to the need for clear criteria for study termination also in Section 6.2.
701	1	**Comment:** ”characterize” **Proposed change:** “characterise”
702	24	**Comment:** The process of unblinding of safety information is critically important and should be mentioned here. **Proposed change:** Procedures and systems for the identification, monitoring, *unblinding*, and reporting of safety concerns including….
702-703	20	**Comment:** Consider splitting and rewording into two sentences for improved clarity. **Proposed change:** “Procedures and systems for the identification, monitoring and reporting of safety concerns during the study should be clearly specified. This should include the timing of all aspects of safety reporting as well.”
704	12	**Comment:** Safety data can impact on trial design and conduct so it is essential that the systems and processes are robust for the timely

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		collection, processing and interpretation of data whilst protecting blinded information when relevant.
704	35	**Comment:** Safety data can impact on trial design and conduct so it is essential that the systems and processes are robust for the timely collection, processing and interpretation of data whilst protecting blinded information when relevant.
704-705	31	"The approach should reflect the risks to the study subjects and what is known about the drug and the study population." **Proposed change:** "The approach should reflect the risks to the study participants and what is known about the drug and the study population (see ICH E19).
706-707	13	**Comment:** add ICHE2F **Proposed change:** Pharmacovigilance (A, B, D and F), and ICH E6
708	39	6.2.2 Withdrawal criteria **Comment:** "Clear criteria for stopping the treatment…" We recommend refining in "Clear criteria for temporary or definitive discontinuation of treatment…"
708-712	23	**Comment:** withdrawal criteria should be defined based on all clinical or non-clinical information of the study drug
708-712 (section 6.2.2)	34	**Comment:** Withdrawal criteria (section 6.2.2) is an unhelpful phrase since it confuses a number of issues: For example, patients may wish

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		to: - stop taking study treatment - stop attending study visits in person - stop being contacted by the study staff - stop study staff accessing their medical records - stop study staff analysing their samples, etc. Some of these preferences may have implications for individual patient safety and others for the reliability of the result.
711-712	2	**Comment:** Propose to add a cross-reference to data protection requirements. **Proposed change:** .....are necessary to ensure the protection of the subjects; however, consideration ~~could~~ **should** be given to methods that will preserve the subjects' safety and rights, including data protection, while still minimising loss of critical data, if possible.
712	9	**Comment:** Especially in studies with unvalidated surrogate endpoints, crossover of patients from one study arm to the other based on preliminary results bears the risk of invalidating analyses of patient relevant outcomes. This leads to study results that are inconclusive, which results in problems in decision making and is unethical towards study participants. **Proposed change:** Add: Crossover of participants from control to intervention (or vice versa) should be limited to cases, where interim analyses regarding the patient relevant primary endpoint severely change the study equipoise.
713	13	**Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		As well as the primary responsibility of safety monitoring, a DMC can also evaluate the scientific validity and merit of the clinical trial. It might be helpful to expand this section to mention these additional responsibilities.
713	15	**Comment:** The role of the Data Monitoring Committee should be broadened. It would be recommendable that they performed a routine review of safety information and selected the relevant data to be sent to participating centers, to avoid important signals getting lost in an unmanageable amount of safety information.
713-721	23	**Comment:** there is a commenting process for Questions to be answered upon DMCs currently running. This process showed that the terminology to be used for the different types of DMCs is unclear and requires specification especially when DMCs in early phase trials are to be differentiated against DMCs in later phases. AGAH has already commented here. It is strongly recommended to harmonise terminology between guidelines.
713-721 (section 6.2.3)	31	**Comment and proposed change:** Early phase trials usually use "internal" blinded safety review committees including sponsor and investigator for decision making during the trial. Please add.
714	1	**Comment:** an in "independent" when referred to data monitoring committee **Proposed change:** the use of "an independent data monitoring committee"
714	12	**Comment:** In phase I dose escalation trials there is a review of data before the next level of dosing can go ahead. This could be referred to in this section also; specifically the need to quality data on which those decisions are made.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
714	21	*"…the use of an independent data monitoring committee…"* **Comment:** The members of the DMC should be external and independent with regard to the sponsor.
714	35	**Comment:** In phase I dose escalation trials there is a review of data before the next level of dosing can go ahead. This could be referred to in this section also; specifically the need to quality data on which those decisions are made.
715	19	**Comment:** Here abbreviation used is DMC, but in the ICH E6 it is Independent data monitoring committee IDMC
715	39	6.2.3 Data Monitoring Committee **Comment:** *"…A DMC **independent** monitors…"* We suggest to precise that the DMC should be independent.
717	13	**Comment:** You use the term "safety monitoring committee" only once here? Is a DMC meant? Or is it something different? The reference to two different terminologies, "DMC" and "external safety monitoring committee", is potentially confusing. **Proposed change:** Suggest keeping to DMC.
717	21	**Comment:** *'external safety monitoring committee'*. Please use terms that are properly defined, e.g. use established terms like *'data monitoring committee'* or '*independent data monitoring committee*' to avoid confusion.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
717-721	16	*If a data monitoring committee is needed for either an individual study or the entire development programme, procedures governing its operation and, in particular, the review of unblinded data while preserving study integrity (ICH E9) should be established* **Comment:** Some data monitoring committees include patients' representatives. **Proposed change:** If a data monitoring committee is needed for either an individual study or the entire development programme, procedures governing its operation and, in particular, the review of unblinded data while preserving study integrity (ICH E9) should be established. Its composition can include trained representatives of patients.
718	10	**Proposed change:** safety data across studies in a development programme ~~may~~ should also be assessed
718-721	25	**Comment:** A DSMB should be established BEFORE the start of the study. **Proposed change:** …while preserving study integrity (ICH E9) should be established *prior to study start*.
720	21	*" {...} procedures governing its operation, selecting its members and the required scientific backgrounds {...} should be established (Charta). "* **Comment:** Clarification.
721	1	**Comment**:

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Add in about recommendation to use DMC charter to establish remit and function of DMC **Proposed change:** "…while preserving study integrity (ICH E9) should be established, ideally with use and agreement to a data monitoring committee charter"
722ff	24	**Comment:** The relevance of reliable and complete reporting and dissemination of all studies' results, independent of their outcome, should be stressed in this guideline as a critical to quality factor in clinical studies. Consequences of omissions could be explained.
722 - 732	13	**Comment:** Wouldn't it be better to recommend that subjects and patients be accessible? It seems that this will promote patient participation/involvement in clinical trials. Why don't you mention it in this section?
722-732	28	**Comment:** Section 6.3 Study Reporting; makes no mention of the requirement in E6 5.0.7 to summarise important deviations from the predefined QTLs and remedial actions taken in the clinical study report. **Proposed change:** Add a comment regarding reporting of QTLs and the appropriate reference to E6.
723	12	**Comment:** It is essential that reports are of a high quality and accurately reflect the conduct and results from the trial - without this the effort in enshrining QbD in the clinical study has been wasted.
723	25	**Comment:** Study reporting is a crucial quality element in a study and should get more clearly defined in this guidance. Especially the presentation of the results, answers to the study questions and presentation of the protocol-conform performance and

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		deviations should be requested. **Proposed change:** *Clinical study reports should comprehensively present the study results, give answers to the study objectives, report the protocol-conform performance of the study and possible deviations, and express relevant conclusions for future research and treatment.* ICH E3…
723	35	**Comment:** It is essential that reports are of a high quality and accurately reflect the conduct and results from the trial - without this the effort in enshrining QbD in the clinical study has been wasted.
723-726	33	**Comment:** ICH E3 was released in 1995, and is used as standard for reporting of trials during the marketing approval process. However, the majority of post-approval trials are not intended for submission to regulatory bodies; indeed many of them are performed by academic sponsors und funded by public funding agencies. Since 1995, several widely accepted and rather rigorous scientific reporting guidelines have been developed and are regularly refined. They are available e.g. via the EQUATOR (Enhancing the QUAlity and Transparency Of health Research) network website (http://www.equator-network.org/). Please consider referring to the CONSORT guideline and its several extensions for different trial types as the standard for reporting trials outside the scope of marketing authorization approval.
724-725	26	**Comment:** ICH E3 format of report is only applicable to studies with registration purpose. This heavy format is not fit for purpose of pragmatic studies and other studies without any registration purpose (though other formats of reports are of course required for transparency purposes). **Proposed change:** EORTC suggests clearly stating that ICH E3 format shall not be necessarily applicable to studies not part of a registration dossier.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
725-726	9	**Comment:** It is important to ensure that reporting of observational studies is appropriate. Therefore, the development of an ICH-guideline on these is encouraged.
725-726	13	**Comment:** Please provide specific examples of the "other reporting formats appropriate for the type of study and information being reported "such as for observational studies. Please consider adding such concrete description in ICH-E3 when it is revised.
725-726	18	**Comment:** We agree that non-interventional studies should use reporting formats appropriate for the type of study and information being reported. It would be helpful to include references to appropriate published reporting templates for these types of studies. **Proposed change:** Add appropriate references.
726	3	**Comment:** appropriate for the type of study and information being reported. **Proposed change:** should use reporting formats **accepted** by the scientific community for the type of study and information being reported.
726	24	**Comment:** It is important to align with GCP reporting requirements. **Proposed change:** … and information being reported *with transparency on protocol compliance, ethical considerations and GCP.*
727–729	16	*The transparency of clinical research in drug development includes the registration of clinical trials on publicly accessible and*

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		recognised databases, and the public posting of clinical trial results. **Comment:** The posting of results should be timely. Often, results are posted too long after the end of the study. **Proposed change:** The transparency of clinical research in drug development includes the registration of clinical trials on publicly accessible and recognised databases. The public posting of clinical trial results should be timely.
727-732	20	**Comment:** No comments have bene included on the importance of communicating results to study subjects who participate. Why involve them in the design and obtain their input if no feedbacks are made about results and conclusions of the clinical study before/in addition to sponsor's press releases. Additionally, solely rely on publication through public databases is limitative, as such databases may not always exist in all world regions or for populations with no or limited access to such databases (for technical, language or educational reasons). This section should emphasize on the importance of communication of trial results even if they are negative, to trial participants. Additional research information on this topic is available: https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.0050091 https://www.ncbi.nlm.nih.gov/pubmed/19064746 **According to the Declaration of Helsinki (2008)** *"33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits."* **CIOMS 2017 Guideline 24** *- Commentary states: " Knowledge resulting from the research should be made accessible to the communities in which the research was conducted, either through publication in scientific journals or through other channels.*
727-732	39	6.3 Study Reporting

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Comment: In addition to the registration of clinical trials and publication of results and to support "reducing unnecessary clinical studies" we recommend to add an incentive in the guidelines to setup or to reinforce regulatory or legal provisions with regards to publication of results regardless of the nature of results or regulatory decisions, in order to improve availability of data and reduce non-disclosure of scientific and health knowledge and evidences.
729	9	**Comment:** We support the wish for registration of observational studies. **Proposed change:** Add sub-clause: … and should be established
732	3	**Proposed change:** add: "and increasing trust in the medical science."
732	5	**Comment:** Could we also promote clinical trial data sharing ? **Proposed change:** add sentence: Individual patient-level data sharing should be encouraged, to promote secondary use of clinical study data for re-analyses, meta-analyses or secondary analyses, according to a data sharing plan.
732	24	**Comments:** There is no mentioning of the need and benefit of Lay Summaries in this draft guidance. We find it relevant to introduce this requirement into this guidance. **Proposed change:** … and informing decisions in clinical practice. *Lay Summaries of study results are an appropriate additional tool to inform study*

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		participants, health care providers and the public about the outcome and relevance of the study performed.
733	24	**Comment:** This headline is not clear. The following bullets are a type of summarizing conclusions of what has been described before. The headline should make this clear to enable understanding of the following text.
733	27	**Comment:** I would like to add an extra point about the material to be used to inform the patients, including the Informed Consent. It is essential that the information is understandable for the patients and that the patient understands/agrees with the critical aspects of the study and the choices that will be made. This can improve the patient compliance and thus the quality of the data and the study.
733-772	13	**Comment:** Section 7 could be streamlined and embedded in section 3 as this is repetitive. **Proposed change:** Delete section 7 "CONSIDERATIONS IN IDENTIFYING CRITICAL TO QUALITY FACTORS" and embed content in section 3.
733-772	23	**Comment:** Section 7 describes the need for proactive, cross-functional discussions and decision making at the time of study planning. Such discussions involve study investigators and study teams, as appropriate. In the context of the prerequisite non-clinical studies, and where applicable, clinical studies to support the study being designed, reference should be made to the Investigator Brochure as critical document summarising the relevant information. It is therefore suggested that the requirement of a comprehensive and updated Investigational Drug Brochure should be included in the considerations provided in this Section.
733 to 772	29	**Comment:** An indication regarding a non-conflict of interest by the principal investigators is missing. Such information is needed and should be included in Paragraph 7.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
733-772	31	**Comment:** Section 7 should be placed much earlier in the document e.g. section 2 as this helps understanding throughout document.
733-772 (Section 7)	34	**Comment:** **Section 7. Considerations in identifying critical to quality factors** **This section is generally helpful. There are a few minor wording changes needed in places (see marked up PDF copy).** **For example, the extent of the feasibility assessment necessary (line 752) will vary considerably** depending on factors such as the level of experience of the clinical and trial teams, the similarity of the study methods with routine practice or previous trials, the hazards associated with the treatment, etc. (It would be unhelpful to spawn a new industry of "feasibility experts" generating piles and piles of paper, unduly delaying study start-up, and driving up costs unnecessarily!) The phrasing around *"integrity of critical study data"* (line 767) needs to be more nuanced. (There needs to be a sense of proportionality here. Even for "critical" data, some errors, including unclear provenance, may have little impact on the participants or the results.) The principal should be to avoid critical data errors or integrity issues that would have a meaningful impact on study participants or the reliability of the results. A similar need for proportionality applies to the following bullet point on monitoring (lines 768-769) where it might be helpful to mention the concept of risk-based monitoring.
738-739	27	**Comment:** In designing a study, applicable aspects such as the following should be <u>considered</u> to support the identification of critical to quality factors: The use of the word considered suggest a recommendation rather than a rule. I would have expected regulators to be more precise to make this happen in a systematic way. **Proposed change:** In designing a study, applicable aspects such as the following <u>must be implemented</u> to support the identification of critical to

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		quality factors:
738-772	28	**Comment:** The activities described in this section, to be conducted during the design phase of the protocol, should be linked to E6 Section 5.0.1 Critical Process and Data Identification, which are also required to be conducted during the protocol development. **Proposed change:** Review E6 and E8 and add relevant language and references to connect with E6 section 5.0.1.
740	18	**Comment:** As noted above in our comment on lines 76-85, consultation should not be restricted to patients but may also involve healthy volunteers. **Proposed change:** Change "patients" to "potential study subjects".
740-770	16	**Comment:** A critical quality factor is the readability and understandability of the informed consent and trail information **Proposed change:** To add another bullet Information to target population and study subjects is clear and understandable
742	12	**Comment:** this should be complete, accurate and adequate
742	35	**Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		this should be complete, accurate and adequate
751	12	**Comment:** Training (and competency) applies to all stakeholders, i.e. sponsor/CRO as well as investigator site
751	35	**Comment:** Training (and competency) applies to all stakeholders, i.e. sponsor/CRO as well as investigator site
752	9	**Comment:** As mentioned earlier, feasibility is seldom objective but depends on the will to take appropriate measures. **Proposed change:** Add sub-clause: … taking into account possible measures to overcome hindrances.
755	28	**Comment:** Eligibility criteria should also consider restrictions necessary to ensure the safety of subjects with respect to the known safety profile of the investigational product or other relevant medical characteristics of the target subject population. **Proposed change:** Add wording such as "The eligibility criteria should be reflective of the study objectives and safety profile of the treatment under study and be well documented in the clinical study protocol."
755-756	25	**Comment:** The eligibility criteria should not only be reflective of the study objectives but also of the safety profile and the accumulative knowledge of the IMP. **Proposed change:** … should be reflective of the study objectives, *the IMP's safety profile and the accumulative knowledge on the product,* and

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		should be well…
755-756	27	**Comment:** The eligibility criteria should be reflective of the study objectives and be well documented in the clinical study protocol. Often recruitment criteria does not reflect real patients population so the outcomes my not be the same when we move to real world. This change should be promoted any regulators, to amplify the benefits in real clinical practice. Registries could and should be key partners to ensure all patients distinctive characteristics are well represented. **Proposed change:** And reflective of the real patients population in real world
760	24	**Comment:** Critical to quality factors are not only the right subjects in the study and the other topics mentioned in lines 740 to 760 but also the competence of the staff performing all study tasks. **Proposed change:** Add a bullet: *The selection of competent staff and study-specific training are in place before start of study conduct*
761	39	7. Considerations in identifying critical to quality factors **Comment:** "… and the methods to assess them are well-defined…" **Proposed change:** We recommend adding "… and the methods to assess them are prospectively planned and well defined…" in consistency with the pre-specification requirements previously mentioned in the document with regard to study protocol and statistical analysis plan.
761-762	18	**Comment**:

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		We recommend the following change to the text. **Proposed change:** Replace "…. are well-defined and support evaluation…." with "…. are well-defined, validated if necessary, and support evaluation…."
761-762	24	**Comment:** Optimal data collection is key. It should occur with validated tools and should be limited to collection of data that are really relevant for answering the research questions **Proposed change:** The choice of *carefully selected* response variables and the accurately validated methods to assess them are well-defined and enable evaluation of the *drug's* effects.
763	28	**Comment:** With the text "Clinical study procedures include adequate measures to minimise bias (e.g. randomisation, blinding)." **Proposed change:** Add text such as "...and to prevent unintentional breaches of such measures".
765-766	22	**Comment:** The term "pre-specified" is unclear. More emphasis should be put on the fact that there is a general requirement to have a statistical analysis plan, and this early enough. **Proposed change:** The statistical analysis plan ~~is pre-specified~~ has to be created early enough depending on the design of the study and defines the analysis methods appropriate for the endpoints and the populations of interest.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
766	31	"… appropriate for the endpoints and the populations of interest." **Proposed change:** "… appropriate for the endpoints and the ~~populations~~ **analysis sets** of interest."
770	24	**Comment:** A bullet should be added concerning the reporting of the study results and the course of the study as this is a crucial element of the planning for a critical to quality factors approach **Proposed change:** *Comprehensive and timely clinical study reporting is well prepared, ensuring accurate and complete description of all results and of those aspects of the study that went according to plan as well as all relevant deviations.*
773	24	**Comment:** Also in this Annex 1 table the possibility of combined Phase 1/2, 2/3, etc. studies should be presented.
773-777 (Appendix 1)	18	**Comment:** We welcome the inclusion of this Appendix. However, the set of trial designs described in E8 is limited and does not reflect the range of designs in use today across the project lifecycle. For example, the objectives of the listed study types are all aligned with those of a clinical trial involving a medicinal product and the study types do not extend to those such as Disease Registries or studies which don't include medicinal products. **Proposed Change:** Recommend to revert back to use of clinical trial and clarify that scope is only for clinical trials. Or, if intent is to expand then there needs to be an agreed set of definitions with all ICH stakeholders and Appendix 1 needs clarity with regard to studies such as registries and those which don't involve medicinal products
773-777 (Annex 1)	34	**Proposed Change:** This section could be removed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		It is unclear how this informs "General considerations for clinical studies". This is just a list and provides no guidance.
774	13	**Comment:** The word 'ideally' is referenced in a number of places throughout this document. Considering that the drug development process may follow a variety of different sequences, we suggest considering using a different term here. **Proposed change:** "Drug development usually follows a logical, step-wise process in which information from small early studies is used to support and plan later larger, more definitive studies"
777	2	**Comment:** The definition of bioequivalence is not the same in all ICH regions since this topic has not been harmonized yet **Proposed change:** A definition that is compatible with the current definition of regions should be used. Alternatively, a more general definition should be provided.
777	6	**Comment:** It may not always be relevant to do assessment of cross-reactivity. **Proposed change:** Suggest to change the sentence "Assess immunogenicity and cross-reactivity" to "Assess immunogenicity"
777	12	**Proposed change:** - add to table for non clinical 'assess pharmacology, prim, sec.' - add to examples for confirmatory efficacy and comparative effectiveness studies
777	9	**Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
(table)		1) Type of study – Exploratory // Study examples – Biomarker exploration studies: Biomarkers do not only have to be explored, they additionally need to validated appropriately to ensure the predictive value of their use and the applied thresholds. 2) Type of study – Confirmatory // Study examples – Randomised controlled clinical trials: In confirmatory trials, the use of surrogate endpoints needs to be limited to those surrogate endpoints, that have been validated to substitute for patient relevant outcomes. 3) Type of study – Post-approval // Objective(s) of studies – Refine understanding…: Refining the understanding of benefit/risk relationship is an important issue, but insufficient. Especially in cases of accelerated approvals (but not limited to), the confirmation of the assumed benefit/risk relationship is necessary. **Proposed change:** 1) Change example to Biomarker exploration and validation studies. 2) Add "validated" in front of "surrogate or pharmacological endpoints" 3) Add: confirm the assumed benefit/risk relationship
777 table	13	**Comment:** Suggestion to remove line listing non-clinical development as this guideline has clinical development in scope. **Proposed change:** Delete first line in **Table** ANNEX 1: TYPE OF STUDIES. ~~"Non-clinical testing to support and supplement clinical investigations."~~ **Comment:** Consideration to add human-factor studies to table, particularly to align with reference to drug-device combination products (line 238). **Comment:** add into the table below micro dose studies to the section Human pharmacology, study examples

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Comment: In the table listing the different types of studies, it should also be mentioned that modern exploratory clinical research studies may expand and extend multiple times thus increasing the overall duration (e.g. Umbrella & basket studies, master protocols). **Comment:** 6th row: The example of a "post-authorization safety study (PASS)" is not provided. Given the high importance and frequent used of these types of studies, perhaps this should be added. **Proposed change:** Add "Post-authorization safety study (PASS)"
777 f table	23	**Comment:** Safety pharmacology is missing under non-clinical testing….
777 table	39	**ANNEX 1: Types of Studies** **Comment:** We recommend adding "**Ethno-bridging**" in *Study Examples* for *Confirmatory* studies. Also, we suggest adding in the non-clinical studies: - Objectives of study: **assess shedding in the environment** - Study examples: **environmental studies**
778 (table)	12	**Comment:** post approval box should include 'explore treatment regimes in combination with other drugs - such as oncology studies' and change/improve prescribing practise
778 (table)	35	**Comment:** post approval box should include 'explore treatment regimes in combination with other drugs - such as oncology studies' and change/improve prescribing practise

Line no.	Stakeholder no.	Comment and rationale; proposed changes
779-787 (Appendix 2 and 3)	18	**Comment:** The work carried out by ICH under the Efficacy heading is also listed as being concerned with the design, conduct, safety and reporting of clinical trials. **Proposed Change:** Revert to use of 'clinical trial' within ICH E8R1 or clarify how the expansion of study types in ICH E8R1 aligns with guidance in the other ICH Efficacy documents.
779-785 (Annex 2)	34	**Comment:** See comment on next appendix.
783	24	**Comment:** in addition to the use of ICH guidelines in a holistic way, local legislation must be considered. **Proposed Change:** …in isolation of the others; *local legislation must be respected.*
786 (annex 3)	12	**Comment:** data Quality, Study and site feasibility, data Recording, Data monitoring and statistics should also include E6 We do not know what is meant by accrual in this table
786 (annex 3)	35	**Comment**: data Quality, Study and site feasibility, data Recording, Data monitoring and statistics should also include E6 We do not know what is meant by accrual in this table
786 table	13	**Comment:** Clarify how dissemination of study results may be a critical to quality factors. Is it dealing with transparency of results? Add a

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		tick in ICH E3 for study reporting – dissemination of study result. **Comment:** ICH E6 is expected to change a lot with GCP Renovation, but ICH E6 will be applicable to all except Accrual and Dissemination of Study Result.
786 table	37	**Comment:** This table stipulates the overlap in all the ICH guidelines; e.g. 8 ICH guidelines need to be consulted when one wants to read about randomization.
786 (Annex 3)	34	**Comment:** It is very helpful to see this set out but probably not for the reason the authors intended! The selected examples of CTQ factors listed down the left is useful but could be brought into the main text of section 7. But what this table illustrates is just how unnecessarily complex the current "ICH E Family of Guidelines" is, impairing understanding and implementation of quality approaches.
Page 30: line "Post-Approval"	8	**Proposed change:** as Objectives of Study: please add: Develop clinical practice guidelines; Provide guidance for optimal use in clinical practice.
Page 30: line "Post-Approval"	8	**Comment:** Study Examples: please add: Real life effectiveness studies. It may be better to have critical-to-quality factors rather than critical to quality factors to remove any possibility of confusion.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
2.3 Patient input into study design (76- 85) 161-163; 193-201 545	11	**Comment:** On the one hand the trend of patients/patient organisations in participation in commenting their needs, sharing experience form CTs is welcomed, but on the other hand: this article has been written in such way that it gives patients (laypersons mainly without any medicine educations, relevant background etc.) opportunities to act as person with scientific background or education in this fields, but it should not be possible (as the main responsibility for the Clinical Trial and the Clinical Trial Protocol has the Sponsor). It should be more clear in which way they could influence CT through patient organization. Input of patients / patient organisations should not be overvalued. **Proposed change:** The wording should be changed.
2.3 Patient input into study design 76-85 (Also applicable to 161-163; 193-201; 545)	12	**Comment:** On the one hand the trend of patients/ patient organisations in participation in commenting their needs, sharing experience form CTs is welcomed, but on the other hand this article has been written in such way that it gives patients (laypersons mainly without any medicine educations, relevant background etc.) opportunities to act as person with scientific background or education in this fields , but it should not be possible. It should be more clear in which way they could influence CT through patient organization. Should not be overvalued the input of patients /PO. **Proposed change:** The wording should be changed.