Informing the Renovations to the ICH E6 GCP Guideline for Good Clinical Practice

Open Comment Opportunity Findings

FINAL Report
March 16, 2020

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1 PURPOSE OF ACTIVITY

The Clinical Trials Transformation Initiative (CTTI)—a public-private partnership between Duke University and the U.S. Food and Drug Administration—independently conducted 1) a global online survey, 2) qualitative, in-depth telephone interviews, and 3) an open comment platform, to provide opportunities for stakeholders affected by ICH E6 GCP to identify areas in ICH E6 GCP that are of greatest need for renovation, to suggest realistic ways for renovation, and to describe their experiences with implementing ICH E6 GCP. All participants reviewed ICH E6 (R2).

In this report, CTTI provides the final findings from the from the open comment opportunity to ICH for their consideration as they renovate ICH E6 GCP. The report of the survey findings and in-depth interview findings are provided as separate documents.

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2 FINDINGS

2.1 General Principles

Stake-holder	Section & Line	Comment: GENERAL PRINCIPLES
11	Principle #1	Leaving aside the contradictions and incongruences EU/US, perhaps it is time to incorporate an "ICH version" of the salient points of the Declaration of Helsinki (DoH) directly into the E6 text? This would remove the issues relating to DoH versioning and also create a coherent, stand-alone document.
16	Principle #1	This text is circular: The Principles of GCP are that "clinical trials should be conducted in accordance with the ethical principles ...that are consistent with GCP" Likewise, since "applicable regulatory requirement(s)" means "nay law(s) and regulation(s) addressing the conduct of clinical trials..." [1.4], this is often also circular. Suggest keep it simple and focused on the principle: "Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki." (and delete the remaining text)
18	Principle #1	If there are plans to extend the scope of GCP e.g., to device as well as IMP studies, it would be helpful to make reference to this fact. Any revision to ICH E6 R2 needs to align with revisions proposed to ICH E8R1 - e.g. ICH E8R1 proposed to change the word 'trial' with 'study'. The two terms are not synonymous with each other - e.g. a Non-Interventional Study means a clinical study other than a clinical trial. It's not clear from the GCP renovation project whether there is an intent to expand GCP principles into non interventional trials, but if there are and a workable solution to do so can be found, then terminology needs to be consistent across all ICH documents. Recommendation is to retain scope as limited to clinical trials, but, if expanded then this needs to be a formally adopted definition change agreed by the ICH body/stakeholders and all impacted documents/ICH website need to be updated and aligned. For purposes of commenting on this questionnaire it is assumed that the scope will remain limited to clinical trials only - i.e., treatment involving an investigational product.
20	Principle #1	Often discussion on which version of the Declaration to follow, due to some controversy or some pharma companies not willing to following one of the later versions. Suggestion to refer to the most recent version of the DOH.
30	Principle #1	Should there be reference also to the Declaration of Taipei linking to big data, research health databases and biobanks as samples and consent may be obtained in clinical trials, but information used outside of them? Compliance with the declaration would be necessary at the time of the sample/data collection?
34	Principle #1	Clinical trials should be conducted in accordance with the highest scientific and ethical principles, in accordance with international and national Good Clinical Practice standards and following applicable legal and regulatory requirements.
1	Principle #2	Currently, healthcare providers and patients place too high a value on inconclusive observational data and misjudge anticipated risks and benefits of study participation as a result. This prevents timely study enrollment and may result in bias populations in randomized trials. This is often done in the name of GCP. Regulatory agencies should give more specific guidance on assessing for equipoise.
2	Principle #2	Inconveniences are not relevant.

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Stake-holder	Section & Line	Comment: GENERAL PRINCIPLES
9	Principle #2	The therapeutic effect of drugs can be individual, no one is immune from side effects, and it is necessary to note them on an individual list.
11	Principle #2	Given the key role played by healthy volunteers (HVs) in the development of new therapeutics, a sentence recognizing the specific situation of HVs should be added in part also to provide some recognition to volunteers.
16	Principle #2	Weighing against "anticipated benefit for the individual trial subject and society" is a reasonable starting point but could be improved to include the concept of proportionality. That is, the potential risks and inconveniences should be assessed relative to the standard of care for the relevant clinical condition. This should take into consideration the nature of the intervention and of the study investigations and procedures, in each case comparing with the alternatives. For example, although a new form of chemotherapy for advanced cancer may come with a number of very serious risks (infection, bone marrow suppression, etc.), the alternative treatments (existing forms of chemotherapy) also have many of these risks. Suggested rewording: “Before a trial is initiated; foreseeable risks and inconveniences should be assessed relative to those of the standard of care for the relevant clinical condition. A trial should be initiated and continued only if the anticipated benefits justify the risks.”
17	Principle #2	…the anticipated benefit or opportunity…
22	Principle #2	… for the individual trial subject (if applicable) and society.
23	Principle #2	Who is responsible for this? For clarification purpose it would be helpful to add responsible party.
29	Principle #2	Suggest adding those risks should be clearly explained before a trial starts (e.g. during the consent process) and reflected throughout the trial in an ongoing manner.
30	Principle #2	Add: those risks should be clearly explained during the consent process and reflected throughout the trial in an ongoing manner.
34	Principle #2	Before a clinical trial is initiated, within the trial protocol, foreseeable risks and inconveniences should be identified and evaluated in relation to potential benefits for patients and their communities.
35	Principle #2	A trial should be initiated and continued only if the anticipated benefits justify the risks according to stakeholders involved in the trial (patients, PIs and sponsor).
1	Principle #3	Yes, but when it comes to patients who withdraw from randomized trials, there is an issue. Trials become uninterpretable, and potentially useful therapies are denied approval by regulators. There should be allowance given to record vital status for ALL patients who were randomized in a clinical trial to ensure the validity of large studies.
2	Principle #3	…are critically important and should be. balanced against…
10	Principle #3	…and should be evaluated over interests of science and society. Note: chemotherapy or transplantation are associated with cure but affect well-being.
16	Principle #3	This principle is embedded in Principle #1—the ethical principles that have their origin in the Declaration of Helsinki. However, it could usefully be modified to be one of only two over-arching principles:

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Stake-holder	Section & Line	Comment: GENERAL PRINCIPLES
		"The Principles of ICH GCP are to ensure that clinical trials (1) adequately protect the rights, safety, and well-being of trial participants, and (2) deliver results that are sufficiently reliable to inform the care of future patients."
30	Principle #3	Perhaps this should be principle no.1?
34	Principle #3	The interests of science and society may only be pursued in the context of a clinical trial when respect for the dignity, well-being, and rights of clinical trial participants (subjects) is assured.
35	Principle #3	over interests of science, society and stakeholders' financial interests
11	Principle #4	Suggest deleting "available".
29 and 30	Principle #4	Suggest adding a statement to clarify and cover clinical trial specific to advanced therapy medicinal products to recognize that it may not always be feasible to generate relevant non-clinical data before the product is tested in humans. Reference: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/atmp_guidelines_en.pdf (European Commission Guidelines on Good Clinical Practice specific to Advanced Therapy Medicinal products, accessed 17 Oct 2019)
33	Principle #4	Section 6.2.1 investigational product: Broaden the scope of describing the aim of the trial (human pharmacology, non-interventional trials, investigational products that already have market authorization). Reasons: there may be several investigational products or none at all, when the focus is shifted from current practice (licensing trials for patent-protected medicines) to serving clinical medicine in general.
34	Principle #4	The current knowledge of an investigational intervention should be reflected in the clinical trial protocol and provide a foundation for the trial hypothesis, methodology, and endpoints. The protocol should be scientifically sound. Equipoise should be ensured at the initiation of a clinical trials and (as appropriate) periodically evaluated.
35	Principle #4	"Adequate" is too vague. What does adequate mean? Please clarify.
1	Principle #5	Yes. But some allowance should be given to retaining biological materials (blood, etc.) for FUTURE study without the need to reconsent patients when new analyses are conceived.
8	Principle #5	And any documents linked to this trial would have to be consistent with this protocol and its amendments. Like ICFs, CRFs, ... With clear procedures and the most objective measurements permitted by the contemporaneous Evidence Based Medicine.
10	Principle #5	described in a clear and concise detailed protocol
16	Principle #5	The emphasis should be on clarity rather than excessive detail (which often reduces understanding by burying important information in a mass of detail). Suggested rewording: "Clinical trials should be scientifically sound and should be described in a clear protocol."
18	Principle #5	Recommend expanding to make reference to QbD/CTQ principles as per ICH E8 R1 and section 5 of ICH E6R2 e.g. "Clinical trials should be scientifically sound and operationally feasible. Details should be described in a clear, detailed protocol, which avoids unnecessary complexity, procedures and data collection."

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Stake-holder	Section & Line	Comment: GENERAL PRINCIPLES
24	Principle #5	Clinical trials should be scientifically sound, and described in a clear, succinct but sufficiently detailed protocol.
25	Principle #5	I suggested changing to “Clinical trials should be scientifically sound, and described in a clear, succinct but sufficiently detailed protocol.”
30	Principle #5	Add: “Any changes to a study must follow regulatory and ethically required processes for protocol amendments.”
33	Principle #5	Section 6.3 trial objectives: Broaden the scope of describing the aim of the trial (human pharmacology, non-interventional trials, investigational products that already have market authorization). Reasons: the trial design depends on the objectives. Objectives should be broadened beyond current practice (licensing trials for patent-protected medicines) to serving clinical medicine in general.
34	Principle #5	[Delete this principle. See the revised principle #4 above.]
35	Principle #5	Described in a clear succinct but sufficiently detailed protocol
2	Principle #6	Need to have leeway for overly cumbersome protocol additions or components that don't enhance safety
3	Principle #6	Opinion, and the approval of the Competent Authority, which is usually the National Drug Agency, or a body delegated for this task.
8	Principle #6	… with the protocol and other documents like ICF, manuals, … that has received… …with the protocol and the "aligned", consistently derived ICF that has received…
9	Principle #6	the drug can be used according to the individual characteristics of the patient, his constitutional features, disease, in accordance with comorbid conditions
17	Principle #6	IRB/IEC --> IEC (local or national). Merge the definitions. No interest in making a difference (lines 463 to 474 + 495 to 500)
20	Principle #6	Approval by regulatory authorities (local or regional) are often required, suggest adding
30	Principle #6	Add: Deviations to the protocol must be impact assessed and reported on at the end of the trial, where these are significant. <It is noted outside of ICH E3 reporting deviations are rarely commented on except where they result in the exclusion of patients or data, as a result issues in trial design or practicability may not be evident>
4	Principle #7	…dentist, who must prove to have adequate training in clinical trials and, more generally, in the principles and responsibilities of drug development.
7	Principle #7	How will we approach this criterion if the society moves more to remote care with the use of wearables that can send signals to a remote center for analysis and council?
9	Principle #7	For formation of the qualified doctor it is necessary practical and research work of each physician, certainly under the guidance of the qualified expert, otherwise it is not possible to increase qualification of the beginning experts.

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Stake-holder	Section & Line	Comment: GENERAL PRINCIPLES
12	Principle #7	Add licensed independent practitioners (who are qualified by licensure)
16	Principle #7	This confuses several issues, e.g.: 1. Does this relate to the medical care in relation specifically to the protocol (including medical assessment, management and treatment of any safety issues caused by the trial treatment or the trial procedures) or does it relate to all medical issues that a trial subject encounters (e.g. management of hip fracture following a road traffic accident for a patient who is in a trial of eczema treatment!)? 2. In routine practice (i.e. outside the context of a clinical trial) not all medical decisions are made by qualified physicians/dentists. For example, medical care in the form of physiotherapy, cognitive behavioral therapy, podiatry may be delivered by professions allied to medicine - often this is without the oversight of a physician/dentist. In many ways the concept described in this principle is covered by Principle #8. Medical management decisions in the context of a trial should be conducted by someone who is suitably qualified by education, training, and experience. Suggested rewording: “Responsibility for the care and management of medical issues that are related to a subject’s participation in a clinical trial should rest with a qualified physician, or when appropriate, of a qualified dentist.”
18	Principle #7	No change if scope of GCP remains unchanged. If intention is to expand scope beyond interventional clinical trials then consideration should be given as to whether it is necessary for all non-interventional studies to be under the responsibility of a qualified physician.
21	Principle #7	Consider the use of the term "participants" or "research volunteers" rather than "subjects." The latter term is considered dehumanizing and disrespectful to some trial participants. Also, consider whether non-physician providers (e.g., advanced care physicians' assistants or nurse practitioners) may also be responsible for medical care and decisions for participants. Any concerns that they may be "less qualified" for this than physicians (or dentists) is addressed separately in principle #8.
25	Principle #7	I suggested changing to - subjects should always be the responsibility of a qualified INVESTIGATOR (PHYSICIAN, DENTIST, OTHERS).
27	Principle #7	Additionally, suggestions from relevant subject matter experts e.g. Biochemist, Pharmacologist and Epidemiologist can be incorporated into medical decisions to ensure holistic benefit of the subjects.
30	Principle #7	Add: …qualified, and where required by National Requirements current registered physician or, …a qualified, nationally registered dentist. <To clarify the need for practicing, registered clinicians, not just those with educational qualifications which are potentially historic>
34	Principle #7	The clinical trial protocol should indicate the medical care provided to the research participants (subjects) and how medical decision-making will be made during the course of the trial.
35	Principle #7	Qualified: qualified means MD qualification ? Who will decide whether or not a physician is qualified … CROs?
4	Principle #8	…..tasks. This training must be documented by participation in University courses and must be repeated at regular intervals (no more than 3 years).

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Stake-holder	Section & Line	Comment: GENERAL PRINCIPLES
8	Principle #8	And these education, trainings and experiences would have to be documented adequately. All trainings, qualifications and experiences must be documented.
9	Principle #8	We must treat, diagnose patients regardless of their education, race and origin.
10	Principle #8	…conducting a trial should be qualified medical doctor by education, training to perform…tasks. Note a medical doctor needs qualification, training.
12	Principle #8	Each individual involved in conducting a trial should be qualified by education, training and licensure to perform his or her respective task(s).
16	Principle #8	This is a very good definition. It embodies the concept of proportionality—not everyone needs to be an expert in everything, but they must be competent in the role that they are expected to perform.
23	Principle #8	PI/Deputy at each site is responsible to define the qualification needed by his study team. By signing the delegation log PI confirms that individual is qualified. (Background: many different stakeholders define "qualified" differently. Should be clarified in advance to avoid problems during study conduct.)
24	Principle #8	Each individual involved in conducting a trial should be qualified by education, training, and professional experience to perform his or her respective task(s).
25	Principle #8	I suggested Changing to - Each individual involved in conducting a trial should be qualified by education, training, and PROFESSIONAL experience to perform his or her respective task(s).
30	Principle #8	Suggest adding in the ICH definitions a definition for trial conduct which would include collection and analysis of samples as laboratories often believe the guidance does not apply to them.
34	Principle #8	The institutions and individuals involved in a clinical trial should demonstrate their qualifications for their role in the trial as well as a commitment to institutional and individual research integrity.
35	Principle #8	This applies to all stakeholders including CROs. Today, this is the major issue, most CROs and CRO employees have zero experience in clinical trials and in drugs, they only know about ICH overinterpretation. The term experience has to be clarified, same for training etc.
2	Principle #9	Not applicable to minimal risk trials, policy trials, some cluster trials, trials comparing 2 standards of care.
4	Principle #9	participation.... Adequate time should be given to subjects to reach their decision, and study personnel must be available to offer explanations on study aims and procedures.
5	Principle #9	For studies using anonymized data from health records for purpose of real-world evidence it is not possible to obtain consent. In such cases, can it be suggested that the study protocol should be reviewed by at least one ICH GCP compliant ethics committee?
8	Principle #9	With the first name, the name, the signature and the date (permitting identifying the patient, his, her approval and the start of the trial for him, her).
11	Principle #9	Suggest adding "written". "Freely given, written informed consent should..."

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Stake-holder	Section & Line	Comment: GENERAL PRINCIPLES
16	Principle #9	This is not true in all cases (e.g. clinical trials involving infants, emergency settings, or in those who lack capacity either temporarily or permanently). Other safeguards (including IRB/IEC favorable opinion) are necessary but there is not an absolute requirement for informed consent prior to participation (as stated in the current wording). Suggest wording: “Freely given informed consent should be obtained from every subject prior to clinical trial participation unless explicit approval/favorable opinion for alternative arrangements has been granted by an IRB/IEC.”
18	Principle #9	Per principle 10, consider wording to clarify that this is irrespective of media used (to cover modernization through e-consent usage).
20	Principle #9	Specify this informed consent should be documented, in writing (electronically or manually).
21	Principle #9	Again, consider replacing "subjects" throughout with "study volunteers" or "participants."
22	Principle #9	… from every subject or legal representative (as applicable) ... Not always is the subject able to give consent.
25	Principle #9	I suggested Changing to – with time enough to read the protocol, solve doubts and make up the decision of participation in the trial.
28	Principle #9	To avoid confusion with other consents that may/ may not be required by local law (e.g., under personal data privacy legislation), we suggest amending the statement to "Freely given informed consent to participate in the trial should be obtained from every subject prior to clinical trial participation."
29	Principle #9	Principle #9 is not consistent with section 4.8.15 in emergency situations. “4.8.15 In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject’s legally acceptable representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favorable opinion by the IRB/IEC, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements…” Suggest adding “Freely given informed consent should be obtained from every subject or subject's legally acceptable representative as applicable prior to clinical trial participation. This should be justified as a case by case basis e.g. in emergency situations (see section 4.8.15).”
33	Principle #9	Section 6.4 Trial design: trial types and data sources other than RCTs should be emphasized (e.g. real-world data, prospective cohorts, observational studies). Reasons: there is an increasing need for high-quality medical data for purposes other than licensing patent-protected new medicines for about one decade. Judgement of clinical utility and quality-of-life aspects require additional data.
30	Principle #9	Add: “Except in protocol-defined, ethically approved situations when prior consent of the subject or their legal representative is not possible (for example in emergency situations), freely given informed consent.” <To align with section 4.8.15>
34	Principle #9	The procedures for the informed consent of research participants (subjects) should be described in the research protocol or in a protocol addendum.
1	Principle #10	This is poorly described and may not be currently applicable to all countries of the world.

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Stake-holder	Section & Line	Comment: GENERAL PRINCIPLES
8	Principle #10	that allows its accurate reporting, EASY (or easiness of) interpretation and verification.
10	Principle #10	Addendum, medical records should be referenced and be source of clinical trial information.
16	Principle #10	It is not clear that the addendum text is necessary – “all clinical trial information” naturally includes all types of media. Whilst the concepts of accuracy and verification are understood, these are open to over-interpretation (e.g. every data point must be accurate and verifiable). Not all pieces of information that make up a clinical trial are of equal worth and not all require absolute accuracy in order to protect the rights, safety, and well-being of subjects or ensure the reliability of the results (which influence the care of future patients). Suggested wording: “Clinical trial information should be recorded, handled, and stored in a way that demonstrates how the rights, safety, and well-being of trial subjects and the reliability of the trial results have been maintained.”
20	Principle #10	Suggest adding ALCOAC principles here
30	Principle #10	Add: ALCOA principles should be preserved (including those applicable to electronic systems ALCO C++)
33	Principle #10	Section 6.11: Quality control and assurance: shift to quality-by-design instead of extensive monitoring requirements, wherever possible. Reasons: care should be taken to encourage both scientists and participants to do high-quality research in humans (rather than deter them by disproportionally high administrative hurdles).
34	Principle #10	The integrity of the data processed during a clinical trial should be assured and demonstrably in agreement with the ALCOA+ Principles and the FAIR Principles. The clinical trial protocol should demonstrate an investigation of all relevant data related to the science of the study while also ensuring data governance and management principles for the greatest utility of the data processed.
35	Principle #10	it is an open field for over-monitoring without scientific background. Replace "All clinical trial information" by "predefined clinical trial information related to endpoints of the trial, primary objectives and secondary objectives only". It is non-sense to put the same effort to collect all data including data without interest. This sentence should encourage to limit multiplication of data acquisition in favor of data transfer.
1	Principle #11	Evolving field now given EMRs which can be de-identified at source.
16	Principle #11	This is encompassed in the principle of maintaining the rights and well-being of the participants. In any case, trials must comply with all applicable regulatory requirement(s) – which includes all relevant privacy requirements.
25	Principle #11	All subjects must know where they can exercise your rights of access, rectification, cancellation and opposition of personal data.
34	Principle #11	Research participants (subjects) should be assured of the privacy and confidentiality of the data they provide as well as the means to protect that privacy and confidentiality and the measures to be taken in cases of data breaches. Research participants (subjects) should also be provided the opportunity to contribute to the greatest scientific and health utility of the data they provide.
4	Principle #12	……They MUST be used…….

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Stake-holder	Section & Line	Comment: GENERAL PRINCIPLES
8	Principle #12	with the approved protocol and study pharmacy manual(s), if existing.
13	Principle #12	This is a comment: this aspect is crucial but many times the pharmacy dossier included in the general protocol is not presented at the approval of the ethical committee. Sometimes some aspects cannot be evaluated because the absence of this important part.
16	Principle #12	Could be combined with Principle #4.
30	Principle #12	Add: and subject to detailed chains of custody, respecting the nature of the product and their risk profile.
33	Principle #12	Section 2: Add to the ICH GCP principles: a flexible risk-based attitude should be applied throughout GCP. Reasons: E6 has too much focus on commercial sponsors that develop new medicines with a focus on return on investment. But clinical medicine also needs a) new medications in commercially unattractive areas such as antibiotics or pain management, b) repurposing and label expansions for existing safe medicines. These unmet medical needs require more investigator-initiated trials and non-interventional trials. Academic researchers and public-private partnerships do not have the resources to handle the administrative overhead.
34	Principle #12	All clinical trial interventions should meet currently accepted standards, either as standards of current best practices or standards for acceptable experimental interventions.
1	Principle #13	In general, yes, but some things like AE reporting consume enormous time and resource and really don't add much (in most trials).
2	Principle #13	This is very vague.
8	Principle #13	A Quality Management System with procedures that assure ….
10	Principle #13	……. the quality of main aspects of trial …. reliability of main statistical endpoints of the trial
11	Principle #13	Suggest replacing "assure" with "ensure".
14	Principle #13	Instead of "quality of every aspect" it should read "of all relevant aspects" to be able to follow a risk-based approach.
16	Principle #13	The original text lacks proportionality or focus. Suggested wording: “Trial systems and procedures should focus on ensuring that the rights, safety, and well-being of study participants and the reliability of trial results are maintained.”
22	Principle #13	Systems with procedure that manage the quality of every aspect of the trial … "Assure" is often only interpreted as measures coming from the QA Unit. With the risk-based approach, Quality Management was introduced to apply QA and QC in an appropriate manner.
23	Principle #13	It lies in the responsibility of the Sponsor to implement such systems.
25	Principle #13	Patient information provided within the context of informed consent should be prepared in collaboration with patient representatives.

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Stake-holder	Section & Line	Comment: GENERAL PRINCIPLES
28	Principle #13	We recommend these contradictory statements are consolidated to read: "Systems with procedures that assure the quality of those aspects of the trial that are essential to ensure human subject protection and reliability of the trial results."
29	Principle #13	Suggest adding consideration of a risk-based approach.
30	Principle #13	Add: i.e. a risk-based/risk proportionate approach should be adopted.
33	Principle #13	1. Section 2: Add to the ICH GCP principles: a flexible risk-based attitude should be applied throughout GCP. Reasons: E6 has too much focus on commercial sponsors that develop new medicines with a focus on return on investment. But clinical medicine also needs a) new medications in commercially unattractive areas such as antibiotics or pain management, b) repurposing and label expansions for existing safe medicines. These unmet medical needs require more investigator-initiated trials and non-interventional trials. Academic researchers and public-private partnerships do not have the resources to handle the administrative overhead. 2. Scope of GCP: Provided the risk-adapted attitude has been installed into GCP and mechanisms are in place to avoid administrative overloading, a uniform set of rules could be applied to all research on humans: medicines, devices, surgeries, psychosocial interventions, public health interventions etc. Reasons: General principles are uniform (e.g. quality by design, stakeholder involvement, transparency) but care should be taken to encourage both scientists and participants to do high-quality research in humans (rather than deter them by disproportionally high administrative hurdles). This balance can only be achieved, when all stakeholders are involved in the revision of ICH guidelines. 3. Scope of GCP: should be broadened to reflect the needs for high-quality data of health care in general. Reasons: clinical practice guidelines, such as developed by AWMF members in Germany, depend on high-quality data. Trials that are run for market authorization of new patent-protected medications should be designed also for this later use of the same data. Both efficacy and safety data should also be collected outside those trials using real world data.
34	Principle #13	Clinical trials should only be implemented where reliable systems are in place to ensure the respect and protection of human subjects and the integrity of the data collected and processed in the trial.
35	Principle #13	Please delete. This should not be a principle. The principle of clinical trial IS NOT to guarantee systems with procedures but to improve medicine for human beings. Procedures are tools but not principles. Procedures are at the service of humans and not the other way around. By adding this #13 as a principle clinical research will become even more the slave of the useless procedures established by lobbies whose interest is not to make progress the medicine.
1	Missing Principles	Plan for a financially sustainable set of rules for conducting clinical trials.
1	Missing Principles	Commitment to evolving GCP to reflect new study designs (i.e. EMR-based, etc.).
4	Missing Principles	A more detailed training of all Investigators and study personnel must be added. It is important to ensure that this training must be received by an independent body (University). No commercial and sponsor courses are acceptable.

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Stake-holder	Section & Line	Comment: GENERAL PRINCIPLES
7	Missing Principles	Focus attention on areas of highest risk to patient safety and data integrity.
8	Missing Principles	Consistency between all the documents issued for a clinical trial from the protocol, IBs to the CSR. The integrity of the data involved in the CSR have to follow the ALCOAC+ principles.
9	Missing Principles	Each study should be confirmed by clinical, instrumental, laboratory methods and recorded in the patient's questionnaire for further continuation.
10	Missing Principles	Safety reporting should be clearly medical reporting.
10	Missing Principles	Clinical trial should be in agreement with clinical practice.
13	Missing Principles	The drug management when need to be prepared in the pharmacy.
13	Missing Principles	The responsibility at any level of the clinical trial.
16	Missing Principles	The Principles of ICH GCP are to ensure that clinical trials (1) adequately protect the rights, safety, and well-being of trial participants, and (2) deliver results that are sufficiently reliable to inform the care of future patients.
17	Missing Principles	Add a principle related to risk-based management/ approach.
19	Missing Principles	Clinical trials should be performed and reported such that the reliability and robustness of results are ensured.
20	Missing Principles	Data integrity should be guaranteed.
22	Missing Principles	Involvement of patient representatives in the planning and oversight of the trial.
22	Missing Principles	Transparency rules for trial related information and results.
23	Missing Principles	A clear benefit for each study participant needs to be specified in the protocol. If there is no therapeutic benefit due to e.g. placebo-arm or short treatment period, other benefits (like financial support) need to be provided.
23	Missing Principles	Burden of study participants through study participation should be limited to the lowest possible situation. This means e.g. reducing number of visits and assessments, using virtual or homecare visits for some of the study visits, reducing technical complexity).
24	Missing Principles	Patient information provided within the context of informed consent should be prepared in collaboration with patient representatives.
25	Missing Principles	Rights of access, rectification, cancellation and opposition of personal data.

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Stake-holder	Section & Line	Comment: GENERAL PRINCIPLES
25	Missing Principles	Biological samples destination: only for the trial, for future research, biobanking...
27	Missing Principles	There should be a Data Safety Monitoring Board (DSMB) in a clinical trial.
27	Missing Principles	There should be a country specific policy for Material Transfer. Suppose, the country of study conducted does not have adequate test facilities. In this situation, you need to send samples to a foreign country for further investigation.
27	Missing Principles	In clinical trials, subjects may be exposed to potential risks. To minimize the risks, there should be a compensatory policy.
29	Missing Principles	Data protection especially in the aspects of data exchange and data transfer. This also should be further explained in the informed consent section especially data protection in clinical trial context.
29	Missing Principles	Data Integrity in trial.
29	Missing Principles	Patient centric approach/ consideration and Engagement of patients or patient views in applicable clinical trial processes, e.g. study design, information consent development. And include patients as the 4th stakeholder of clinical trials in addition to IRB/IEC, INVESTIGATOR, and SPONSOR all along ICH E6.
30	Missing Principles	Samples collected during clinical trials should be collected, analyzed, reported and stored in a way which preserves their integrity and provides assurance of the validity of the results. GCP is applicable to the end-to-end management of clinical trial samples. On completion of a study, consideration must be given to the fate of the samples, which may require transfer to applicable, registered storage facilities. <In clear consideration of study laboratory aspects>
30	Missing Principles	Suggest extending principle 2.11 in regard of data protection in the consideration additionally of data exchange and data transfer. This also should be further explained in the informed consent section regarding data protection in the clinical trial context.
30	Missing Principles	Engagement of patients or patient views in the feasibility of clinical trial processes, e.g. study design, information consent development and as a true 4th stakeholder throughout the guideline.
33	Missing Principles	Section 2: Add to the ICH GCP principles: a flexible risk-based attitude should be applied throughout GCP. Reasons: E6 has too much focus on commercial sponsors that develop new medicines with a focus on return on investment. But clinical medicine also needs a) new medications in commercially unattractive areas such as antibiotics or pain management, b) repurposing and label expansions for existing safe medicines. These unmet medical needs require more investigator-initiated trials and non-interventional trials. Academic researchers and public-private partnerships do not have the resources to handle the administrative overhead.
33	Missing Principles	Scope of GCP: Provided the risk-adapted attitude has been installed into GCP and mechanisms are in place to avoid administrative overloading, a uniform set of rules could be applied to all research on humans: medicines, devices, surgeries, psychosocial interventions, public health interventions etc. Reasons: General principles are uniform (e.g. quality by design, stakeholder involvement, transparency) but care should be taken to encourage both scientists and participants to do high-quality research in humans (rather than deter them by

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Stake-holder	Section & Line	Comment: GENERAL PRINCIPLES
		disproportionately high administrative hurdles). This balance can only be achieved, when all stakeholders are involved in the revision of ICH guidelines.
33	Missing Principles	Scope of GCP: should be broadened to reflect the needs for high-quality data of health care in general. Reasons: clinical practice guidelines, such as developed by AWMF members in Germany, depend on high-quality data. Trials that are run for market authorization of new patent-protected medications should be designed also for this later use of the same data. Both efficacy and safety data should also be collected outside those trials using real world data.
34	Missing Principles	The roles and responsibilities of each party to a clinical trial should be clearly defined in the protocol, including those of the sponsor, investigator, trial participants, IRB/IEC, and regulatory authority.
35	Missing Principles	Patient information provided within the context of informed consent should be prepared and approved in collaboration with patient and MD representatives.
35	Missing Principles	Safety reports in clinical trial are under the direct sponsor responsibility and cannot be delegate to a third party.
35	Missing Principles	All stakeholders involved in the trial have to be experienced enough and qualified to perform its task. Each stakeholder must be able to demonstrate his qualifications to others upon request.

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2.2 IRB/IEC

Stake-holder	Section & Line	Comment: IRB/IEC
3	3.1 IRB/IEC: Responsibilities Line 770	Perhaps clarify 'vulnerable' subjects (children, elderly people, etc...)
3	3.1 IRB/IEC: Responsibilities Line 777	Current CV = CV to date or last week, month, year?
5	3.1 IRB/IEC: Responsibilities Line 772	In case of non-printed documents like mobile apps, the applicant can add supportive documentation such as transcripts or submit screenshots.
8	3.1 IRB/IEC: Responsibilities Line 843 Line 781	843 … according to written operating procedures, charters, ... 781 With a documented assessment??? And especially for the review of the amendments!?
12	3.1 IRB/IEC: Responsibilities Line 773	Trial protocol(s)/amendment(s), informed consent form(s) and consent form
12	3.1 IRB/IEC: Responsibilities Line 775	(e.g., advertisements), information to be provided to subjects, Investigator's
12	3.1 IRB/IEC: Responsibilities Line 777	compensation available to subjects, the investigator's
14	3.1 IRB/IEC: Responsibilities Line 774	that the sponsor proposes
16	3.1 IRB/IEC: Responsibilities Line 798 Line 805	3.1.4: Delete ", but at least once per year" since the appropriate interval depends on the degree of risk (which for some very long-term trials may be less frequently than annually). 3.1.6 What does "non-therapeutic trial" mean. This phrase is used elsewhere but not defined.
17	3.1 IRB/IEC: Responsibilities Line 799 Line 818	799: 1 year --> 2 years as first subject to be included within 2 years from authorization according to Regulation (EU) 536/2014 818 : payment and compensation

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Stake-holder	Section & Line	Comment: IRB/IEC
18	3.1 IRB/IEC: Responsibilities	New item: Add clarity on the focus of the IRB review e.g. IRB to consider the operational feasibility of the trial, and, appropriateness of the trial methodology for the trial population e.g. is there opportunity to utilize decentralized methods which may be favorable to the population or are technologies being proposed which are inappropriate for e.g. an ageing trial population?
19	3.1 IRB/IEC: Responsibilities Line 769	Please make sure there are no contradictions to EU Clinical Trial Regulation 536/2014
30	3.1 IRB/IEC: Responsibilities Line 772 – 779 Line 782 Line 808 Line 827	772-779: Suggest “flexibility” in the format of records is permitted by the text; for example, recorded/audio-visual/electronic information may be provided to subjects which successfully supports the informed consent process. Submission of these materials may or may not be “in writing”. 782: add to text: identifying the trial, the documents AND VERSIONS reviewed and… 808: add “for such trials USING A RISK-BASED APPROACH“ 827: add “The ethical committee should consider the design of the trial relevant to the proposed locations; for example in studies where patients are treated in central specialized locations, following treatment (and potential improvement or patient decline) local treatment may be the most suitable and lowest inconvenience to trial subjects, but consideration must be given to long-term data collection.”
34	3.1 IRB/IEC: Responsibilities Line 769 Line 778 Line 826	769: An IRB/IEC should promote and safeguard respect for the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects. 778: and any other documents that the IRB/IEC may need to fulfil its responsibilities. [delete this clause entirely and do not replace] 826: Add after, The IRB should review the manner and extent of patient and community input into the clinical trial protocol, patient recruitment, and the informed consent procedures.
6	3.2 IRB/IEC: Composition, Functions and Operations Line 847	An IRB/IEC should make its decisions at announced meetings at which at least a quorum, as stipulated in its written operating procedures, is present.
12	3.2 IRB/IEC: Composition, Functions and Operations Line 778 Line 782 Line 795	778: qualifications, and any other documents that the 782: document its views, clearly identifying the trial, the documents reviewed and 795: as documented by any relevant documentation
14	3.2 IRB/IEC: Composition, Functions and Operations	independent of the investigator and the trial (explanation: in investigator-initiated trials, the university hospital as sponsor is employer of IRB members and investigator)

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Stake-holder	Section & Line	Comment: IRB/IEC
	Line 838	
18	3.2 IRB/IEC: Composition, Functions and Operations Line 856	Recommend strengthening wording to recommend that nonmembers with expertise in special areas are co-opted as appropriate - important for increasingly complex therapies or studies using complex technologies.
28	3.2 IRB/IEC: Composition, Functions and Operations Line 836 Line 853	836: Replace text with "At least one patient representative" 853: Replace "The investigator" with "The investigator and/or sponsor"
30	3.2 IRB/IEC: Composition, Functions and Operations Line 832 Line 839	832: Insert “and ethics of the proposed trial. THE IRB/IEC MUST BE CONSTITUTED IN ACCORDANCE WITH APPLICABLE LOCAL REQUIREMENTS. It is recommended” <Reflecting also 3.2.2> 839: Add “on a trial related matter, AND THIS MUST BE EVIDENT IN THE ETHICS RECORDS.”
34	3.2 IRB/IEC: Composition, Functions and Operations Line 841-843	841: A list of IRB/IEC members and their qualifications should be made public. 842: Only legally registered IRBs/IECs may provide a valid review of a clinical trial protocol. 843:The IRB/IEC should perform its functions according to written operating procedures, should maintain written records of its activities and minutes of its meetings, and should comply with GCP and with the applicable regulatory requirement(s). All IRB/IEC SOPs, meeting dates, titles of protocols reviewed (including the names of the sponsors and investigators), and decisions on the protocols should be publicly available.
5	3.3 IRB/IEC: Procedures Line 860	Is documentation in writing mandatory? is it possible to add: The IRB/IEC should establish, document in writing (paper or electronic), and follow its procedures, which should include
6	3.3 IRB/IEC: Procedures Line 900-901	900-901 Ensuring that the IRB/IEC promptly notify in writing the responsible party according to national legislation.
8	3.3 IRB/IEC: Procedures Line 899	This is not clearly procedures, how this must be considered? As notifications in IRB/IEC documents, correspondences???
12	3.3 IRB/IEC: Procedures Line 860	The IRB/IEC should establish, document and follow its procedures, which should

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Stake-holder	Section & Line	Comment: IRB/IEC
19	3.3 IRB/IEC: Procedures Line 887-898	Please make sure the communication requirements are in line with the EU Clinical Trial Regulation 536/2014.
29	3.3 IRB/IEC: Procedures Line 865-866 Line 874-876	865-866: To be consistent with the requirement 5.11.1, suggest adding IRB/IEC should also provide the investigator/institution a statement that it is organized and operates according to GCP and the applicable laws and regulations. 874-876: To be consistent with the requirements 5.11.2 and 5.11.3, suggest adding – the IRB/IEC conditions its approval/favorable opinion upon change(s) in any aspect of the trial, such as modification(s) of the protocol, written informed consent form and any other written information to be provided to subjects, and/or other procedures, the IRB/IEC should provide the investigator/institution a copy of the modification(s) made and the date approval/favorable opinion. This also includes any IRB/IEC reapprovals/re-evaluations with favorable opinion, and of any withdrawals or suspensions of approval/favorable opinion.
30	3.3 IRB/IEC: Procedures Line 865-866 Line 874-876 Line 881 Line 899	865-866: To be consistent with the requirement 5.11.1, suggest adding – IRB/IEC should also provide the investigator/institution a statement that it is organized and operates according to GCP and the applicable laws and regulations. 874-876: To be consistent with the requirements 5.11.2 and 5.11.3, suggest adding – the IRB/IEC conditions its approval/favorable opinion upon change(s) in any aspect of the trial, such as modification(s) of the protocol, written informed consent form and any other written information to be provided to subjects, and/or other procedures, the IRB/IEC should provide the investigator/institution a copy of the modification(s) made and the date approval/favorable opinion. This also includes any IRB/IEC reapprovals/re-evaluations with favorable opinion, and of any withdrawals or suspensions of approval/favorable opinion. 881: Add “Specifying that no PREPLANNED deviations from, or changes of, the protocol”. 899: Add (e) Significant deviations which impact upon trial data integrity and compliance with GCP and/or the study protocol as required by local regulations (for example Serious Breaches of GCP) .
34	3.3 IRB/IEC: Procedures	Please note that in the Glossary the definition of an Independent Ethics Committee (IEC) at line 463 and an Institutional Review Board (IRB) at line 1.31 are not identical. However, throughout the guideline IRB/IEC are used to mean the same. The glossary should not reflect a difference in definition since the function is the same. Following our work on European and WHO ethical review guidance and in cooperation with ethics committees in Europe, Africa, Asia, Latin America, CIS Countries and North America, we suggest the following definition be use for both IEC and IRB: An independent body (a review board or a committee, institutional, regional, national, or 464 supranational), constituted of medical professionals and non-medical members, whose 465 responsibility it is to ensure respect for the dignity, well-being, and rights research participants in clinical trials by, among other things, reviewing and approving/providing favorable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial participants as well as the appropriateness of the trial to the health populations to which the intervention is addressed. The legal status, composition, function, operations, and regulatory requirements pertaining to the IRB/IEC should be described in the constitution and SOPs of the IRB/IEC and be publicly available.

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Stake-holder	Section & Line	Comment: IRB/IEC
3	3.4 IRB/IEC: Records Line 913	Why 3 years and not 2, 4, 6?
8	3.4 IRB/IEC: Records Lines 911-912	Records of protocol and documents assessment or CTA evaluation!
28	3.4 IRB/IEC: Records Line 913	Replace "for a period of at least 3 years" with "as required by local regulation and at least for a period of 3 years"
30	3.4 IRB/IEC: Records Line 912-913	912: Add " all relevant records,Ä¶ submitted documents AND MATERIALS"<to allow for multimedia submissions as permitted by IRB/IEC capabilities and procedures> 913: It is noted the 3-year retention period is short compared to National and ICH requirements for trial records; potentially consideration should be given to a longer retention period for advanced therapy medicinal products.

2.3 Investigator

Stake-holder	Section & Line	Comment: INVESTIGATOR
3	4.1 Investigator: Investigator's Qualifications and Agreements Line 929	Up-to-date curriculum, previously 'current cv'
3	4.1 Investigator: Investigator's Qualifications and Agreements Line 933	Thoroughly familiar; how is that going to be assessed?
8	4.1 Investigator: Investigator's Qualifications and Agreements Line 929 Line 938	929: Must be clarify if it is only the PI and/or sub I but also the personnel of the PI team to provide an updated CV. 938: Not only the PI but all investigators concerned! Taken into account actually and presently in the inspection but not officially stated!
10	4.1 Investigator: Investigator's Qualifications and Agreements	the investigator should be a medical doctor

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Stake-holder	Section & Line	Comment: INVESTIGATOR
	Line 926	
12	4.1 Investigator: Investigator's Qualifications and Agreements Line 926	The investigator(s) should be qualified by education, training, and licensure to assume
12	4.1 Investigator: Investigator's Qualifications and Agreements Line 929	such qualifications through
12	4.1 Investigator: Investigator's Qualifications and Agreements Line 930	documentation during the sponsor qualification assessment and thereafter whenever new investigators are added to the study.
29	4.1 Investigator: Investigator's Qualifications and Agreements Line 933-936 Line 938-939 Line 979-981	933-936: suggest adding that the investigator should provide evidence of such “thoroughly familiar” with the appropriate use of the investigational product(s), as described in those sources provided by the sponsor. This could be through documenting in the form of dated signature on the documents, a statement indicating his review for example. 938-939: suggest adding the investigator should provide evidence of his awareness of GCP and the applicable regulatory requirements, as a minimum confirmation or certification of GCP training. 979-981: “A qualified physician (or dentist, when appropriate), who is an investigator or a sub- investigator for the trial, should be responsible for all trial-related medical (or dental) decisions including medical decisions taken by machine learning / artificial intelligence system.”
30	4.1 Investigator: Investigator's Qualifications and Agreements Line 927-928 Line 933-936 Line 938-939 Line 945	927-928: Insert “should meet all the qualifications AND REGISTRATIONS specified by the applicable regulatory AND LOCAL PROFESSIONAL requirement(s)”. 933-936: add – the investigator should retain documented evidence of their “thorough familiarity” with the appropriate use of the investigational product(s), as described in those sources provided by the sponsor. For example, this could be through documenting in the form of dated signature on the documents, a statement indicating his review of the protocol, IB etc. 938-939: add – the investigator should retain, and provide when requested, evidence of his awareness of GCP and the applicable regulatory requirements, as a minimum confirmation of, or certification of, GCP training. 945: Add – to whom the investigator has delegated significant trial-related duties AND MAINTAIN EVIDENCE OF OVERSIGHT OF THEM <linking with 4.2.5>
8	4.2 Investigator: Adequate Resources Line 960	This point would have to be more detailed on its expectations about its documentation, extensiveness, ...

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Stake-holder	Section & Line	Comment: INVESTIGATOR
14	4.2 Investigator: Adequate Resources Line 969-973	Add: If data derived from not trial-related routine procedures are to be used for the trial they are considered reliable if generated by procedures following institutional standards.
16	4.2 Investigator: Adequate Resources Line 969	"the investigator… should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated." This wording is open to over-interpretation. It is not clear what "integrity" means in this context. In particular, what it should generally *not* means is that the investigator has to double-check every procedure or every data point.
29 and 30	4.2 Investigator: Adequate Resources Line 960-962 Line 970-971	960-962: suggest adding the investigator should provide evidence of ensuring that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions. 970-971: suggest modification “the investigator/institution should ensure and provide evidence that this individual or party is qualified to perform those trial-related duties and functions.”
26	4.2 Investigator: Adequate Resources Line 966-967	4.25-The investigator is responsible for overseeing any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site. Consider Clarifying , withdrawing from the study vs withdrawing from study drug (but continued for survival follow-up ,etc.) See also 4.8 and 6.5.3 "Premature" is superfluous - can't withdraw after complete.
12	4.3 Investigator: Medical Care of Trial Subjects Line 979	A qualified physician or licensed independent practitioner (or dentist, when appropriate), who is an investigator or a sub.
16	4.3 Investigator: Medical Care of Trial Subjects Line 979-992	This wording on the medical responsibility is much clearer - and specific to the trial-related medical issues - than that in Principle #7.
16	4.3 Investigator: Medical Care of Trial Subjects Line 977	This section is not about "Medical Care of Trial Subjects". Furthermore, it needs to be much more carefully worded. There are distinctions between a subject's wish to stop a trial treatment, stop having protocol-mandated visits or tests, stop being contacted in person by the trial team, or stop the trial team accessing their medical records vs. completely withdrawing from the trial. These have different impacts on issues such as respecting patient preferences or privacy, maintaining patient safety, and ensuring reliable (unbiased results) which influence the care of future patients. In particular, there needs to be a careful articulation of how and why loss-to-follow-up (at random or in one particular arm) may distort study results. This is an issue that is not just relevant to the Investigator but to the whole scientific and ethical robustness of the trial. (A trial that produces biased or uninformative results is an abuse of the faith that the subjects had in the research and the risks to safety and inconvenience that they were prepared to take.)
18	4.3 Investigator: Medical Care of Trial Subjects	Recommend that where the subject is not already known to the Investigator or Sub-I that the notification to primary care physician also requests that the primary care physician notifies the investigator of any reasons why they consider the subject not to be suitable for inclusion in the trial and /or any previous trial participation (rationale to

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Stake-holder	Section & Line	Comment: INVESTIGATOR
	Line 989	identify any serial trialists and subjects who may be hiding relevant medical history which may be an exclusion for trial participation)
29	4.3 Investigator: Medical Care of Trial Subjects Line 989-991	The investigator should inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.
30	4.3 Investigator: Medical Care of Trial Subjects Line 979 Line 981 Line 995	979: Add "A qualified (AND WHERE LOCALLY REQUIRED, PROFESSIONALLY REGISTERED) physician" 981: Add "including medical decisions taken by machine learning / artificial intelligence system" 995: Add: "respecting the Subject's rights. WHERE POSSIBLE, THE SUBJECT'S WISHES REGARDING ANY APPLICABLE LABORATORY SAMPLES SHOULD BE CLEARLY DOCUMENTED."
6	4.4 Investigator: Communication with IRB/IEC Line 997	Communication with IRB/IEC: The tasks described in 4.4 fall under the responsibility of the sponsor in several regions (and with applicability of regulation (EU) 536/2014 in at least all of Europe).
6	4.4 Investigator: Communication with IRB/IEC Line 997	Add a comment like, "in accordance with national legislation" or "not under the responsibility of the sponsor".
6	4.4 Investigator: Communication with IRB/IEC Line 997-1010	If there is consistency over all ICH-regions that the responsibility for 4.4 lies with the sponsor this should be transferred to chapter 5.
12	4.4 Investigator: Communication with IRB/IEC Line 999	Before initiating a trial, the investigator/institution should have documented.
12	4.4 Investigator: Communication with IRB/IEC Line 1004	As part of the investigator's/institution's application to the IRB/IEC, the
14	4.4 Investigator: Communication with IRB/IEC Line 1005-1010	1005 investigator/institution or sponsor (depending on local law) 1007 investigator/institution or sponsor (depending on local law) 1010 investigator/institution or sponsor (depending on local law)

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Stake-holder	Section & Line	Comment: INVESTIGATOR
18	4.4 Investigator: Communication with IRB/IEC Line 999-1008	Adapt language for situations where multiple investigator sites may be associated with a single Central EC/IRB and communication with the IRB / IEC may be through a Chief Investigator for the country. Include reference to seek any additional country or site-specific bodies from which approval must also be obtained.
19	4.4 Investigator: Communication with IRB/IEC Line 997-1011	Please make sure the communication requirements are in line with the EU Clinical Trial Regulation 536/2014.
28	4.4 Investigator: Communication with IRB/IEC Line 1004-1011	The text should reflect that, when a central IEC/IRB is used, the sponsor may be responsible for submitting the required information to the IEC/IRB.
29	4.4 Investigator: Communication with IRB/IEC Line 1010-1011	During the trial the investigator/institution should provide to the IRB/IEC all documents subject to review. Suggest adding clarification of documents to provide to the IRB/IEC e.g. clinical trial documents that permit evaluation of the conduct of a trial and the quality of the data produced.
32	4.4 Investigator: Communication with IRB/IEC Line 1002 Line 1006	1002: advertisements), and any other written and/or electronic information to be provided to subjects. 1006: Investigator's Brochure (or other safety information used as reference in the trial). If the Investigator's Brochure is updated during the trial, the
30	4.4 Investigator: Communication with IRB/IEC Line 1001-1002 Line 1004	1001-1002: suggest changing consent form to consent DOCUMENTS to permit flexibility in permitted records and “future-proofing” the guidance, and also similarly in line 1002 delete “written” as information may be in multi-media format. Add also “(e.g., advertisements and multi-media materials)”. 1004: related to the above, suggest deleting “written” so the text reads “As part of the investigator’s/institution’s application to…”
14	4.5 Investigator: Compliance with Protocol Line 1030	any relevant deviation
16	4.5 Compliance with Protocol Line 1015-1018	This is one of the most important principles - not just for the Investigator but for all involved in the trial. A good trial is one for which there is a clear ethically and scientifically robust protocol and where all involved follow it.
26	4.5 Compliance with Protocol Line 1020 Line 1023	1020: deviation from the approved protocol AND REFERENCED DOCUMENTS. 1023: Need clearer definition on immediate (may take language from SAE “Life threatening”)

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Stake-holder	Section & Line	Comment: INVESTIGATOR
16	4.6 Investigational Product(s) Line 1042-1070	This section fails to explain what is trying to be achieved or why it is important. For example, what matters is that subjects get given the correct medication in the right dose by the correct route at the right time. It is unclear how records of delivery, inventory and return/destruction impact on the reliability of the result or the safety of the subjects. Furthermore, there is often a disconnect between the detailed tracking/logging that occurs before a packet of trial medication is handed to the subject vs. the very varied, uncontrolled and undocumented ways in which that medication is stored, consumed, or lost once it is in the subject‚Äôs possession. This is a good example of emphasizing details, distorting priorities, and failing to focus on what really matters.
30	4.6 Investigational Product(s)	Question – should not requirements for a risk-based quality management system also be reflected in the Investigator section to ensure quality throughout the trial? This need not be extensive or bureaucratic but proportionate to the risks and experience of the trial and Investigator's team/delegations?
18	4.6 Investigational Product(s) Line 1052	Add clarity that records should be maintained for the full chain of custody - i.e. if IP is moved from a pharmacy to ward prior to subject administration records demonstrating that movement and any required confirmation of temperature, storage at both locations etc. should be available
28	4.6 Investigational Product(s) Line 1063	Add "Investigators should maintain records that document adequately that the product was stored in accordance with the storage conditions specified by the sponsor."
29	4.6 Investigational Product(s) Line 1047-1050	Where allowed/required, the investigator/institution should assign some or all of the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.
30	4.6 Investigational Product(s) Line 1060	Add: Where records are captured in third party electronic systems (such as IXRS systems) the Investigator must have uninterrupted access to the records and the ability to retain a local copy of the records during and after the study. Traceability of accountability records must be maintained and, where necessary safeguard trial blinding arrangements without compromising the traceability. QUESTION: Should consideration be given to a risk-based approach for records related to treatments considered standard of care with a precautionary note that it is necessary for Sponsor's to verify treatment designated standard of care, is standard in all trial locations? (This type of adaption is permitted by European legislation for example)
16	4.7 Investigator: Randomization Procedures and Unblinding Line 1072	Responsibility for randomization and unblinding does not rest solely with the Investigator. There is no explanation about what or why this is important.
8	4.8 Investigator: Informed Consent of Trial Subjects Line 1109 Line 1126 Line 1165	1109: Provided that the information in the ICF is consistent and aligned with the information in the protocol!!! 1126: Should also be named by the subject with name and first name for easier identification of the patient! Not really stated in GCP. 1165: That the investigator(s) will provide any medical care needed in case of AE during the CT.

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Stake-holder	Section & Line	Comment: INVESTIGATOR
10	4.8 Investigator: Informed Consent of Trial Subjects Line 1114	The text of informed consent should have a limited number of pages to be read by patient.
10	4.8 Investigator: Informed Consent of Trial Subjects Line 1145	The list is too long and should be restricted to medical information of the trial.
12	4.8 Investigator: Informed Consent of Trial Subjects Line 1087	the trial, the investigator should have the IRB/IEC,Äôs documented approval/favorable opinion
12	4.8 Investigator: Informed Consent of Trial Subjects Line 1088	of the informed consent forms and any other information to be provided to
12	4.8 Investigator: Informed Consent of Trial Subjects Line 1091	The informed consent form and any other written information to be provided to
14	4.8 Investigator: Informed Consent of Trial Subjects Line 1150	In blinded trials the assigned treatment will only be revealed in medical emergencies.
18	4.8 Investigator: Informed Consent of Trial Subjects Line 1084 Line 1119 Line 1125	1084: Include language related to alternative resources for providing information to subjects and obtaining consent - e.g. e-consent /animations etc. 1119: Add language related to the provision of the consent process remotely 1125: Add language related to use of electronic signatures; 4.11 - Add language as to how the information should be provided if using e-consents
16	4.8 Investigator: Informed Consent of Trial Subjects Line	this could all be simplified: The Investigator's responsibility is to follow the procedures for consent set out in the protocol and related documentation approved by the IRB/IEC. All the rest is for those designing the trial to consider and the IRB/IEC to review and approve. Consequently, the whole of 4.8 could be replaced with a single line. "The Investigator is responsible for ensuring that procedures for obtaining and documenting informed consent of study subjects are followed in accordance with the ethically approved protocol and related documentation."
28	4.8 Investigator: Informed Consent of Trial Subjects Line 1084	1084: To avoid confusion with other forms of consent that may/ may not be required under local law (e.g., under personal data privacy legislation), replace "In obtaining and documenting informed consent" with "In obtaining and documenting informed consent to participate in the clinical trial".

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Stake-holder	Section & Line	Comment: INVESTIGATOR
	Line 1127	1127: Add "The term 'written informed consent form' includes those provided in electronic form. Consent may be confirmed by electronic signature in accordance with local regulations."
29	4.8 Investigator: Informed Consent of Trial Subjects Line 1168 Line 1199	1168: The anticipated prorated payment, if any, to the subject for participating in the trial. Suggest adding the amount and method of payment to subjects so that this requirement is consistent with 3.1.8 (The IRB/IEC should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject.) 1199: Suggest adding (u)/ additional element of providing subject of clinical trial results/ treatment results related to the subject at the end of study in a non-technical language as practical that should be understandable to the subject or the subject's legally acceptable representative.
30	4.8 Investigator: Informed Consent of Trial Subjects Line 1088 Line 1086 Line 1127 Line 1168 Line 1199 Line 1145	1088: in future-proofing guidance CHANGE written informed consent form to “informed consent documents and any other information to be provided to subjects”. If accepted similar changes should be followed through in the section e.g. Line 1091, 1093, 1104, etc. 1086: Add--origin in the Declaration of Helsinki (AND DECLARATION OF TAIPEI, IF APPLICABLE). 1117: Add--Multi-media methods may support comprehension of the study, and methods may be employed by the Investigator/Sponsor to verify this during the informed consent process. 1127: Add--Where necessary, requirements of local legislation for multiple signatories should be considered in the design of the consent documents for example where two parental signatures are required, each witnessed by the Investigator, and when these might not be obtained on the same date. 1168: “The anticipated prorated payment, if any, to the subject for participating in the trial.” Suggest adding the amount and method of payment to subjects so that this requirement is consistent with 3.1.8 (The IRB/IEC should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject.) 1199: Add an additional element: (u) Subjects should be provided with clinical trial results/ treatment results relevant to the subject at the end of study in a non-technical language that should be understandable to the subject or the subject's legally acceptable representative. 1145: Add a consideration regarding the fate of any collected samples on subject withdrawal Question--should the section include consideration for the capture of electronic signatures for clarity that these are acceptable? Consider adding statements regarding translations of consent documents to assure equal access and facilitate patient understanding.
32	4.8 Investigator: Informed Consent of Trial Subjects Line 1088 Line 1091 Line 1146	1088, 1091, 1146, 1203: any other written or electronic information to be provided to subjects 1094, 1103, 1114: written or electronic information

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Stake-holder	Section & Line	Comment: INVESTIGATOR
	Line 1203 Line 1094 Line 1103 Line 1114	
5	4.9 Investigator: Records and Reports Line 1255	Source data may not be original when data is recorded electronically with print function: e.g. mobile apps, digital BP or thermometer. The CRA will not be able to verify original. The revised version should be able to accommodate use of digital tools without original prints.
3	4.9 Investigator: Records and Reports Line 1279	2 years, rationale?
8	4.9 Investigator: Records and Reports Line 1259	The investigator should ensure and review…. + source documents signed and dated by the PI or a sub-I
10	4.9 Investigator: Records and Reports Line 1253	Medical records are source documents and should be kept according to legal requirements.
10	4.9 Investigator: Records and Reports Line 1265	and following: change or corrections should be signed/dated only for major endpoints of the trials listed in the protocol. Other changes should be just noted on the CRF
12	4.9 Investigator: Records and Reports Line 1103	None of the information concerning the trial, including the
12	4.9 Investigator: Records and Reports Line 1111 Line 1114	1111: acceptable representative, of all pertinent aspects of the trial. 1114: The language used in the oral and documented information about the trial, including the
14	4.9 Investigator: Records and Reports Line 1284	…with the sponsor. Academic sponsors should retain all essential documents for 10 years or longer if required by applicable law.

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Stake-holder	Section & Line	Comment: INVESTIGATOR
16	4.9 Investigator: Records and Reports	4.9. The concept of proportionality is missing. Not all data and documents have equal importance. Not all errors or issues make a material difference. For example, in a randomized clinical outcome trial, it may be possible to draw robust and reliable conclusions even if 20% of relevant events are missing provided that they are missing at random with respect to the allocated treatment; by contrast small amounts of loss-to-follow-up (see comment on 4.3.4 - withdrawal from study) can substantially bias the conclusions. 4.9.3: In "Sponsor should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator." Change to "Sponsor should have written procedures to govern the circumstances in which changes to CRF data may be made, by whom, and how they should be recorded." In some circumstances, the Investigator may not be available (e.g. site closed) or may not be in a position to know whether or why the change is appropriate (e.g. pre-dates the investigator's involvement in the trial), or may be the one responsible for recording the wrong information and therefore not willing to acknowledge the fault even if there is good evidence. 4.9.3: Delete: "The investigator should retain records of the changes and corrections." It is not at all clear what this is trying to achieve. This is a good example of focusing on what must be done/stored, by whom, and where, rather than on why this matters and what we are trying to achieve or protect against. 4.9.4: The trial documents listed in Essential Documents for Conduct of a Clinical Trial are often not documents (e.g. medical qualifications are often best viewed through publicly available medical registration websites), not essential to quality (e.g. shipping records), and could be stored or made accessible via a number of means (i.e. the concept of "located at" Investigator/Institution vs. Sponsor is outdated). The effect of this requirement and of section 8 is to distract attention from what really matters and place it on what is easy to check.
18	4.9 Investigator: Records and Reports Line 1279	Recommend stipulating a fixed period rather than current wording of 2 years after last marketing approval in an ICH region as this is hard to quantify to investigators e.g. 25 yrs as per EU CTR.
30	4.9 Investigator: Records and Reports Line 1260 Line 1272 Line 1277	Recommend consideration is given to "virtual trials" and/or direct data capture from patient to Sponsor to support innovative trial designs. Suggest also that this should be linked with an adapted role of Investigator involvement/oversight. 1260: add at the end: Investigators should consider review of CRF data in a timely manner, related to critical trail decisions (such as interim analyses, independent data monitoring committee review, dose escalation etc.). 1272: additional consideration: Investigators/Sponsors should consider procedures for periodic review of the audit trail. 1277: add at the end: in a medium which preserves their integrity and completeness (including any applicable audit trails).
6	4.10 Investigator: Progress Reports Line 1295-1304	In Europe, this task belongs to the Sponsor. There is no direct notification from the investigator to the IRB/IEC foreseen. Furthermore, with applicability of regulation (EU) 536/2014 this will be done via the portal.
6	4.10 Investigator: Progress Reports	Add these tasks under chapter 5

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Stake-holder	Section & Line	Comment: INVESTIGATOR
6	4.10 Investigator: Progress Reports Line 1295-1304	Delete.
12	4.10 Investigator: Progress Reports Line 1115 Line 1125 Line 1131	1115: informed consent form, should be as non-technical as practical and should be 1125: Prior to a subject's participation in the trial, the informed consent form should be 1131: the informed consent form and any other information to be provided to
14	4.10 Investigator: Progress Reports Line 1297 Line 1302	1297 and 1302: the investigator or sponsor (depending on local law)
16	4.10 Investigator: Progress Reports Line 1298	Frequency of submission should be determined by the IRB/IEC. Delete "annually, or more frequently,"
19	4.10 Investigator: Progress Reports Line 1295-1304	Please make sure the communication requirements are in line with the EU Clinical Trial Regulation 536/2014.
28	4.10 Investigator: Progress Reports Line 1297-1304	The text should reflect that, when a central IEC/IRB is used, the sponsor may be responsible for submitting written summaries and reports to the IEC/IRB.
12	4.11 Investigator: Safety Reporting Line 1138 Line 1139 Line 1140	1138: signed and dated the informed consent form, the witness should contemporaneously sign and 1139: date the consent form. By signing the consent form, the witness attests that the 1140: information in the consent form and any other information was accurately
16	4.11 Investigator: Safety Reporting Line 1310	Delete "The immediate reports should be followed promptly by detailed, written reports." This makes no sense for the many SAEs (hospitalizations, serious illnesses, etc.) that happen in sick populations. Individual reports (or small series) on rare events that are highly likely to be related to drug (e.g. SJS, anaphylaxis, aplastic anemia, non-traumatic tendon rupture, Reyes' syndrome) may be informative. But other safety issues are only reliably detected by unblinded comparison by randomized treatment group. FDA and others have done some useful work in this area which should be reflected in revised text. The responsibility for safety reporting rests not just with the investigator but with the whole trial team.
18	4.11 Investigator: Safety Reporting Line 1313	Add language to clarify expectations for Investigator's required action on safety reports provided by Sponsor.

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Stake-holder	Section & Line	Comment: INVESTIGATOR
16	4.12 Investigator: Premature Termination or Suspension of a Trial	There are other ways to achieve the same ends - for example the sponsor/representatives could inform subjects, IRBs, etc. Rather than specifying who should do what, describe what needs to be achieved and why.
6	4.12 Investigator: Premature Termination or Suspension of a Trial Line 1325-1346	In Europe, this task belongs to the Sponsor. There is no direct notification from the investigator to the IRB/IEC foreseen. Furthermore, with applicability of regulation (EU) 536/2014 this will be done via the portal. Add these tasks under Chapter 5. Please delete 1325 – 1346.
12	4.12 Investigator: Premature Termination or Suspension of a Trial Line 1145 Line 1146 Line 1202	1145: Both the informed consent discussion and the informed consent form and any 1146: other information to be provided to subjects should include explanations of the 1202: representative should receive a copy of the signed and dated informed consent
28	4.12 Investigator: Premature Termination or Suspension of a Trial Line 1138-1341	The text should reflect that, when a central IEC/IRB is used, the sponsor may be responsible for informing the IEC/IRB and the investigator.
6	4.13 Investigator: Final Report(s) by Investigator Line 1348-1352	In Europe, this task belongs to the Sponsor. There is no direct notification from the investigator to the IRB/IEC foreseen. Furthermore, with applicability of regulation (EU) 536/2014 this will be done via the portal. add this task under chapter 5. Please delete 1348 – 1352.
16	4.13 Investigator: Final Report(s) by Investigator	Why should the investigator do this? So long as it is done, it shouldn't matter who does it (and there may be better / more efficient ways to do this in different trials). Focus on the objective not the mechanism or the personnel.
12	4.13 Investigator: Final Report(s) by Investigator Line 1203 Line 1206 Line 1212	1203: form and any other information provided to the subjects. During a subject's 1206: amendments to the information provided to subjects. 1212: should contemporaneously sign and date the informed consent form.
14	4.13 Investigator: Final Report(s) by Investigator Line 1351	the investigator or sponsor (depending on local law)

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Stake-holder	Section & Line	Comment: INVESTIGATOR
19	4.13 Investigator: Final Report(s) by Investigator Line 1348-1352	Please make sure the communication requirements are in line with the EU Clinical Trial Regulation 536/2014.
28	4.13 Investigator: Final Report(s) by Investigator Line 1351-1352	The text should reflect that, when a central IEC/IRB is used, the sponsor may be responsible for providing the IRB/IEC with a summary of the trial's outcome. Also, irrespective of whether a central IEC/IRB is used, the sponsor (rather than the investigator) may be responsible for providing the regulatory authority(ies) with any reports required.
29	4.13 Investigator: Final Report(s) by Investigator Line 1348-1352	Suggest adding the investigator should also inform the study subjects/ trial participants or the subject's legally acceptable representative a summary of the trial,Äôs outcome, the treatment results related to them in a non-technical language as practical that should be understandable to them.
30	4.13 Investigator: Final Report(s) by Investigator Line 1348-1352 Line 1352	1348-1352: Suggest adding the investigator should also inform the study subjects/ trial participants or the subject's legally acceptable representative a summary of the trial's outcome, the treatment results related to them in a non-technical language as practical that should be understandable to them. 1352: Suggest text is added regarding the responsibility of the investigator to ensure there is a mechanism for ensuring any returned electronic records from the Sponsor are a complete and accurate reflection of the source data submitted by the Investigator Site.

2.4 Sponsor

Stake-holder	Section & Line	Comment: SPONSOR
8	5.0 Sponsor: Quality Management Line 1436	to build a Quality Management System! Example of ISO 9000 family etc...
12	5.0 Sponsor: Quality Management Line 1216 Line 1228 Line 1335	1216: personally give consent and who sign and date the informed consent form. 1228: of such subjects, and the documented approval/ favorable opinion covers this aspect. 1335: provide the sponsor and the IRB/IEC a detailed documented explanation of the termination or
14	5.0 Sponsor: Quality Management Line 1405 Line 1408	1405: Please define "systematic safeguards" as training is mentioned separately. 1408: If feasible, predefined...

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Stake-holder	Section & Line	Comment: SPONSOR
16	5.0 Sponsor: Quality Management	5.0 Addendum: this section on QbD should come at the front of the guidance. The guidance should be rewritten to outline (a) the principles of subject protection and reliable results (b) the need for QbD and (c) the key objectives (e.g. consent, safety reporting, data management, etc.). As it is, Quality Management is an afterthought and the principles of proportionality that are included here may not be appropriately applied to the earlier sections. 5.0. It would be helpful to include the idea that trial quality may be impacted by the interaction of several different factors. For example, study power may be influenced by the combination of recruitment, adherence to therapy, event rate, and duration of follow-up. Lower than projected event rate may be mitigated by higher than anticipated recruitment or treatment adherence. 5.0.4. I am not convinced that it is always possible or desirable to predefine quality tolerance limits. As illustrated in my comment above, the impact on quality (e.g. reliability of results) may be influenced to different extents and in different directions by multiple factors. I am concerned that such a recommendation will lead to people focusing on precisely what those limits should be and how to justify and document them when time and resource would be better spent designing and implementing strategies to deal with the underlying drivers.
17	5.0 Sponsor: Quality Management Line 1386 Line 1410 Line 1423	1386: both the process level (instead of system level) 1410: subject protection (instead of subject safety). Wider scope 1423: Chapter Risk Review. Risk assessment should also be reviewed periodically
18	5.0 Sponsor: Quality Management Line 1399	Provide additional guidance with respect to Quality Tolerance Limits
19	5.0 Sponsor: Quality Management Line 1408-1415	From the statistical point of view, predefined tolerance limits are only interpretable if they are applied in situations where large numbers of observations are available. This requirement should be put into perspective.
26	5.0 Sponsor: Quality Management Line 1399	Using the word “deviation” to describe meeting or exceed the threshold is causing quite a bit of confusion with regard to protocol deviations. The concepts of protocol deviations and QTLs are different, but both related to the overall quality of the protocol and/or program.
29	5.0 Sponsor: Quality Management Line 1408	The term of “Predefined quality tolerance limits” should be defined, for example, adding its description under section 1 GLOSSARY.
30	5.0 Sponsor: Quality Management Line 1406 Line 1426 Line 1432	1406: Add -- Engagement with patients in the study design process and amendment, (where patients are significantly concerned), is recommended to ensure acceptability of the protocol design and promote compliance (reflecting proposals in ICH E8).

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Stake-holder	Section & Line	Comment: SPONSOR
		1426: Add -- Both the trial design and risk assessment may require adaption during any period of long-term follow-up (for example for advanced therapy medicinal products). 1432: Add at the end “or publication”.
10	5.1 Sponsor: Quality Assurance and Quality Control Line 1436	Written SOP should be discussed with investigators and limited to main end points.
10	5.1 Sponsor: Quality Assurance and Quality Control Line 1461	transferred to and assumed by a CRO should specified in writing from sponsor to investigators
10	5.1 Sponsor: Quality Assurance and Quality Control Line 1437	SOP should remain simple and avoid unnecessary procedures (i.e.) not affecting the main endpoint of the trials
12	5.1 Sponsor: Quality Assurance and Quality Control Line 1340	inform the IRB/IEC, and provide the IRB/IEC a detailed documented explanation of the
14	5.1 Sponsor: Quality Assurance and Quality Control Line 1446	applied to all relevant stages of data handling
16	5.1 Sponsor: Quality Assurance and Quality Control Line 1428	replace "important deviations from the predefined quality tolerance limits" with "important issues that threaten the reliability of the study results or the rights, safety, and well-being of the trial subjects"
17	5.1 Sponsor: Quality Assurance and Quality Control Line 1437	Use Quality Document instead of SOP which seems too restrictive - even if definition is clear
18	5.1 Sponsor: Quality Assurance and Quality Control Line 1446	Add that evidence of QC activities must be filed in the TMF
29	5.1 Sponsor: Quality Assurance and Quality Control Line 1441	Does direct access mean to medical histories as well? Recommend to explicitly state other documents and database that can come under direct access.

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Stake-holder	Section & Line	Comment: SPONSOR
30	5.1 Sponsor: Quality Assurance and Quality Control	Might also responsibilities not transferred to a CRO be the responsibility of the patient in the case of digital and virtual trials? Consider clauses directly related to patient engagement and involvement with applicable quality assurance and quality control procedures/mechanisms.
10	5.2 Sponsor: Contract Research Organization Line 1458	Sponsor cannot transfer the responsibility or duties concerning SAE
10	5.2 Sponsor: Contract Research Organization Line 1461	There is gap in responsibilities between the sponsor and CRO. Transfer should be limited to the non-medical aspect of the study. Sponsor has the same legal obligation than the medical investigator. That is crucial for definition of SAE
10	5.2 Sponsor: Contract Research Organization Line 1481	CRO has no medical expertise
10	5.2 Sponsor: Contract Research Organization Line 1500	CROs have generally poor medical expertise and conflict may occur on that field between investigator and sponsor.
16	5.2 Sponsor: Contract Research Organization	5.2.1: Delete "The CRO should implement quality assurance and quality control" since this is just one of the tasks covered by 5.2.4 "Al references to a sponsor in this guideline also apply to a CRO to the extent that a CRO has assumed the trial related duties and functions of a sponsor" 5.2.2 Addendum: "The sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf..." has been over-interpreted by some. As a consequence, a new layer has been introduced with some sponsors employing an army of people to check and double-check on the CRO. Oversight, like so much else, should be proportionate. In the same way that a senior doctor may oversee and guide the actions of junior colleagues, the Lab Director oversees the work of those running the analyzers, and a PhD supervisor oversees and guides the work of the student. In none of these examples does the senior responsible officer check every detail let alone repeat every action of those more junior.
17	5.2 Sponsor: Contract Research Organization Line 1457	Replace 'quality assurance and quality control' by 'quality management system' (QMS). QMS includes quality control by an expert team and quality assurance activities managed by independent persons.
30	5.2 Sponsor: Contract Research Organization Line	Suggest considerations are added relating to Clinical Laboratories responsible for the analysis of clinical trials, highlighting the relevance of GCP compliance to those aspects of the clinical trial which impact both the safety of subjects and the integrity of trial data and results.
8	5.3 Sponsor: Medical Expertise Line 1479	and have got documented training, have documented qualifications and job descriptions...

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Stake-holder	Section & Line	Comment: SPONSOR
30	5.3 Sponsor: Medical Expertise	QUESTION: Should the Sponsor's medical staff be registered Clinicians as well as those treating patients?
10	5.4 Sponsor: Trial Design Line 1531	Medical records are the source of documentation and software should be simple to make the translation between records and CRF. It not the responsibility of investigator to check the software for safety. With electronic records it may possible to transfer data from computer to computer for biology.
10	5.4 Sponsor: Trial Design Line 1539	electronic signature should be automatically done with the name of the person who is making change
16	5.4 Sponsor: Trial Design Line 1485	Should also include mention of patient representatives to keep in line with the proposed revisions to E8.
30	5.4 Sponsor: Trial Design Line 1485-1488	In reflection of current regulatory guidance, consider also the engagement of patients in trial development, design and data capture tools.
8	5.5 Sponsor: Trial Management, Data Handling, and Record Keeping Line 1495	Principles of data management could be developed in defining key documents for this activity like edit check validation, UAT, etc...
10	5.5 Sponsor: Trial Management, Data Handling, and Record Keeping Line 1611	data recording reporting should be kept with easy written procedures and avoid unnecessary signature
14	5.5 Sponsor: Trial Management, Data Handling, and Record Keeping Line 1585	add: Academic sponsors should retain all essential documents for 10 years or longer if required by applicable law.
16	5.5 Sponsor: Trial Management, Data Handling, and Record Keeping	5.5.1. Delete "to verify the data" since it is unclear what this means, why it matters, or how it would be achieved. 5.5.1. This section could be replaced with the text from Principle #8 and could be combined with section 4.1.1 i.e. all staff (including investigators, site staff, and staff at the sponsor staff organization or contracted research organizations) should be qualified by education, training, and experience to perform his or her respective task(s). 5.5.6 - 5.5.12. See earlier comments about the issues with the concept of "Essential Documents". some of this text overlaps with similar sections in the Investigator section. This illustrates the structural challenge with this document - the requirements or principles may be relevant to the trial but could be delivered in a number of different ways by the sponsor, CROs, investigators or others etc.
17	5.5 Sponsor: Trial Management, Data	Is 'verify' not too restrictive considering that in risk-based approach data review is different from data verification

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Stake-holder	Section & Line	Comment: SPONSOR
	Handling, and Record Keeping Line 1498	
26	5.5 Sponsor: Trial Management, Data Handling, and Record Keeping	5.5.3 ADDENDUM the SOPs should cover system setup, installation, and use AND REPORTING. must better reflect current data management practices 5.54-If data are transformed OR DERIVED during processing, must reflect current practices. Examples are welcome (such as calculation of BMI)
30	5.5 Sponsor: Trial Management, Data Handling, and Record Keeping Line 1556	Include laboratories as an explicit reference to support compliance: The sponsor, or other owners of the data (INCLUDING CLINICAL LABORATORIES RESPONSIBLE FOR THE ANALYSIS OF CLINICAL TRIAL SAMPLES) should retain
10	5.6 Sponsor: Investigator Selection Line 1595	Investigator should be a qualified medical doctor in the field of the trial
16	5.6 Sponsor: Investigator Selection Line 1594	This repeats earlier sections on the needs for investigators to be qualified by training & experience, etc.
30	5.6 Sponsor: Investigator Selection Line 1596	Add at the end: AND THE SPONSOR IS RESPONSIBLE FOR A DOCUMENTED EVALUATION OF THE INVESTIGATORS RECORD-KEEPING SYSTEMS FOR SOURCE DATA COLLECTION.
32	5.6 Sponsor: Investigator Selection Line 1603	Up-to-date Investigator's Brochure or other referenced safety information (such as SmPC)
8	5.7 Sponsor: Allocation of Responsibilities Line 1624	Documentation of all this allocation + changes!
16	5.7 Sponsor: Allocation of Responsibilities Line 1624	This is an ongoing process - as staff come and go, and the trial moves through different phases (e.g. recruitment, treatment, follow-up) different staff will be needed. This requirement needs to be carefully worded and implemented - some trial-related duties (e.g. pharmacist processing a prescription; phlebotomist taking blood; radiologist taking an X-ray) are no different to their routine job. We need to be careful not suggest additional barriers or documentation just because they perform these functions in relation to a clinical trial.
17	5.7 Sponsor: Allocation of Responsibilities Line 1626	Complete with 'and keep them updated during the trial'
29	5.7 Sponsor: Allocation of Responsibilities	It is not clear what is expected here? It will be good to have more elaboration of this section 5.7 here.

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Stake-holder	Section & Line	Comment: SPONSOR
	Line 1624	
16	5.8 Sponsor: Compensation to Subjects and Investigators Line 1630-1642	This section is covered by compliance with applicable regulatory requirements. There is therefore no need to include this section in the guidelines.
17	5.8 Sponsor: Compensation to Subjects and Investigators Line 1642	Add that this should be assessed by IRB/IEC
10	5.9 Sponsor: Financing Line 1646	IEC are not receiving compensation for the work done after approval. That represent a serious concern on the feasibility of the whole procedure.
10	5.10 Sponsor: Notification/Submission to Regulatory Authority(ies) Line 1664	Finding and IEC/IRB can raise problems depending on the burden involved.
6	5.11 Sponsor: Confirmation of Review by IRB/IEC Line 1659-1671	Communication with IEC is sponsor task in Europe. “required by regulation” or an analogical phrase should be added. Another option would be to change the wording to make clear that the sponsor receives the information from the investigator/institution or IRB/IEC. 1659 - 1671 delete all.
10	5.11 Sponsor: Confirmation of Review by IRB/IEC Line 1671	Compensation during the trial should be made in agreement of the time spend by IEC for reviewing the documents
10	5.11 Sponsor: Confirmation of Review by IRB/IEC Line 1671	Compensation during the trial should be made in agreement of the time spend by IEC for reviewing the documents
14	5.11 Sponsor: Confirmation of Review by IRB/IEC Line 1661, 1677, 1680	Delete: from the investigator/institution
19	5.11 Sponsor: Confirmation of Review by IRB/IEC Line 1659-1682	Please make sure the communication requirements are in line with the EU Clinical Trial Regulation 536/2014
28	5.11 Sponsor: Confirmation of Review by IRB/IEC	Throughout this section, the text should be extended to reflect that, when a central IEC/IRB is used, the sponsor (rather than the investigator) may be

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Stake-holder	Section & Line	Comment: SPONSOR
	Line 1659-1682	responsible for ensuring IEC/IRB review of the clinical trial and for communication with the IEC/IRB.
30	5.11 Sponsor: Confirmation of Review by IRB/IEC	5.11.1(c) and 5.11.2 reflect broader consent DOCUMENTS in place of Forms (as previous proposals)
6	5.12 Sponsor: Information on Investigational Product(s) Line 1684	Does not take into consideration that in some clinical trials the investigational products will be prescribed (over the counter).
6	5.12 Sponsor: Information on Investigational Product(s)	Information about clinical trials with authorized medicinal products should be added
29 and 30	5.12 Sponsor: Information on Investigational Product(s) Line 1686-1688	When planning trials, the sponsor should ensure that sufficient safety and efficacy data from nonclinical studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied. This may not be applicable to clinical trial specific to advanced therapy medicinal, as it may not always be feasible to generate relevant non-clinical data before the product is tested in humans. Reference: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/atmp_guidelines_en.pdf (European Commission Guidelines on Good Clinical Practice specific to Advanced Therapy Medicinal products, accessed 17 Oct 2019). Suggest modifying section 5.12.1 to take consideration of clinical trial specific to advanced therapy medicinal as relevant non-clinical data before the product is tested in humans may not be available.
16	5.14 Sponsor: Supplying and Handling Investigational Product(s) Line 1742-1753	It is unclear how this information materially affects the rights and well-being of trial subjects or the reliability of the results.
19	5.14 Sponsor: Supplying and Handling Investigational Product(s) Line 1724-1725	The special case of publicly funded trials in which the investigational product is part of the patient's standard care financed by health care providers should be addressed.
28	5.14 Sponsor: Supplying and Handling Investigational Product(s) Line 1722-1754	The text should be extended to reflect that, where an appropriate risk assessment has been performed, appropriate and validated arrangements may be put in place for product to be shipped directly to trial subjects and not via the investigator/institution. In such cases, it is important that the sponsor should keep the investigator informed of these shipments.
16	5.15 Sponsor: Record Access Line	This repeats earlier sections covering similar issues under the Investigator section.
10	5.16 Sponsor: Safety Information Line 1780	Sponsor should not transfer the safety evaluation to CRO.

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Stake-holder	Section & Line	Comment: SPONSOR
16	5.16 Sponsor: Safety Information Line 1783	This needs to be proportionate. The timing and content of any such notification will depend among other things on what action may need to be taken and how promptly.
6	5.17 Sponsor: Adverse Drug Reaction Reporting Line 1788	With applicability of regulation (EU) 536/2014, the process described here will no longer be valid in Europe. There will be no direct information from the sponsor to the investigators and the IECs about ADRs which are both serious and unexpected. An opening clause should be added to take new legislation into account.
10	5.17 Sponsor: Adverse Drug Reaction Reporting Line 1792	The sponsor is responsible for reporting SAE directly and not by the CRO to investigator.
10	5.17 Sponsor: Adverse Drug Reaction Reporting Line 1792	A list of concerned investigators receiving ADR should be established in the protocol and restricted to the study involved. Serious and unexpected should be precised with grading of the observed effect. A list of expected events should be precised in the protocol and reported with statistics.
16	5.17 Sponsor: Adverse Drug Reaction Reporting Line 1790	The definition of adverse reaction is internally inconsistent. Providing information on SUSARs (which by definition are only on the active treatment) without considering contextual information (e.g. the rates of similar events in the placebo arm) or providing advice on whether any particular mitigation strategy is needed may not be the best way to improve safety of study subjects. This section (and the related E2 guidances) needs to be re-thought, focusing on what signals different approaches are capable of detecting, what implications there may be for subject safety, etc. For example, in a recent review of serious adverse reaction reports across 3 large CV outcome trials the number of "related" cases that were in fact on active was the same as the number that were on placebo. In other words, the reporting investigators were not able to reliably identify those cases that were "with reasonable probability" related to study treatment.
3	5.18 Sponsor: Monitoring Line 1819	Evidence of training of monitor to be shown to the investigator?
10	5.18 Sponsor: Monitoring Line 1861	Statistical analysis should be used on regular basis
10	5.18 Sponsor: Monitoring Line 1882 Line 1957	1882: control of medical qualification and facilities are made by medical trained person 1957: Authorization of change should be in an automatic electronic format by the authorized person.
10	5.18 Sponsor: Monitoring Line 1960	Determination of an AE is done by medical doctor(and not the CRO) according to definition provided in the protocol for low risk-based study
14	5.18 Sponsor: Monitoring Line 1881	Add: ...trial site, i.e. not all of the tasks have to be performed at each visit or in each trial according to the risk assessment:

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Stake-holder	Section & Line	Comment: SPONSOR
16	5.18 Sponsor: Monitoring Line	5.18.1. Points (a) and (b) neatly summarize the key principles of GCP. It is a shame to bury them back here! 5.18.1. In a CTTI workshop, the purpose of monitoring was redefined as (a) checking compliance with the protocol and (b) providing an opportunity for further quality improvement. This latter point includes the concept of mentoring and continuing training/support of study staff. 5.18. This section should be re-written. Much of the original text is obsolete and focusses on detailed mechanics rather than the principles that are in the Addendum.
17	5.18 Sponsor: Monitoring Line 1832 Line 1906	1832: Add the notion of risk-based approach in accordance with addendum (1842) 1906 : investigator and delegated staff
19	5.18 Sponsor: Monitoring Line 1888-1904	This section is not pertinent for trials were the investigational product is part of the standard care financed by health care providers.
26	5.18 Sponsor: Monitoring Line 1829	Risk-based approaches apply to multiple facets, such as protocol deviations, auditing (5.19), etc. Suggest building out a bit more. Not appropriate to take risk-based approaches in all areas (SUSAR as an example) WRT protocol deviations: identify which bits are anticipated to be discovered via centralized monitoring and which are on-site (note in plan). By following this approach, you should find all important protocol deviations (and many non-important).
28	5.18 Sponsor: Monitoring Line 1954-1958 Line 1833-1835 Line 1899, 1902	1954 - 1958: The text should be amended to reflect that changes to data in the CRF may be confirmed by initialing each change in the case of paper CRFs or by electronic means. 1833 - 1835: We recommend deletion of the statement "In general there is a need for on-site monitoring, before, during, and after the trial; however, in exceptional circumstances". The way in which a clinical trial is monitored should be determined by a risk assessment of the specific characteristics of the individual trial. 1899, 1902: the phrase "at the trial sites" should be deleted as it is possible that product may be shipped directly to trial subjects rather than via the trial site.
29 and 30	5.18 Sponsor: Monitoring Line 1960 Line 1928-1929 Line 300, 1835, 1946, 1851	5.18.4 Monitor's Responsibilities: are manual-heavy QC checks, whereas a combination of Central and On-site monitoring mechanisms may provide a proportionate risk-based approach to trial monitoring; is it possible to describe examples of ways in which the activities may be adjusted? 1960: "Determining whether all adverse events (AEs) are appropriately reported within the time periods required by GCP…" – suggest revision/modification to: "Determining whether all subject safety information [e.g. adverse events (AEs), serious adverse events (SAEs] are appropriately reported within the time periods required by GCP…See 4.11 Safety Reporting." 1928-1929: To be consistent with the requirement 4.9.0 (Source data should be attributable, legible, contemporaneous, original, accurate, and complete.), suggest modification to "(k) Verifying that source documents and other trial

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Stake-holder	Section & Line	Comment: SPONSOR
		records are attributable, legible, contemporaneous, original, accurate, complete, kept up-to-date and maintained." 300, 1835, 1846, 1851: "centralized monitoring". Per our experience, the term centralized monitoring and central monitoring often were mis-interpreted by different stakeholders, suggest defining the terms and adding clear descriptions under GLOSSARY section 1.
36	5.18 Sponsor: Monitoring Line 1816	Adding the following text: "Monitoring of a study should be performed by a person who is not involved in other trial related duties of the specific trial(s) for which this person is monitor."
10	5.19 Sponsor: Audit Line 2028-2030	Qualification means medical qualification. Audit should focus on main end point of the study and not only on administrative procedure.
10	5.19 Sponsor: Audit Line 2051	Compliance endpoint on main objectives of the study;
16	5.19 Sponsor: Audit Line 2016	The section starts "If or when sponsors perform audits". It should be clearer what, if any, is the purpose of audits (which some interpret as an external monitoring of the monitors who monitor the trial conduct by the investigators". It is not clear what value this has. It is not clear what "independent of the clinical trials/systems" really means (or why it is necessary). This is an areas of spiraling cost and complexity with little evidence of value.
18	5.19 Sponsor: Audit Line 2036	Add that the audit plan should take a risk-based approach aligned with the identified critical processes and data as outlined in the protocol / monitoring plan.
26	5.19 Sponsor: Audit	Recommend completely reviewing this section as the role of audits is not clearly defined. When should Sponsor's consider performing audits? What level of independence in necessary? In line with risk-based approaches in QC should consider remote auditing.
29 and 30	5.19 Sponsor: Audit Line 2026-2031	This section did not give enough details or expectation in competence of auditors. Per our experience and several discussions among the industry stakeholders & peers, qualification of auditors is based on different interpretation of GCP standard. There is no golden rule in a guideline has been developed. Often, we referred to specific expectation in the EMA GVP module IV on pharmacovigilance audits which gives more information on expectation of Competence of auditors. Reference: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices (EMA Good pharmacovigilance practices accessed 16 Oct 2019). Suggest adding additional details and expectation for competence of GCP auditors in the next revision of ICH E6.
17	5.20 Sponsor: Noncompliance Line 2074	…the sponsor should notify promptly the regulatory authority(ies) and the IRB/IEC if applicable
18	5.20 Sponsor: Noncompliance	5.20 - consider amending language to notify RA of any significant noncompliance which has an impact on subject safety or data integrity to bring consistency in this area (currently country specific)

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Stake-holder	Section & Line	Comment: SPONSOR
28	5.20 Sponsor: Noncompliance Line 2074	Text should be added to reflect that, where a central IEC/IRB is used, the sponsor should also notify the IEC/IRB.
18	5.21 Sponsor: Premature Termination or Suspension of a Trial	5.21- consider adding language related to notifying the EC of any termination of an individual site as well as the trial as a whole
6	5.22 Sponsor: Clinical Trial/Study Reports Line 2085	It must be pointed out even more clearly that a final report according to ICH E3 is only required for studies relevant to marketing authorization and that a summary of the results (at least in Europe) is sufficient, especially for studies that are not carried out in the context of marketing authorization.
16	5.22 Sponsor: Clinical Trial/Study Reports	More important would be to emphasize the need to publish the results and conclusions of all clinical trials regardless of their conclusions and regardless of whether they achieved their goals or were completed.
10	5.22 Sponsor: Clinical Trial/Study Reports Line 2089	Clinical study report for academic trial should focus on main end point of the study and should be associated whenever possible with peer review publication.
29	5.22 Sponsor: Clinical Trial/Study Reports Line 2085-2095	Suggest adding the sponsor should also consider working with investigator to provide the study subjects/ trial participants or the subject's legally acceptable representative a summary of the trial's outcome, the treatment results related to them in a non-technical language as practical that should be understandable to them.
30	5.22 Sponsor: Clinical Trial/Study Reports Line 2096 Line 2085-2095	2096: Add new clause: Sponsors must also ensure (when applicable) that trial registries are completed with trial results and outcomes. 2085-2095: suggest adding the sponsor should also consider working with investigator to provide the study subjects/ trial participants or the subject's legally acceptable representative a summary of the trial's outcome, the treatment results related to them in a non-technical language as practical that should be understandable to them.
14	5.23 Sponsor: Multicentre Trials Line 2111	Please add definition of coordinating investigator to chapter 1 glossary.
16	5.23 Sponsor: Multicentre Trials	It is unclear why this section is needed. The requirements are the same as those specified elsewhere. If there's to be a section on multicentre trials, why not have one for trials with no centres or sites at all (e.g. postal or smartphone trials)?

2.5 Clinical Trial Protocol and Protocol Amendments

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Stake-holder	Section & Line	Comment: CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENTS
10	6.1 Clinical Trial Protocol and Protocol Amendments: General Information Line 2126	Amendments should be described and differentiated as minor or major. Only major amendment affecting the trial can be subject to a new signature from patient.
12	6.1 Clinical Trial Protocol and Protocol Amendments: General Information Line 2145	Name, title, address, and telephone number(s) of the qualified physician or licensed independent practitioner (or dentist, if
14	6.1 Clinical Trial Protocol and Protocol Amendments: General Information Line 2128	Please add chapter on risk-based quality management
18	6.1 Clinical Trial Protocol and Protocol Amendments: General Information Line 2302	Include details of any situations for which copies of redacted medical records will be requested to be sent to the Sponsor (per EMA GCP FAQ document)
19	6.1 Clinical Trial Protocol and Protocol Amendments: General Information Line 2121-2319	In 1996, this list was an important tool for development of trial protocols. Meanwhile, the SPIRIT statement, guidelines and checklists are available (https://www.spirit-statement.org). SPIRIT provides very detailed and well-structured guidance for the content of trial protocols. Therefore, the whole section 6 should be deleted, and a reference to SPIRIT should be included.
33	6.1 Clinical Trial Protocol and Protocol Amendments: General Information Line 2156	Broaden the scope of describing the aim of the trial (human pharmacology, non-interventional trials, investigational products that already have market authorization). Reasons: there may be several investigational products or none at all, when the focus is shifted from current practice (licensing trials for patent-protected medicines) to serving clinical medicine in general.
33	6.3 Clinical Trial Protocol and Protocol Amendments: Trial Objectives and Purpose Line 2174	Broaden the scope of describing the aim of the trial (human pharmacology, non-interventional trials, investigational products that already have market authorization). Reasons: the trial design depends on the objectives. Objectives should be broadened beyond current practice (licensing trials for patent-protected medicines) to serving clinical medicine in general.
16	6.4 Clinical Trial Protocol and Protocol Amendments: Trial Design Line 2204	Need to be clear to distinguish between medical or protocol-specified rules for stopping or adjusting treatment; subject requests to stop/adjust treatment, cease certain forms of contact or assessment, cease further collection of information from third parties/records, cease processing of samples or data, and withdraw from the study entirely.
33	6.4 Clinical Trial Protocol and Protocol Amendments: Trial Design	Trial types and data sources other than RCTs should be emphasized (e.g. real-world data, prospective cohorts, observational studies). Reasons: there is an increasing need for high-quality medical data for purposes other than licensing patent-protected new medicines for

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Stake-holder	Section & Line	Comment: CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENTS
		about one decade. Judgement of clinical utility and quality-of-life aspects require additional data. Section 6.4.1 Trial design and 6.7.1 Efficacy: core outcome sets should replace the focus on (sometimes artificial) primary endpoints. Reasons: clinical utility and patient-related outcomes can best be represented in compound scores (core outcome sets), and often not in a single primary endpoint. Section 6.4.3 Bias reduction: Efforts should be made in the upcoming revisions of E6 to identify additional acceptable bias reduction methods beyond randomization and blinding. Reasons: real world data require other aspects of quality by design than those in RCTs for licensing purposes. Section 6.4.3 Bias reduction: Efforts should be made in the upcoming revisions of E6 to identify additional acceptable bias reduction methods beyond randomization and blinding. Reasons: real world data require other aspects of quality by design than those in RCTs for licensing purposes.
16	6.5 Clinical Trial Protocol and Protocol Amendments: Selection and Withdrawal of Subjects Line 2223	Need to be clear to distinguish between medical or protocol-specified rules for stopping or adjusting treatment; subject requests to stop/adjust treatment, cease certain forms of contact or assessment, cease further collection of information from third parties/records, cease processing of samples or data, and withdraw from the study entirely.
26	6.5 Clinical Trial Protocol and Protocol Amendments: Selection and Withdrawal of Subjects Line 2223	Recommend adding a bit about re-screening criteria [to whole section] 2223: similar comment as before with withdrawal of…..
33	6.8 Clinical Trial Protocol and Protocol Amendments: Assessment of Safety Statistics Line 2251-2260	A distinction should be made explicitly between a) new medicines to be licensed, vs. b) medicines with existing market authorization. Reasons: to avoid unnecessary administrative overhead, safety reporting on licensed medications may be fed into existing systems of drug safety monitoring for those medicines.
33	6.9 Clinical Trial Protocol and Protocol Amendments: Statistics Line 2274	Estimation of effect sizes should be an acceptable endpoint rather than a p-value. Reasons: in real world data collection this may be sufficient to know, and effect sizes are needed for planning subsequent studies.
16	6.10 Clinical Trial Protocol and Protocol Amendments: Direct Access to Source Data/Documents Line 2289-2291	This is inherent in the need to follow GCP.
28	6.11 Clinical Trial Protocol and Protocol Amendments: Quality Control and Quality Assurance Line 2295	We recommend the addition of a statement that the protocol should include a brief summary of the arrangements for monitoring and audit by the sponsor.

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Stake-holder	Section & Line	Comment: CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENTS
33	6.11 Clinical Trial Protocol and Protocol Amendments: Quality Control and Quality Assurance Line 2294	Shift to quality-by-design instead of extensive monitoring requirements, wherever possible. Reasons: care should be taken to encourage both scientists and participants to do high-quality research in humans (rather than deter them by disproportionally high administrative hurdles).
28	6.13 Clinical Trial Protocol and Protocol Amendments: Data Handling and Record Keeping Line 2303	We recommend a statement that there should be a brief summary of the arrangements for data handling and record keeping.

2.6 Investigator's Brochure

Stake-holder	Section & Line	Comment: INVESTIGATOR'S BROCHURE (IB)
28	7.2 Investigator's Brochure: General Considerations Line 2327-2365	We recommend that this section should include a statement that local regulations may require specific additional information or formatting to be included in the IB (e.g., the requirement in EU law for a specific section headed Reference Safety Information).
1	7.3 Contents of the IB	Some thought should go into decision to change protocols or notify sites for minor changes in the IB.
15	7.3 Contents of the IB Line 2518-2535	Add some guidance on inclusion of preliminary safety data from ongoing clinical trials. You now suggest including data from completed clinical trials. Mention whether or not any blinded data can be presented. Some IBs contain blinded data from placebo-controlled trials, but that is not always clearly stated and may lead to confusion.
21	7.3 Contents of the IB Line 2500-2555 Line 2521	2500-2555: It should be clarified whether data form ongoing, double-blinded, placebo-controlled clinical trials should be included and if it should be included, guidance regarding the importance of noting that any attribution is blinded and the limitations of using data from ongoing, treatment-blinded trials to understand the safety profile of an experimental product 2521: "that were obtained from preceding COMPLETED trials in humans"

2.7 Essential Documents

Stake-holder	Section & Line	Comment: ESSENTIAL DOCUMENTS
6	8.1 Essential Documents: Introduction	The documents which are asked for in the additional text of the addendum (e. g. monitoring plan, validation documents for computer systems, Risk analysis etc.) have not been added to the list of essential documents in Chapter 8.

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Stake-holder	Section & Line	Comment: ESSENTIAL DOCUMENTS
	Line 2678-2679	Confirmation about system validation, Monitoring plan, documents regarding risk analysis and risk review should be added to the list of essential documents to avoid misunderstandings and discrepancies.
16	8.1 Essential Documents: Introduction	This list and style of presentation is very unhelpful. It focuses attention on things that can easily be checked rather than processes and objectives that can materially influence the trial subjects and the reliability of the results. For example, "these documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of GCP." What they serve to demonstrate is Good Filing Practice which is not the same thing at all. "The minimum list of essential documents..." yet in the Addendum it says that this list "should be supplemented or may be reduced where justified".
18	8.1 Essential Documents: Introduction	Clarify that certified copies are only needed where a document irreversibly replaces an original document . Add language aligned with EMA TMF Guidance document related to the need to establish which party is responsible for which aspects of the TMF, and that the TMF must contain all documents necessary to reconstruct the trial without additional explanation; also language related to the need to ensure secondary locations are listed and accessible.
26	8.1 Essential Documents: Introduction	1.) These two controls bit duplicated, CRF is part of records generated by the site. What about e-diary which is generated by subjects, not directly by investigator/institutions? 2.) would consider put under the responsibility of Investigator, to enhance the awareness.
28	8.1 Essential Documents: Introduction Line 2650 - 2687	The introduction to the Essential Documents section should make clear that the minimum list provided is intended as a guide only and that, in practice, all records and documents that are essential to reconstruct the conduct of the clinical trial are required to be retained in the trial master file. The only exceptions would be those documents where an appropriate rationale for their absence is included in a formal risk assessment undertaken as part of a risk-adapted approach to trial management.
30	8.1 Essential Documents: Introduction	Emphasize the text to indicate content may be scaled proportionally to objectives of the trial.
33	8.1 Essential Documents: Introduction Line	Section 2: Add to the ICH GCP principles: a flexible risk-based attitude should be applied throughout GCP. Reasons: E6 has too much focus on commercial sponsors that develop new medicines with a focus on return on investment. But clinical medicine also needs a) new medications in commercially unattractive areas such as antibiotics or pain management, b) repurposing and label expansions for existing safe medicines. These unmet medical needs require more investigator-initiated trials and non-interventional trials. Academic researchers and public-private partnerships do not have the resources to handle the administrative overhead.
36	8.1 Essential Documents: Introduction	Add additional text in chapter 8 essential documents on: 1) Documentation about design, development and validation of the research database (including data management/data validation plan), 2) Documentation on IMP for example: IMPD, GMP license, QP signed batch certification form, temperature records (storage conditions)

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Stake-holder	Section & Line	Comment: ESSENTIAL DOCUMENTS
12	8.2 Essential Documents: Before the Clinical Phase of the Trial Commences Line 2703 Line 2704	2703: Licensure and/or other relevant documents 2704: Remove requirement for lab normals from investigator/institution files as reference ranges are contained on all printed laboratory results reports
14	8.2 Essential Documents: Before the Clinical Phase of the Trial Commences Line 2704 Line 2728	2704: if respective normal range is not provided with each individual value Explanation: Modern lab equipment delivers the normal range with each value. 2728: if respective normal range is not provided with each individual value
36	8.2 Essential Documents: Before the Clinical Phase of the Trial Commences Line	Add text in 8.2.1: other research staff who have performed significant tasks in the study (besides the PI and the SI)
12	8.3 Essential Documents: During the Clinical Conduct of the Trial Line 2727 Line 2728 Line 2738	2727: Licensure for new investigators 2728: Remove requirement for updates to lab normals from investigator/institution files as reference ranges are contained on all printed laboratory results reports 2738: Delegation of responsibilities log - To document responsibilities, training, and signatures of all persons authorized to perform trial specific activities and/or procedures.
18	8.4 Essential Documents: After Completion or Termination of the Trial	Add clarity that documents must be able to be retrieved and reviewed throughout the archiving period, meaning that where technology migrations / updates occur it is ensured that the information is still accessible.

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2.8 Additional Comments

Stake-holder	ADDITIONAL COMMENTS
6	ICH E6 is an important standard besides the approval-relevant clinical trials and is even legally binding in Europe. Unfortunately, clinical trials with already approved drugs are not sufficiently addressed and considered in ICH E6, which leads to problems in the GCP-compliant implementation of these studies.
8	Few topics about the quality management of data, randomization process and statistical analysis quality process before to go on E9
10	The text is fairly difficult to understand for the main player, investigator who are running the trial. Too many references to other documents at a time where reading extensive document is not common practice. It will affect the safety of data collection and reporting. Some parts are extensive, some others absent. Several Addendum are introducing a list which can be far from the goal of medical safety or efficacy. Signing pages does not provide secure information. Here are some points: - If the sponsor is responsible for safety with the investigator, why CROs control so many forms without medical experience. The relation should be clarified. - -A guideline for collection of medical data (SAE, SUSAR) in a way close to practice needs to be elaborated in collaboration with medical doctor. - An excess of procedures is deleterious for the safety collection. ADRs need to be redefined more with grading with simple form (see Australasia?). -In the coming years electronic reports will be the source of data. Translation from one software computer to the other is a matter of information technology. ICH should recognize that many written procedures are obsolete. - Academic studies are not really discussed, however they often change clinical practice as much as new drugs. Main message is to go back to clinical care with essential data. Number of clinical researchers is low, and we need to save time.
12	FDA regulations set forth the criteria under which the FDA considers electronic records, electronic signatures, and handwritten signatures executed to electronic records to be trustworthy, reliable, and generally equivalent to a handwritten signature executed on paper. The E6 definition should be updated to include the use of e-consent, or a separate definition of e-consent added when appropriate approvals and safeguards are in place.
14	Please add definitions (glossary) of non-therapeutic Trial (see 4.8.13) and coordinating Investigator (5.23.3).
15	Would it be possible to add a unique identifier to subsequent releases of the ICH guidelines, such as an ISBN number or other appropriate unique identifier? I, and I suspect others, somethings struggle to find the right version of a technical document. Unique identifiers would help people find the right document and the right version and help make sure people are talking about the same (version of a) document.
16	The structure of this document requires radical changes. My suggestion is: 1. Start with the high-level principles: - The protection of the rights, safety, and well-being of study participants; and - The reliability of the study results (which influence directly or indirectly the treatment of future patients) 2. Delivering this should be achieved through the quality-by-design approach (based on Addendum text from section 5.0) 3. List out the key requirements (largely the current principles form current section 2), e.g. ethics based on Declaration of Helsinki; sound scientific protocol; IRB/IEC approval; monitoring and management of safety

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	signals; all trial personnel should be suitably qualified for the task they are to perform through training & experience; data management. 4. Then for each key requirement explain any more detailed considerations or requirements in separate sections. This should highlight / explain the types of issue that might impact on either the participants or the reliability of the results (drawing on the underlying scientific principles, e.g. the need for adequate sample size, meaningful and measurable endpoints, randomization, minimal loss to follow-up.) This approach would avoid the current duplication (e.g. training appears in at least four places--investigator, sponsor, CRO, monitor), would consistently refer back to the principles, objectives, and application of QbD, and would keep the thread of being proportionate to the risks to participants and the reliability of the results. It would also remove the current emphasis on process and task (who does what, where, to what timeline, and with what pieces of paper). This leaves more room for innovation and evolution (e.g. as IT and communications systems evolve) but keeps focus on what matters. Other Points: 1. Patients and patient advocates have been clear that they do not wish to be referred to as Subjects. A global change to Participants would be preferable. 2. Many of the definitions are unclear or contradictory. a. Example 1: "Adverse Drug Reaction: ...a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out." “i.e.,” is short for “id est” which means “that is,” or “the same as”. But there's an important difference between "at least a reasonable possibility" and "cannot be ruled out". They are at opposite ends of the probability spectrum. b. Example 2: The definition of "Sponsor" is not consistent with the EUCTR or US CFR definitions. It confuses who is paying, who is taking responsibility for the quality of the trial, who is taking responsibility for the drug itself, and who will be submitting for a marketing authorization at the end of the trial. It also fails to deal with the helpful concept of co-sponsorship (which allows the different aspects to be defined).
19	Comment: since the current applicable regulatory requirement(s) are - at least in Europe - much more detailed now than they were 1996, contradictions may occur. It has to be addressed how to handle contradictions between GCP and local laws.
24	Principle #13 is an important clause, since it can limit the risk of over-zealous interpretation (often due to lack of professional experience) detracting from the quality of the trial and that procedures to assure prioritization of information need to be increased.
27	While designing and implementing clinical trials, researchers should keep in mind social, cultural and religious aspects of a country.
28	An important issue that needs to be addressed is clarification of the applicability of the ICH GCP guidelines. The current ICH E6(R2) glossary definition of a clinical trial (section 1.12) includes the statement that “The terms clinical trial and clinical study are synonymous”. However, based on legal definitions in at least two of the original major territories that adopted the ICH guideline, this is not the case and has led to considerable confusion and, in some cases, inappropriate application of the guidelines to studies for which they were not designed. The EU Clinical Trial Regulation (536/2014), for instance, includes distinct definitions for each of "clinical study", "clinical trial", and "non-interventional study", the latter being "a clinical study other than a clinical trial." A clear distinction is also made in the USA where an observational study is defined as a non-interventional clinical study design that is not considered a clinical trial" (Glossary of Framework for FDA,Äôs Real-World Evidence Program - Dec 2018). Further, the ICH Articles of Association state that the purpose of the organization is "to promote public health through international harmonization of technical requirements that contributes ..... to the prevention of unnecessary duplication of clinical trials in humans. The goal of the ICH GCP renovation project is stated to be to provide updated guidance that is both appropriate and flexible enough to address the increasing diversity of clinical trial designs and data sources that are being employed to support regulatory and other health policy decisions. We fully support the initiative to update the E6 guidance to take account of the diversity of clinical trial designs and the varied data sources that are now

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Stake-holder	ADDITIONAL COMMENTS
	used in clinical trials. However, we recommend strongly that the guidance should maintain focus, and ensure that this is clearly stated, on clinical trials to support regulatory decisions and not include other forms of clinical study or wider health policy aims, as this would simply maintain the current confusion over applicability of the guideline. Several international guidelines applicable to observational clinical studies (as opposed to clinical trials) already exist (e.g., CIOMS International Ethical Guidelines for Health-related Research Involving Humans, ISPE Guidelines for Good Pharmacoepidemiology Practices, ENCePP Guide on Methodological Standards in Pharmacoepidemiology) and other projects are in place (e.g. the recently announced Joint Initiative on Good Practice in Clinical Research coordinated by the Wellcome Trust, the Gates Foundation and the African Academy of Sciences) to develop complementary guidance for those studies where ICH GCP is not applicable. Consequently, we recommend strongly that ICH should not duplicate ongoing efforts in the wider clinical studies space and should maintain its focus on clinical trials intended to support regulatory decisions on medicinal (drug and biologic) products, and that the applicability of the guideline should be stated very clearly.
29	1. Lines 349 – 350: "1.3 Amendment (to the protocol) See Protocol Amendment." should be removed or combined with 1.45 since it did not give useful details but referred to 1.45 Protocol Amendment. 2. Lines 555-556: "1.43 Original Medical Record See Source Documents." should be removed or combined with 1.52 since it did not give useful details but referred to 1.52 Source Document. 3. More consideration to be given to patient as the 4th stakeholder of clinical trial in addition to IRB/IEC, INVESTIGATOR, SPONSOR.
30	Glossary Comments: 1. Lines 349-350: 1.3 Amendment (to the protocol) See Protocol Amendment.-- should be removed or combined with 1.45 since it did not give useful details but referred to 1.45 Protocol Amendment. 2. Lines 555-556: 1.43 Original Medical Record See Source Documents.-- should be removed or combined with 1.52 since it did not give useful details but referred to 1.52 Source Document. 3. Definition of informed consent 1.28 to address eConsent specificities Other Comment 4. Please give more consideration to the patient as the 4th stakeholder of clinical trials in addition of EC/investigators/Sponsor 5. in the context of Machine learning and data driven decision, in addition of audit trails, related algorithms should be available and supportive explanatory documentation should be comprehensive. 6. Adaptions of the guidelines may need to be considered for virtual trials/digital trials where interventions by Investigators and visits to Investigator Sites are minimized. Timely review of data by clinically qualified staff would be imperative to safeguard patients, but it is not clear if the expectation is that this would be by clinically qualified staff at Investigator Sites or if Sponsors may do this directly. In Europe expectations are already put forward that the Sponsor should not have direct control of data from the patient/Investigator, but is this something which needs re-evaluation in view of virtual trials/digital trials? It would not negate the involvement of Physicians (or dentists) by other means. In follow-up to (6) above: 4.8.8 in the context of eConsent -- personally dated may be reworded. Consider too rewording "written informed consent" to consider dematerialized documentation. Suggest also Essential Documents accompanied either by an indication of what adaption can take place OR specified proportionality of relevance to the trial.
31	Would be great with guiding documents with examples to avoid over-interpretation of GCP - as this occurs a lot. It increases bureaucracy, is costly and takes away focus from the core requirements and resources that could be used for valuable clinical research instead.
33	1. Section 2: Add to the ICH GCP principles: a flexible risk-based attitude should be applied throughout GCP. Reasons: E6 has too much focus on commercial sponsors that develop new medicines with a focus on return

Stake-holder	ADDITIONAL COMMENTS
	on investment. But clinical medicine also needs a) new medications in commercially unattractive areas such as antibiotics or pain management, b) repurposing and label expansions for existing safe medicines. These unmet medical needs require more investigator-initiated trials and non-interventional trials. Academic researchers and public-private partnerships do not have the resources to handle the administrative overhead. 2. Scope of GCP: Provided the risk-adapted attitude has been installed into GCP and mechanisms are in place to avoid administrative overloading, a uniform set of rules could be applied to all research on humans: medicines, devices, surgeries, psychosocial interventions, public health interventions etc. Reasons: General principles are uniform (e.g. quality by design, stakeholder involvement, transparency) but care should be taken to encourage both scientists and participants to do high-quality research in humans (rather than deter them by disproportionally high administrative hurdles). This balance can only be achieved, when all stakeholders are involved in the revision of ICH guidelines. 3. Scope of GCP: should be broadened to reflect the needs for high-quality data of health care in general. Reasons: clinical practice guidelines, such as developed by AWMF members in Germany, depend on high-quality data. Trials that are run for market authorization of new patent-protected medications should be designed also for this later use of the same data. Both efficacy and safety data should also be collected outside those trials using real world data. 4. Revision process: academic medicine, clinicians that perform trials, clinicians that develop clinical practice guidelines, and appropriate patient representatives should be closely involved in the revision of all ICH guidelines. Reasons: these stakeholders are important users of the ICH guidelines and of data produced according to them.
34	Good Clinical Practice is driven by the principle of scientific and ethical responsibility. It is unacceptable that major parties to the ICH E6 (and ICH E8) Guideline have not included their own proper responsibilities in GCP. As with IRBs/IECs, Investigators, and Sponsors, a full section outlining Regulators/Government responsibilities in clinical trials should be included. The failure of the original ICH regulatory bodies (the European Commission, the US FDA, and the Japanese MHLW undermines the credibility of the guideline and ICH generally. An additional full section should also be included on clinical trial participant responsibilities. Without such a section GCP will continue to fail to meet the health needs of patients and their communities. For ICH E6 to be properly reviewed and have its fullest impact, ICH needs to further reform in order to include patient and community representation, ethics committee representation, and representation from academic and not-for-profit groups that are actively involved in health research. This reform needs to include representation from all parts of the world and society and be reflected in the governance structure of ICH.

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3 METHODS

3.1 Recruitment

CTTI leadership established relationships with organizations who have robust global professional networks who would be willing to forward the survey invitation to those networks. The CTTI advisory group members also identified specific groups in which to send the survey invitation, and CTTI staff conducted internet searches to identify research networks to contact. We sent a recruitment email to all these groups with a link to the online survey, and also requested that recipients forward the recruitment email to others who might be interested in completing the survey. The initial response from stakeholders residing in North America, Europe, and Australia was very strong, although few participants from other parts of the world. Therefore, we conducted a second wave of recruitment, focusing on stakeholders who were part of research networks in ICH member countries, specifically Brazil, China, South Korea, Japan, and Singapore. We also reached out to research networks that conduct research in Africa. CTTI also posted the survey link via Twitter and LinkedIn.

3.2 Data collection

We administered the online Open Comment Opportunity via Qualtrics. The purpose of the Open Comment Opportunity was to elicit feedback on areas in ICH E6 participants believed should be revised and their specific suggestions on how those revisions should be made. Participants were invited to either complete the Open Comment Opportunity either as an individual or as a representative of the organization where they were employed, and instructed that their responses would be linked to their name and affiliation. The Open Comment Opportunity was offered in English only, the official language of ICH. Participants were asked to 1) answer demographic questions such as their name, organizational affiliation, and country of primary place of employment, and 2) suggest specific changes to the text of ICH E6 GCP.

The Open Comment Opportunity was open to participants from September 23 to October 18, 2019.

3.3 Participant eligibility

Individuals were eligible to take part if they self-reported that they conduct research for which the findings will be used for regulatory purposes.

3.4 Data analysis

Comments and suggestions made via this platform are listed verbatim in the report. No data analysis was performed.

4 STAKEHOLDERS/RESPONDENTS

Stakeholder #	Name of organization or individual	Country(ies) where research is conducted
1	Jeff Heaely	Canada
2	William McIntyre	Canada
3	Marianne de Visser	Netherlands
4	Domenico Criscuolo, Genovax	Italy
5	Vijay Prabhakar	Singapore
6	Peggy Houben	Germany
7	Kristel Van de Voorde	Belgium
8	Dominique Delforge, FAMHP	Belgium
9	Matlyuba Sanoyeva	Uzbekistan
10	Christian Gisselbrecht	France
11	Goran Westerberg, La Crocina Pharmaceutical Consultants	Italy
12	Colleen Rouse, Cleveland Clinic	USA
13	Piera, EAHP	Italy
14	Bärbel Kastner, Britta Schröder, KKS Heidelberg	Germany
15	Huub Gelderblom	USA
16	Martin Landray	United Kingdom
17	Anne De la Gorce, Institut de Recherches Internationales Servier	France
18	Helen Howitt, Syneos Health	United Kingdom
19	Oana Brosteanu	Germany
20	Robrecht Tistaert	Belgium
21	Shelly Karuna	USA
22	Dagmar Chase	Germany
23	Bettina Bergtholdt, Emovis GmbH	Germany
24	Elizabeth Macintyre	France
25	Raul Cordoba	Spain
26	Deborah Driscoll, Merck	USA
27	Mahmood-uz-jahan, Bangladesh Medical Research Council	Bangladesh
28	John Poland, Association of Clinical Research Organizations	United Kingdom
29	Medical Quality Assurance, Pfizer	USA
30	Louise Mawer, European Forum for GCP Auditors Working Party	Belgium
31	Else Munksgaard Pedersen, Zealand Pharma	Denmark
32	Anjo den Decker, Astellas Pharma Europe BV	Netherlands
33	Rolf-Detlef Treede	Germany
34	Francis P. Crawley, Good Clinical Practice Alliance - Europe (GCPA) & Strategic Initiative for Developing Capacity in Ethical Review (SIDCER)	Belgium

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Stakeholder #	Name of organization or individual	Country(ies) where research is conducted
35	Le Gouill	France
36	Sonja Kwadijk – de Gijsel, Farmaceutical Affairs, Health and Youth Care Inspectorate, Ministery of Health, Welfare and Sports	Netherlands

5 STUDY TEAM

Team Leads:

- Annemarie Forrest, RN, MS, MPH, CTTI Director of Projects.
- Pamela Tenaerts, MD, MBA, CTTI Executive Director.

Research Assistant: Adora Nsonwu, Clinical Research Specialist, Duke University Department of Population Health Sciences.