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

In-Depth Interview Findings

FINAL Report
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1. PURPOSE OF RESEARCH

The Clinical Trials Transformation Initiative (CTTI)—a public-private partnership between Duke University and the US 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 in-depth interviews to ICH for their consideration as they renovate ICH E6 GCP. The report of survey findings and open comment opportunity report are provided as separate documents.

CTTI determined that while the stated focus of ICH E6 GCP is clinical research that generate data for submission to regulatory authorities, it was important to report on the significant and repeated concerns participants expressed beyond this purpose so that ICH is aware of the reality of the experiences of researchers, and can consider how best to address these concerns as part of the renovation.

CTTI also provided lengthy participant responses in the Appendices to mimic the level of detail ICH has been provided on renovation through other mechanisms.

2. SUMMARY OF THE QUALITATIVE INTERVIEWS

2.1 Aspirations for ICH E6 GCP

Described below is a summary of participants' narratives on their aspirations for the ICH E6 GCP renovation. Appendix B provides additional participant quotations on their aspirations for ICH E6 GCP renovations. Appendix C lists examples participants gave related to their aspirations for ICH E6 GCP. We provide references in the sections below to link the summary information with participant quotations and examples in Appendices B and C.

Almost all participants (n=21) named general aspirations that they had for the renovation of the ICH E6 GCP guidance. Of these, many provided general aspirations that cut across all sections of the guidance, then followed with additional suggestions for improving specific sections. We describe participants' general aspirations followed by participants' aspirations for each section of ICH E6 GCP.

2.1.1 General aspirations for ICH E6 GCP

2.1.1.1 Provide flexibility to accommodate different types of research

Fifteen participants said that their aspiration for the revision was that it incorporate enough flexibility to be able to accommodate different types of research. Of these participants, seven specified that the revised guidance should clarify whether and how ICH E6 GCP applies to nonregulatory drug trials. Types of trials mentioned in this regard included non-IMP trials for standard of care, postmarketing trials, postauthorization safety trials, pragmatic trials, and procedural studies to determine whether one drug is better than another:

> *And it's funny because when we talk about regulatory trials, what if it's a pragmatic trial that won't lead to regulatory indication? We call it a regulatory trial in the intervention because we have to submit it to a regulatory agency, but what if we go into this big data stuff, and it isn't particularly regulatory? To give you an example, I've seen some retrospective chart reviews, kind of doing a case-control type methodology where you look back and say they took/they didn't, and I've always wondered, "Why is that not a regulatory trial? You're just not doing it prospectively." And is ICH only about if we could do harm to people or is it about the things you should think about no matter what you're doing? [ID# 13]*

Although hope was expressed that the guidelines would be able to adapt to new innovations in research, some participants noted that as types of trials have evolved, the ICH E6 GCP guidance has not been entirely successful in keeping up with advances. Participants specifically noted that the current guidance is being applied to a much wider range of clinical research than was its original intent, and that despite the addition of the risk-adapted approach in the most recent revision, more

work could be done to adapt the guidance to different types of research (see also Appendix B, reference B1); for example, by developing standards for noninterventional trials:

> *I would expect that we broaden the scope of GCP also to other types of studies. Not necessarily only the interventional study, but also the data after authorization of our product because we see the trend that these data are more important now. The marketing authorization might come a little earlier, but with obligations and with impositions of collecting more data, and even in a non-interventional scenarios. I understand that—the noninterventional studies, they are lacking standards. And I mean, many companies of course apply standards they have learned in the interventional trials also to noninterventional studies, but it's not required by any regulations or guidelines, so I think we need to prepare ourselves to have good standards beyond the randomized controlled trials, the traditional development trial. [ID# 23]*

Two participants described situations in which following the current ICH E6 GCP guidance as written had proven detrimental to trial conduct. One said that, as ICH E6 GCP has become the norm for all trials, even nonregulatory studies that are not intended for an ICH regulatory submission, the expectation that ICH E6 GCP will be followed has limited or eliminated their ability to conduct certain forms of research (eg, small single-site trials, for which the necessity of engaging in ICH E6 GCP quality control, quality management, and oversight activities was prohibitive) (see also Appendix C, reference C1). Another participant noted instances where certain activities were performed as part of a study, even if they were not reasonable for the type of trial, because the expectation from reviewers was that ICH E6 GCP would be followed (see also Appendix C, reference C2).

Six participants noted that the revised guidance should also clarify whether and how ICH E6 GCP applies to nondrug studies. Participants described that, while it is obvious that the principles of GCP should be followed regardless of the type of study being done, it is not clear from the current ICH E6 GCP guidelines which components of ICH E6 GCP should be applied to nondrug studies and which can be omitted, leaving research teams to make their best guess on how to apply the guidance:

> *More quantitative research…the type of research that I did, was quite different than different clinical trials…the type of research doesn't work then and people are not sure where they're following. And those are the discussions that we actually have to make today. Is my study a GCP type of study? I think they're all need GCP, and somehow they all need to fall back [on it]…by looking at it from a different aspect. So, there's a lot of data driven research that sometimes when you read the guideline, you sort of have to have fish out information [to fit] uncommon processes. [ID# 01]*

Some participants pointed out that clinical research encompasses much more than drug and device trials and that, while it would be helpful to have a quality standard that encompasses all research, the

way ICH E6 GCP is currently written applies only to regulatory drug/device trials. However, in the absence of other guidelines, it is "GCP or nothing," including for those trials for which it does not make sense to apply ICH E6 GCP because, for example, SAEs are not being collected (see also Appendix C, reference C3):

> *Clinical trials and clinical research are much bigger than new drugs. What if I want to do emotional support versus non-psycho, referral to a psychologist or not in somebody who's currently diagnosed with a cancer? What if that's the trial? Tell me, what's the regulatory aspects about this man? I'm simply doing a study where we're saying we're going to provide half the patients with psychological support and half are not, and we're going to measure the outcomes. Because they're paying better, that's the trial. Where's the regulatory input? Where's the regulatory requirement? And that's what everyone keeps talking about is a clear development—you know, providing psychological support is not a regulatory issue. And the trial that tests whether psychological support relieves your pain or not, more than just giving the normal treatment, is not a regulatory issue. I mean, that's the problem, see. That we're all stuck in this mindset of GCP is about developing new drug and the regulators got to be happy. Well, regulators not involved in many trials that are going on. [ID# 02]*

A participant commented that, should the ICH E6 GCP guidance be expanded to encompass nondrug studies, there are many concepts in the existing ICH E6 GCP guidance that can easily be repurposed and applied to other types of research. For example, the roles of investigator and sponsor could be carried over, minus some of the topics that are specific to regulatory research (see also Appendix B, reference B2).

Participants recognized that while it may not have been the intent of the ICH E6 GCP renovation to include nondrug studies, given that this is not necessarily the purview of the ICH, it would still be extremely useful for ICH to address the issue and provide such guidance, since they are viewed as the organization that sets a worldwide standard for research, and their original guidance is being applied to types of research for which it was not originally intended. Furthermore, participants described that some of the confusion appears to stem from language provided in the ICH E6 GCP introduction, in which a phrase stating that the principles of GCP can be applied to different types of research has been widely taken to mean that ICH E6 GCP should be applied to nondrug studies. Alternately, should ICH choose not to rewrite the guidance to incorporate nondrug studies, participants stressed that it then needs to be made clear that the guidance is only for regulatory drug studies and should not be applied to research beyond that:

> *One of the problems…is the application of the guidance, we extend the guidance to trials beyond pharmaceutical ones. And it's not the role of ICH, but it would be nice to have a kind of reflection or interpretation because of the reality, because it's not seen as a standard worldwide also for other trials of what GCP means or how can things be translated that are*

written in GCP to other trials. It's nothing for ICH. They are regulatory bodies in the pharma industry. It's none of their problems, but from a political point of view, I think it would be good whether there would be anybody that says, okay, GCP is a foundation and we realize now it's applied also beyond pharmaceutical trials. What does it mean? What's the framework and how can we adapt it or what does it mean for those other trials because reality tells us that it's applied but, yeah, it's not ICH. [ID# 09]

Also, the introduction of GCP states that the principles of GCP can be, as appropriate, applied to different types of research. So this precise introductory phrase has guided, actually, at least in Europe, authorities and ethical committees, basically, applying ICH GCP to all different types of research, which are not even involving drugs, at all. And, some elements of it are truly not applicable. I mean, they just don't make sense in the context [ID# 19] (see also Appendix B, reference B3).

Further elaborating on the idea of flexibility in the types of trials that are covered by the ICH GCP guidelines, four participants noted that what should really apply in clinical research is the "spirit of GCP," or the idea that not every trial needs to fully implement all aspects of ICH GCP. Participants expressed that it would be ideal if such flexibility could be incorporated into the renovated guidance, to allow research teams to choose those components of ICH GCP that make sense for a given study. Participants discussed that, because trials are not identical and have many unique parameters, a one-size-fits-all approach is less appropriate than providing research teams with a set of principles to follow (see also Appendix B, reference B4 and reference B5):

The current document—I think if you would read it in the right way—allows you a lot, but a lot of people read only black and white, which I think is why it's causing difficulty. …From the documentation itself, I'm expecting that we will have documents and outcomes which are not following the "one-fits-all" approach because I think the needs are different between different types of studies and different types of research. … I don't think it should be a corporate recipe. You should not expect a detailed guidance how to do things because then we go back to the one-size-fits-all approach. It should introduce principles, but the principles should be clear enough that all involved parties—if it's an academic institution who wants to run its first trial or a startup who's going or a large pharma company who's on the market for 150 years, that they all know what to do. Even the way they will conduct work will be different. [ID# 05]

Several specific revisions and action steps for the existing guidance were proposed. These included:

- Identify the minimum requirements of GCP necessary for different types of trials, and consider providing a shortcut or hyperlinked "cheat sheet" adjunct to the main guidance to make it more user-friendly and to make it easier for trial personnel to quickly access the information they need to determine which components of GCP to implement in a trial (see also Appendix B,

reference B6):

> *I'm not sure if that's part of an ICH recommendation guidance to say okay, these are the minimal requirements. To consider that a trial conducted has a good quality. The principles—the 13 principles—there could be something on again what does the protocol need to contain? What does the informed consent need to contain? I think things like the definition of an AE and SAE—don't even have to discuss that. That's standard. But to say okay, these are the minimal requirements for—as a consensus—that any clinical trial should adhere. And these are the things that we need to have in place and documented and stored safely if you ever want to use that trial for registration. [ID# 08]*

- Require study teams to develop a plan for use and nonuse of ICH E6 GCP components during the study design phase, which will induce teams to proactively think about and document the required components of GCP in advance. This will allow the presence or absence of these components to be accounted for during later monitoring visits and thus hopefully avoid problems with inspections later (see also Appendix C, reference C4 and reference C5):

- Add a statement to the ICH E6 GCP guidance that the guidelines may be translated into local law and/or procedures, as needed, given that it is intended to serve as a guideline and may be insufficient to meet additional requirements imposed by local laws (see also Appendix B, reference B7):

> *…perhaps you should have some sort of preamble or so, but the purpose is that it gives basic guidelines and it demands a clear transfer into own processes, into local processes which reflect also additional local laws or local demand. It should be very much at the beginning or so to say to people, "Oh, I just followed ICH GCP with 66 pages or so, and that's it," but it's not sufficient, of course. Some people really started—as I mentioned before, they take this chapter 8…and then they start piling up documents like this or so. That's really not enough. So, give very blunt advice at the beginning, that you have to transfer all these things into your own procedures, local procedures, and take all these other things also into consideration. [ID# 06]*

- Add a statement to the ICH E6 GCP guidance that it is acceptable to deviate from ICH E6 GCP as long as the deviation is clearly justified:

> *My first thought would have been in the guidance notes at the introduction section that actually just clarify that the guidance is exactly that; it's guidance. And that—where requirements can't be met, it is acceptable to deviate, and that—or perhaps even to summarize what the overarching principles were...I guess the best example would be, in*

the introduction, to clarify that there was a possibility for the principles to be applied, even if the requirements and the rest of the guidance—weren't explicitly followed; so long as there was clear justification as to why not. [ID# 10]

2.1.1.2 Clarify aspects of the guidance

Eleven participants described aspects of the guidance that could be clarified in order to reduce confusion and inconsistent interpretation and implementation among the people using the guidance. Three participants discussed specific points of language and definitions, including:

- Quality tolerance limits: A participant described that, three years after issuance of the R2 revision, they are serving on a committee looking at how to interpret quality tolerance limits aspects, due to confusion that still exists about this terminology within different companies.
- Certified copies: A participant noted confusion around what counts as a certified copy:

  Just to come into my mind, there's an issue regarding certified copies of what is exactly meant, and just focusing, for example, if you replace an original by a copy, if you copy, for example, an ethical build which normally goes to a sponsor, but then it's distributed to a concerned investigator or other parties—this should also follow some rules that we will provide a copy which is a one-to-one copy of the original because the photocopiers and printers we currently use over all the world are not just making photos; rather, they're scanning information, converting it, and printing it out, and sometimes they give some weird printouts. There should be some clarity. For example, this should also focus on getting clarity on how we should implement processes here. [ID# 06]

- Overall consistency throughout the document, including between terminology used in the R1 and R2 versions: A participant commented that, while ideally the entire document would be overhauled as part of the renovation to ensure consistent terminology throughout, at a minimum, the introduction should clarify which version takes priority in the event of inconsistencies between R1 and R2 (see also Appendix B, reference B8).

Regarding issues that should be clarified in the renovation, three participants said it would be helpful if the revised ICH E6 GCP guidance specified how the revised ICH E6 GCP should be implemented and noted that it would be particularly useful if they were to provide concrete examples, case studies, and scenarios of best practices, since having more details related to implementation could help reduce instances of the guidelines being interpreted differently (see also Appendix B, reference B9):

Well, we're hoping that, with the revision, it provides more clarity, maybe different details that—related to the everyday research. If you—if anyone's had a chance to review the changes in ICH GCP, they're quite broad. Interpretation could be varied depending on what project I'd be

working on. And sometimes…when we're doing these projects, you could see it a different way and obviously different regulations bodies could interpret differently. So, I think sometimes a little bit more detail might be helpful to provide more guidance. We're hoping that could be one of the recommendations that people are thinking about. [ID# 01]

Three participants suggested that, for purposes of clarification, it would be helpful if the renovated guidance included a preamble that clearly states the purpose of the guidelines, including a statement that the document is just guidance and is not intended to be prescriptive, as well as a brief listing of key points, perhaps broken out by role, to which different people should pay particular attention in the guidance:

At least maybe put in the front this is the key information that you really need to look at. And maybe have it more—I don't know, things to just—like infographics, things like that: so that it would highlight just the key information, what are the things that you really need to look at. And maybe you could have it—this is just as I'm talking, thinking about, but maybe could there be like, if you are an investigator, here are the key things that you need to pay attention to? If you're a study coordinator, here are the key things. Maybe it could be real specific, or something like that. And I know they have the sections. But if there was just some way to make it more digestible for people. [ID# 17]

Three participants stated that the ICH E6 GCP renovation should aim for a common understanding of the guidelines across all parties who use the guidance (eg, investigators, auditors, clinical operations personnel, etc). However, these participants also acknowledged that, with the guidance having been created and used by so many different parties, the final content will always be a compromise. A participant stressed it could be helpful for the guidance to rely more on principles and less on trying to serve as a one-size-fits-all type of document, while still establishing firm quality standards see also Appendix B, reference B10; and Appendix C, reference C5):

I think there are, at the minimum, two different pillars. One is really the document or the documents overall, and the other thing is having a common understanding what is meant with the guideline text. There is possibly a big difference between how a principal investigator or an academic institution is reading the document or a health authority inspector. Even there, there are big differences. Or, in the company, as I'm running the quality assurance department, including the auditing department, the auditors are possibly reading the guideline text different than someone from clinical operations, and I think that's caused also some issues because everybody wants to avoid an inspection observation, especially a critical one, a warning letter, and all of that—doing something which compromises the mission and approval, and therefore, it needs to be understood what is the formal deviation from ICH GCP and what is causing problems because it's impacting patient safety and data integrity. [ID# 05]

Finally, participants discussed clarifying the ICH E6 GCP guidelines in the context of training. Two participants suggested that the renovated guidance could include a section of frequently asked questions (FAQs), which could be especially useful during GCP training or for people who are new to research, as well as for helping to ensure consistency in application among people who are using the guidance. Participants also suggested that, following the renovation, ICH should provide training materials for how the revised guidance should (and should not) be used. A participant additionally suggested that it would be helpful if ICH could establish a resource for answering questions about interpretation and implementation (eg, a helpline) (see also Appendix B, reference B11, B12 and B13):

> *I think having FAQs and cases or scenarios would be beneficial as a supplementary document. That's also easily accessible, therefore. And so, a lot of times if you're training, you'll fall back on it. So most of the times when we run our training, we'll reference GCP processes, we fall back on the guideline. But you need to have enough experience to go back and reference it. And unfortunately, a lot of people that are starting the work, they start—or the inherited the template that they learned from somebody else. So—or they don't know where to start. It is pretty much the last thing that is printed because there's other issue clearly from the fact check or an ethics committee that comes back and they go back and look at it. So, unless you're experienced enough you don't need it—having FAQs and scenarios, I think that would be beneficial that applies in a broader group. [ID# 01]*

2.1.1.3 Make more user-friendly and operationally feasible

Ten participants discussed general aspirations for making the revised ICH E6 GCP guidance more user-friendly and operationally feasible. Seven of these participants described the importance of simplifying the guidelines and requirements, where possible (with one expressing concern that the guidance is going in the opposite direction and becoming increasingly complex). Participants indicated their belief that simplifying the guidance would make it more comprehensible and lead to people using ICH E6 GCP more frequently. They also pointed to parallel efforts to simplify documentation provided to patients, such as consent forms, in which recent attempts have been made to lead with the most pertinent information and to reduce the overall amount of information provided, to make it more likely that patients will read the forms (see also Appendix B, reference B14):

> *…look, if you simplify it, people get to use it more often and it becomes the number one tool that people go to. Most of the time…if it's too broad and only one or two people understand it, they don't use it. And usually, they have a policy, and have a cheat sheet, and a guideline, and a lot of information to explain the policy. And then, even the people use the supplementary document rather than the main document. So, I think if the terminology is more relevant and simple, I think people will actually relate to it. [ID# 01]*

My original hope had been for simplification, but I don't think that has been met, per se. I appreciate that ICH provides the stabling and to try and assess people with the conduct of clinical studies in a way that ensures that the data generated then can be used broadly across regions. But I also understand that they are quite prescriptive... And to be honest, in my experience, some of them have started to be viewed as gospel by, for example, ethics committees and regulatory authorities. So, some simplification or leeway and what was permissible was what I hoped. Obviously, that's not been achieved. Instead, it's going towards the other direction, which, it seems to be, providing additional requirements that will have to be followed. [ID# 10]

Participants noted that simplification of the ICH guidance could also extend to simplifying the training requirements, for example, by reducing the number of duplicative trainings that seem to be required under the current guidelines. A participant further expressed that they hoped that the renovation would serve to reduce duplication of effort across all study processes (see also Appendix B, reference B15):

I think also hopefully that there is a lot of systems in place of research that seem to be duplicative. And when you're kind of doing the same thing for different—so just say as an example, for GCP training, a certain sponsor might want you to do their GCP training. And then, another sponsor might come along and say oh no, I've got—for this GCP you have to do ours. So, things where—and now Trancelerate has come out with basically a standard to say okay, if you do this GCP training and it meets the standards, then sponsors will accept that GCP training across the board. So, if there is any way through the revision of these guidelines to make it so that it reduces the inefficiencies and duplication of effort that often occurs in clinical research. [ID# 17]

Some participants also cautioned that excessive complexity in GCP guidelines and/or training could have an adverse effect on patient safety, noting both that as processes become more cumbersome, mistakes become more likely, and that trial personnel may focus on documentation over patient protections. Excessively complicated procedures also increase the number of people who are involved with the data, thus increasing the likelihood that data quality and patient safety may suffer (see also Appendix B, reference B16):

The other point, I think this whole thing needs to be seriously simplified because—and this is outside the type of research, too, applied to—because I believe that the level of bureaucracy hit such a point that even if people are quite intensively trained, it's so huge that, even willing to comply, people make mistakes because it becomes too cumbersome. With, then, all the legislation on top that they need to comply with, it's just becoming too much. And people are so much focused on the documentation that they actually forget about the real protection. [ID# 19]

Five participants elaborated that the complexity of regulations can be a disincentive for investigators, which is ultimately harmful for the research enterprise because, when potential investigators choose not to get involved in research, this may exclude parts of the patient community served by these physicians as well. The burden of trial complexity was described as being particularly high for small single-site trials and for investigator-initiated studies (see also Appendix B, B17):

> *The vast majority of people who are not being put on clinical trials in part because of the complexity of clinical research and the bureaucracy associated with it—because of all the bureaucracy and because of all the effort required to set up a trial and so forth that people are not engaged. And so, we have, depending on the disease or so forth, five to ten people involved in research and in terms of the community, well it should be much higher than that. It should be higher than that because it's a big problem when one thing is that we don't know what the evidence is. [ID# 02]*

This participant further described that ICH E6 GCP ideally needs to be fit for purpose, stating that many of the trial activities that are currently required are not helpful and do not make sense for many types of trials, as well as being time-consuming and burdensome. The participant noted as an example that 20-page consent forms may be required for a chemotherapy trial, but only a one-page consent form is needed when the patient is receiving chemotherapy as part of regular medical treatment. They described that they are not suggesting trials not have oversight, but that this oversight should be applied more judiciously so that it is fit for purpose (see also Appendix B, reference B18).

Finally, one participant commented that, to make the ICH E6 GCP guidance more user-friendly, the guidelines need to integrate and cross-reference other E guidelines, such that people are comfortable working within the family of E guidance documents and are able to seamlessly use sets of related guidelines together:

> *So this R1 has a little bit more reference to other ICH E guidelines… The very first written didn't have any reference at all, and I still think that E6 needs to be—"embedded" is the wrong word—but it needs to be part of the family of E ICH regulations in that you can't just look at E6 without having looked at E8 or some of the population ones. So there has to be, first of all, just a lot more references, but somehow actually making those references really kind of an integral part of how you would actually implement E6.… That's where I think E8 is going to come in. E8 for me is very much, you can't start E6 until you've made some assessments in E8. So I'd be very pleased to see those two kind of hand in hand and people working with both of those guidelines together as opposed to separate. [ID# 12]*

2.1.1.4 Include a variety of stakeholders in the revision process

Five participants noted the importance of including a wide variety of stakeholders in the revision process, specifically proposing that the following be included:

- Patient organizations
- Community organizations
- Representatives from academia
- Representatives from ethics committees
- Noncommercial researchers
- Pharmaceutical representatives
- Regulatory representatives

Participants stressed that having people who represent a wide range of trials experience involved in the revision, and not just pharmaceutical representatives and regulators, can help to ensure that the final set of guidelines is practical and operationally feasible. Giving more types of stakeholders a voice at the table, participants said, can also ensure that different types of research are taken into account when the renovation is created and can enable formerly less well-represented groups, like patients and investigators, to share their views about which parts of the guidance are necessary and which are less helpful from their perspective (see also Appendix B, reference B19):

> *Just don't make it too complicated, and do not only have quality and inspectors sitting around the table in the working group, because then it's possibly—the outcome is possibly a document which is not operationally feasible, more or less. …If auditors and inspectors are sitting around the table, because they are not the ones running the trials, they are the ones inspecting or auditing the trials, it can get very formal because their expectation and documentation and doing things is a little bit different, and it doesn't mean that the expectation is always increasing the quality or is protecting the patient more. Sometimes, you should also get advice from people who are really involved in the clinical trials from a practical point of view, like study nurses, investigators, patients, clinical operations people—these kinds of things. [ID# 05]*

> *The problem is that, currently, the ICH assembly, or the kind of stakeholders which are around the table are regulators and drug manufacturers. And so, I believe that even I do recognize that some of those individuals, personally, may have experience of academic work and some of its challenges, or may have a larger view on the landscape of clinical research, in general, but they are not those stakeholders themselves. So, I believe that if ICH is aiming to be*

applicable beyond its initial remit, they need to enlarge the stakeholders to bring onto board the relevant expertise so that the guidance can be nuanced enough. Because otherwise, it's basically making the research heavy, expensive, without obvious benefit for research participants at the end. [ID# 19]

However, participants said it is also important to include the pharmaceutical and regulatory perspective in the creation of the revision, in order to ensure clear guidance that will not lend itself to misinterpretation and negative consequences from inspections in the future:

I don't know what the process is going to be for the next renovation. But I would hope that pharma would have more than two representatives on this council because we're the ones that are on the forefront of trying to deal with these activities. I'd rather not have regulators putting things together and then us giving feedback; I'd rather it either be more of a collaboration or how can pharma put things forward and have the regulators determine if it's feasible. [ID# 16]

A participant also pointed to the importance of ensuring that the stakeholders involved in the revision represent different geographic regions and that sufficient numbers of stakeholders from each region are included:

The representation of potential stakeholders from different regions of the world. I don't think it's sufficient to appoint one or two people from the global south to say the global south was represented. Or, it depends on, maybe, since the scope is still geographically limited, one could say we don't need the global south to be represented. [ID# 04]

2.1.1.5 Be mindful of length of revision process

Three participants discussed the length of time it can take to revise guidance, indicating that it is not ideal if it takes several years for the renovation to be accomplished (appendix B, reference B20 and reference B21):

I think the other concern we all have about the regulation is that it's going take too long. This is a big problem right now and needs to be addressed now, and it's not being. I know it's going take five years and just an unacceptable time frame really. [ID# 02]

However, participants also acknowledged that there are steps that can be completed while the renovation is being awaited, and that the existing ICH E6 GCP guidance and regulations can be used as a framework for short-term improvements. One participant suggested that existing groups come together to think about short-term fixes while longer-term guidance is being created. Another proposed generating guidelines for best practices and continually updating training to accommodate new best practices as they are created:

We've listened to FDA, and we've listened to EMA. And they are telling us that the technology is moving faster, much faster than the possibility of implementing under regulations. So, everything is happening at a pace that it's difficult to catch up. But I think because GCP is oriented to full-registration research in the way it's written, I think although it's still a guideline for other types of research, there is a window of opportunity there to obtain what is coming as it is incorporated by regulations and to ensure that it is implemented through best practices through the guidelines. And there's a gap of time between new technologies coming up and regulators issuing guidance. And in that window, GCP should be looking at how are we going to go with this process to help people adapt to regulations by using best practices and generating the best type of quality possible from this type of generating evidence procedures… I think the guideline in itself it's guidelines for best practices. And when we are on the ground running studies, working with investigators, training CRAs, they need to adapt to the latest versions and be trained in them. And we keep training them. [ID# 03]

Thinking about how to ensure that the revised ICH E6 GCP guidance will be relevant for the greatest length of time possible, particularly in the face of rapidly changing technologies and systems, two participants suggested that the revision be written at a high enough level that it will still be applicable in the future, so as to avoid the need to continually update it. Thus, the revision should strike a balance between setting forth general principles that will continue to apply with future changes in technology and providing sufficient detail to guide researchers today:

My expectation of ICH E6 is, whatever they're going to write—and I don't know how many documents they're going to talk about—it's really taking the way into consideration how clinical trials are conducted today, but also how they will look like in the future. …I think that's very tricky, especially if you take into consideration the long development process for ICH guidelines. The moment the guidelines are going to be finalized, they're already more or less outdated. Therefore, on one hand, you need to have a general document where the wording is high-level and can also be read for future technology, but on the other hand…the guidelines should give you enough detail that you know what you have to do, and I think that's a tricky way. But the guideline was written in a way before that you were able to work with it 25 years, and you would still be able to work with it. It's just too—For me, it doesn't need to be updated. We could live with it. [ID# 05]

2.1.1.6 Highlight the purpose of ICH E6 GCP

Nine participants, in describing their aspirations for the ICH E6 GCP renovation, discussed the importance of remembering the overall purpose of ICH E6 GCP throughout the renovation process. Of these, five emphasized keeping in mind the fundamental purpose of research and of GCP, stating that, ultimately, clinical research is about improving patient outcomes, and the intention of GCP is to protect patients and ensure data integrity (see also Appendix B, reference B22):

My hope is that for practicing clinicians who are enrolling patients on research trials, I hope that GCP maintains its important role of documenting what the appropriate steps are to ensure the patient safety and keeping patient well-being at the forefront of all of our research efforts. [ID# 18]

Following on the idea that the purpose of GCP is protecting patients and ensuring data integrity, four participants noted that the goal of ICH E6 GCP is to establish guidelines for enabling quality research, allowing well-intentioned people to do good work to the highest standards (see also Appendix B, reference B23 and reference B24):

It should be clear that the principles are exactly that; they're principles, and they're not strict, they're not prescriptive requirements, but rather a recommendation as to how research is conducted well; and that while such requirements may be more strictly applied to pharmaceutical firms or conducting research, such requirements need be less applicable, and there should be an additional scope for investigators to apply the principles more loosely…I think it's good. It applies to all clinical research for pharmaceuticals, and I know that all investigators, as far as I know, are aware of the requirements of GCP and do intend to follow them. Obviously, the doctors are generally very ethically oriented people. They are people that just want to do the best for their patients and always want to conduct high quality research. So, they are aware these guidelines exist and they do try and follow them. [ID# 10]

By contrast, participants also pointed out what the purpose of the ICH E6 GCP guidance should *not* be, namely, that it is not a prescriptive checklist that needs to be followed exactly (n=3), nor is it intended to be used as a policing tool for audits or inspections (n=2):

What I'm going to hope is that, beside keeping the overall intention, like protecting patients and ensuring data integrity, the guideline is moving away a little bit from a checklist exercise and a tool very much misused for audit and inspection to a document or series of documents incorporating new technologies and new ways of working, but also enabling investigators, academics, ethics committees, and sponsor a successful partnership with the outcome that we get drugs to the patient faster, but that these drugs are safe. [ID# 05]

Participants described that the ICH E6 GCP guidelines have begun to turn into a checklist exercise and that adherence to them has become progressively stricter. Participants explained that this could be due, in part, to fear of potentially missing something related to ICH E6 GCP during a trial and the resulting desire to avoid negative consequences during inspection (or at the extreme, even jail time). One participant acknowledged that the current guidelines are written in such a way that it would be easy to convert them to a checklist and/or a legalistic tool that can be used to police whether study personnel are conducting their roles appropriately, but this is not in line with the spirit of the document, which exists to help study teams do their work better and ultimately, to safeguard patient

welfare by ensuring that new products brought to market are safe (see also Appendix B, reference B25):

> *It's kind of nebulous, and we blame a lot on ICH, and I think, well, I don't think Japan, the US, and whatever European states that initially set this are really to blame for this. They made a first effort. The real fault lies in the implementation of them, and the minute we put this in a contract that you have to follow ICH, people seem to go nutty, including regulatory agencies. Everyone thinks they're going to end up in jail, but I'm not sure which jail because I don't know that'd be a big problem in Canada, but in Italy, as we know, they've gone insane and to the point where people won't do research. And I think it has to be a shared responsibility. And we're getting there, right? We're going to more centralized ethics boards, which are great. [ID# 13]*

> *Other than that, it stays in the way it is written now, in a lot of bullet points with small numbers, which you can easily use always as a little law, "You have violated against No. X.6." …From an auditor perspective and a quality assurance perspective, yes, I like it, but I don't think it's the way it should be written. …I would go away from this—it's written like a checklist currently—I would go away from this, and I think it would increase the acceptability of the document in certain areas. From a quality assurance perspective, the document is going because you can absolutely use it in this way—you can go to your investigator and say, "You have to do this, this, this, and this," or you can go to your internal department to your specs department and say, "You have to have your training records, your SOPs, you have to validate your programs, and if you do a data monitoring committee, you have to have this, this, and this in addition." I think that creates a feeling for a lot of people that this document is more or less, like, not a guidance, but it's policing them. That's how I would say it. It's used more like, "Hey, the police are coming, and you violated" instead of "Hey, this is the guidance document which all helps us to do our work better and really ensure that the drugs we are bringing to the markets are safe." [ID# 05]*

Finally, two participants noted that, as part of the purpose of ICH GCP, a goal for the ICH E6 GCP renovation and indeed, for clinical research overall, should be to encourage the reintegration of clinical research into clinical medicine, as this will continue to encourage more of clinical medicine to become evidence-based and will provide more patients with opportunities to contribute to the development of new therapies (see also Appendix B, B26).

2.1.1.7 Modernize to accommodate new technologies/processes

Six participants emphasized that the ICH E6 GCP guidance should be updated to accommodate changes in technology and study processes that have arisen since the guidelines were first developed, most as a result of today's digital environment. Five of these participants commented that

the renovation should specify best practices for ensuring data quality and integrity for a variety of new data capture technologies and procedures, including:

- Paperless trials and electronic documentation such as electronic medical records, eCRFs, and e-consent: Participants described several new forms of digitally based source documentation and requested that the ICH E6 GCP renovation establish guidance and best practices for how study teams can prepare for paperless trials, as well as what the considerations for digitally based communications are with regard to trials (see also Appendix C, reference C6, and Appendix B, reference B27):

  > *Overall, as research evolves, technology evolves—a new way to investigate new type of innovative products appear. I'm hoping the guidelines can also adapt and go with the new incorporations on how to do and run studies and research. And in concrete, we have now more real-world evidence studies where we may fear that the quality may not be in a randomized controlled study where we are generating all the data. We have EMRs, and we see them more and more coming up. And we see institutions using different type of EMRs for the same case—same patients. How does that play in a single study where we need to collect data from one case? We are seeing paperless trials, at least the concept has been introduced. We don't see them happening a lot, but we think they may be coming. So, how we prepare for that or for specific parts of studies that become paperless. [ID# 03]*

- Remote data collection, such as telemedicine or sensor-based data capture: Participants described that the E6 guidance is out of date with regard to the types of digital technologies now used in trials and noted that the provision of guidelines for ensuring data quality and integrity across the numerous new types of remote data collection technologies would be helpful (see also Appendix B, reference B28):

  > *The original document was written in 1996. The addendum came into force in 2016, and they were only allowed to add certain context. Starting to include the new ways we are running clinical trials in the meantime with much more digital technology, electronic stuff, much more global, as well as the involvement of a huge amount of different partners, and that with the increased complexity. That is what's forced into a document which you cannot read fluently. There's also stuff in there which is not up to date anymore, and we have so many different trial types, studies, and data sources in the meantime, like real-world data. We're getting data out of sensors, we're even talking possibly about trials at home that the new document should somehow enable this kind of research. [ID# 05]*

- Machine learning and artificial intelligence: Participants described the rise of diagnostic technologies and potential new product development aided by artificial intelligence and requested that the renovated guidance address documentation in a machine learning environment (see also Appendix B, reference B29):

> *I think what we also need to consider is how the new technology fits into that, not only the new data sources, but also talking about machine learning, where the machine is possibly changing the algorithm and you don't have any documentation anymore, so there's nothing to check because the machine is doing it by itself. Is that going to be acceptable, or because it's not reading the current data integrity principles already out? [ID# 05]*

Process changes arising from technological advances were also discussed, for example, how monitoring and auditing activities are affected by in-home use of an investigational product and in-home data collection (eg, via Fitbit), when the monitor is not allowed to go to the patient's home. Three participants described that their aspirations for ICH E6 GCP included consideration of scenarios such as these and a discussion of quality-by-design, so that study teams will still be able to ensure data quality and integrity, as well as patient safety, in remote trials (see also Appendix B, reference B30):

> *The same if I'm using Fitbit, or Apple Watch, or some other sensor or variable. A huge amount of my trial is run at home. Nobody can inspect or audit the patient at home. What will be the guidelines—the recommended way to give guidance—on how to ensure the principle of data integrity by implementing a quality-by-design process and these kinds of things? How can we ensure that all these ways of running clinical trials can be possible?…I think that is more introducing a proactive quality-by-design thinking, because if you are not allowed to go to the patient's home from an inspector or auditor's perspective—or from a monitor's perspective—and all of the treating physicians and investigators are possibly not seeing the patients so often anymore, or just during video calls, how can you prospectively plan that the patient is taking the drug, the patient is wearing his Fitbit, and that it's not the dog just running with it through the garden? So, you have to think a little bit differently to ensure that the quality of the data you are generating is acceptable for submission because you are sure that the data is reliable, and that's the data you want to create. [ID# 05]*

Another participant described potential new bioethical and legal issues surrounding GCP that have emerged from processes such as long-term sample storage and data sharing. This participant expressed hope that ICH would collaborate with bioethics experts, on a limited basis, to incorporate guidance about these issues into the E6 revision:

There are a number of papers published over the last 20 years and other issues, which are related to GCP about…the medical review of research, about informed consent, about community engagement. More recently, there are "hot topics" concerning the long-term storage of samples collected in clinical trials, ownership and governance of some samples, data sharing. I would really expect [ICH] to be aware of all this debate going on and to—not to take input from them. Otherwise, it's really kind of a schizophrenic approach where on the one side you have academic research of some bioethicists reflecting and on the other side you have ICH writing the GCP and they do not talk to each other. So, what's the point? [ID# 04]

Two participants noted that as technology advances and clinical research continues to enter into digital spaces, new partnerships may arise with vendors who have expertise in digital technology. These participants emphasized the difficulty inherent in regulating digital health partners, particularly those that have a large digital footprint (eg, Google or Amazon) but for whom the health field is new and who may not be familiar with ICH GCP:

How can I regulate players like Google or Amazon, who are much involved in digital health now but have possibly never heard anything about ICH E6? It's a huge burden for the ICH E6 working group, I would say. [ID# 05]

And I do know that some large technology companies that are moving into these areas don't really have a good grasp of what GCP is. …I will say we've worked with a large tech company who is driving forward with this idea of very patient-centric, decentralized trials, site-less trials. And when we've made a comment to them about, "Are you aligned with ICH E6 (R2) and our requirements," then they comment that, "Well, we're building that as we fly the plane." And one company has told me—at one of these companies when they sent the contract back to a big pharma company, their legal x-ed out the Treaty of Helsinki. And they're like, "I guess they didn't understand; maybe they think it's something to do with the European Union or something because they're doing it in the US," not understanding that this is actually a basic tenet of GCP. [ID# 16]

Two participants noted that the ICH E6 GCP guidance is outdated with regard to technology and that old information should be removed from the 1996 version and 2016 addendum so as to modernize and make the guidelines more relevant to the current state of clinical research. In addition, a participant noted that inspections are still being conducted according to the R1 model, instead of following the newer R2 guidance, so the renovation should emphasize that the process of conducting inspections needs to be brought up to date to match the current guidelines:

And I also see companies, when they talk about their inspections, that they are getting inspected relative to what we call the old days. So, if you're trying to implement new things, but

the inspectorate is still working on old things. And so, in some ways, that feedback loop of rewarding those who are implementing, it's still not there yet. [ID# 16]

2.1.1.8 Update study roles

Three participants pointed out gaps in the existing ICH E6 GCP guidance related to study roles and flagged these for overhaul in the revision. Two participants described a need to explicitly include patients and communities as stakeholders in the guidance, with one suggesting that in the same way investigators and sponsors are given their own chapters in the guidance, the renovation might consider adding a chapter on patients, to highlight the important role of patients and caregivers in clinical trials and to thus emphasize the patient-centric focus of research (see also Appendix B, reference B31):

In second place, there are communities and patient organizations, and this is a major shortcoming in the previous ICH guidelines, that the patients and communities are not even mentioned as stakeholders in research. They are regarding investigators, sponsor, ethics committee, regulations, regulatory. But I think, in 2019, we already know very well how important it is to engage with communities and with patients to make research ethics pertinent, etc. So, it's pretty strange that they are not mentioned in the guidelines, as they should, as stakeholders. [ID# 04]

A participant pointed out that one of the most important study roles, that of study coordinator, is not currently listed in the guidance and recommended that this role be added as part of the renovation, due to the critical part that coordinators play in supporting trials logistically and administratively (see also Appendix B, reference B32). Adding this information, perhaps to the glossary or the investigator guidance, could empower and recognize coordinators in the work they do. Similarly, another participant suggested that the roles of monitors, auditors, and inspectors should be updated, as monitor responsibilities have changed substantially since the guidance was first written and many of the tasks that the guidance specifies for monitors are now being carried out by other types of study personnel:

The problem with the monitor itself is that that's possibly something which also needs to be updated, because when the document was written originally, the monitors became a huge amount of responsibility. They are actually the only role which is clearly described under the sponsor section, and this role is not existing in this way anymore. None of the roles and responsibilities which are on the monitoring are done by other people or other functions, and that probably also needs to be clarified. Also, the introduction of roles besides the clinical monitor is useful. [ID# 05]

Finally, a participant noted that the guidance should acknowledge the contributions that noncommercial researchers make to the clinical research enterprise, by calling out these researchers as stakeholders as well.

2.1.1.9 Ensure transparency

Three participants discussed that they would like to see more transparency as part of the ICH E6 GCP renovation. Two participants requested greater transparency surrounding the process of how revisions are created, noting that it is currently unclear whether rules for creating the renovation exist and, if so, what they are, as well as what, if any, pre-work will be done to create the revision, how input on the renovation is being sought ahead of time, and how feedback on the revised guidance will be solicited (see also Appendix B, reference B33):

> *Will they work according to some rules? Will they work by consensus? I don't know what. Did they precede this work by a desk review to get all this input from all the things which have been published about GCP-related issues? So, it's really a little bit a matter of secrecy around the whole procedure itself. [ID# 04]*

A participant also requested that ICH be transparent about the rationale behind the creation of guidelines, noting that this would allow study teams to evaluate the rationale in the context of their own research, enabling them to choose whether they follow the guidance exactly or deviate from it on the basis of differing context or situation:

> *The expectation would be, one expectation would be, for the renovation, I think it would be good to have an explanation, elaboration document on the side that provides more explanation and how ICH arrived at this particular recommendation, and the rationale for it because it would make it easier for the people to understand, and then also to consciously deviate from it because they can then say, okay, look, it was implemented based on this background and this rationale, but in our situation, it's different, so we need to deviate or I can say it's exactly that and it makes good sense. [ID# 09]*

A participant described that they would like to know who is involved in creating the ICH E6 GCP renovation so as to determine if the creators are sufficiently representative of the clinical research enterprise, both from a role perspective, as well as from a geographical perspective:

> *Who is writing [the renovation]?... Who is it sitting around the table? How they have been selected?… I mean, clearly, there is a big need for transparency about the constituents, their role, the representation. [ID# 04]*

Finally, the same participant described that they, along with a team of others, had previously submitted feedback on the R2 addendum to the E6 guidance but did not feel that their comments

were taken into account when that guidance was created. The participant thus expressed a desire for ICH to be transparent about what is being done with any feedback received for the current renovation, commenting that it would be nice to know whether individual contributions have any impact in the creation of the final guidance:

> *I hope that this will be achieved through a transparent process where not only people are given the possibility to contribute, but where it will also feed back to individuals and organizations about what was done with their feedback…because I, with a group of other colleagues, with a group of noncommercial researchers from Belgium and from lower-/middle-income countries, we sent input, feedback about the previous revision of ICH guidelines, the one which was also in the addendum in 2016. We were thanked for the contribution, but I don't think it was taken into account, and it would be nice to know how, why. Yeah, there is a substantial investment in time and the commitment from people who make or give input. So, it would be fair to know what was done with our input, and if it was not taken into account, great. It can be fine. We may have been a minority voice. No problem with that, but it would be nice to know. [ID# 04]*

2.1.1.10 Miscellaneous recommendations

Two participants suggested more sweeping changes to the ICH E6 GCP guidance as part of the renovation. Specifically, one participant proposed restructuring the guidance from a task- or group-oriented approach to a process-based approach that is oriented on the 13 GCP principles. Under this model, the guidance would be reorganized around principles that are shared across groups (such as record keeping, which is required for investigators, sponsors, and IRBs and which is detailed in the current guidance as a task underneath each of these roles). Instead of role-based chapters, the revised guidance would have process- or principle-based chapters (eg, record keeping, oversight, reporting). This participant further noted that, when the ICH E6 GCP guidance was first developed, the concepts it described had not been well detailed elsewhere, and it made sense at the time to organize the guidance around specific roles. However, clinical research has evolved so much since the introduction of the E6 guidance, and the guidance is now sufficiently familiar to most parties, that reorganizing it on the basis of principles should not be too challenging (see also Appendix B, reference B34).

Finally, regarding suggestions for creating the revision, one participant stressed that the existence of the renovated guidance needs to be publicized, and the guidance should be made readily accessible. They speculated that the R2 addendum was not well known, since many researchers in their experience refer to "the 1996 guidance," and recommended that the present renovation be well communicated and easy to find:

> *I think there were some improvements in the addendum, but maybe the addendum is not best known. Also, when I review papers and when I review protocols as an ethical reviewer, I see*

that a lot of researchers keep on referring to the 1996 guideline. So, perhaps, for the next revision, there should be really some much more communication activities about the new guidelines. They should be easier to find in websites, because I really have the impression that the addendum is only known by a limited group of people. Already, this is a problem in academic research. I think it is back in the academic research environment. [ID# 04]

2.1.2 Aspirations for the specific sections of ICH E6 GCP

2.1.2.1 Section 1: Glossary

The three participants who expressed aspirations for the glossary section focused on suggested changes to definitions they felt could lead to confusion. Two commented that the guidance states that the terms "clinical study" and "clinical trial" are to be used synonymously, but legislatively a clinical trial is a subset of a clinical study. Furthermore, the US and the EU use "study" as an umbrella term that could encompass both interventional and noninterventional studies, while "trial" most commonly refers to an interventional trial:

I think one of the main concerns is that it's a bit ambiguous in the guideline in that it actually says, in the definition of a clinical trial, the terms "clinical trial" and "clinical studies" are synonymous, which is not the case when it comes to the actual legislation, certainly in the major territories in the EU and the USA. A clinical trial is a very distinct subset of a clinical study. And I think that's led to the ICH guidance—some people trying to fit that to studies where it isn't appropriate. [ID# 11]

A participant also described confusion arising from the use of the terms "approval" vs "opinion," noting that the guidance uses "approval" when referring to IRBs but uses "opinion" when referring to IECs. Per the participant, the use of the term "opinion" is misleading because, ultimately, an approval is needed from both entities in order for a clinical trial to proceed. The difference in terminology may reflect cultural differences rather than differences in procedure:

A cultural difference is between—let's call it the United States and Europe are a little bit different, of course, in this, because the Europeans say, "Oh, we just need an opinion, and the opinion is nice," but at the end, it's also an approval here in Europe you need, so it should somewhere reflect in these things that we talk about an approval by the IRB or the ethical committee for the clinical trial. And the Europeans don't need an opinion, we need also approval. It's the same in Japan. It must also be an approval—we have the same four steps. It's an approval, an approval with recommendations, an approval with objections, or a denial. The same four steps as in the US, but in the glossary it's just talked about an opinion by the ethical committee, but it's an approval for us also. [ID# 06]

Finally, one participant suggested a change of phrasing around adverse drug reactions, describing that the way the definition is currently written brings the ICH guidance into conflict with another regulation, a conflict that could be resolved by deleting the phrase "the relationship cannot be ruled out" from the definition in the ICH guidance. This participant further noted the importance of having consistent definitions across regulations, particularly for people who are new to or being trained in GCP (see also Appendix B, reference B35).

2.1.2.2 Section 2: The Principles of ICH GCP

Three participants described individually held aspirations for the section on ICH E6 GCP principles. The first requested that a distinction be drawn between GCP in general and ICH GCP, noting that it is important for people to understand that, for nonregulatory or investigator-driven studies such as hypothesis-generating proof of concept or academic trials, the full burden of ICH E6 GCP need not apply:

> *I think one thing is where we have to be careful is what do we define as GCP? Are we talking about good clinical practice or ICH GCP? For me, working now in an area which is resource-constrained where there is a lot of nonregulatory studies and a lot of investigator-driven studies, I think it's important to make sure that everyone understands that not the full gamut of ICH GCP needs to apply for every single investigator-driven trial or hypothesis-generating trial. I would like to see from an ICH GCP with the initial process that it's made clear or it's communicated—I don't know—educated to investigators, to sponsors, to CROs, to funders that not every single trial needs the full, full, full ICH GCP burden. …The 13 grounding principles of GCP, that's what I refer to as GCP. And ICH GCP—is that what you have been sending me. The ICH addendum E6 R2. [ID# 08]*

The participant noted that such studies still need to follow the main principles of GCP in terms of ensuring that study design, monitoring, and reporting are scientifically correct and that patient rights are respected, but complete compliance with ICH E6 GCP regulatory requirements should be reserved for regulatory trials with a marketing indication. Furthermore, particularly for trials in under-resourced areas (eg, malaria research), requiring the full program of ICH E6 GCP could stifle scientific progress. Yet, many funders reflexively require that studies adhere to all components of ICH GCP (see also Appendix B, reference B36).

In the absence of an existing clarification, the participant described that sponsors tend to default to using ICH E6 GCP for everything. Other industry professionals also often do not draw a distinction between general GCP and ICH GCP, with the result that following ICH E6 GCP is seen as the safest option and is also adhered to excessively (eg, with research professionals aiming for far greater than 100% compliance):

Because I feel that very, very often, it's not the ICH or the regulators. But it's the interpretation further down either by funders who just say ICH GCP for everything. And very often, also by the professionals in the industry or in organizations like mine who don't see that difference. GCP is GCP—it's ICH GCP. …very often, regulatory colleagues, quality colleagues, also others in operations, tend to do—if you could do 100%, they would try to do 150% to comply with any guidelines that are… So, there's ICH and there's the 12 guiding principles of GCP. Let's do ICH for everything because then we are on the safe side. [ID# 08]

This participant was careful to note that they were not lobbying for a lesser standard in protecting trial participants, but said that ideally the renovation to ICH E6 GCP would address the issue of when GCP vs ICH E6 GCP should be followed by providing education and clarification in the guidance. One possibility might be for ICH to describe that Section 2 covers essential principles to which all research must adhere in order to protect participants' rights, safety, and welfare and to obtain high-quality data by conducting high-quality trials, but then to specify that the rest of the document is intended for regulatory trials only:

And where I—I think that it's more educational as such and I don't know whether ICH actually could make that clear in some communications, that this is really what we need if we want to consider our clinical trial for the approval or label change of a medication. And these are the things that are essential for everything as a guiding principles Declaration of Helsinki… to make clear, a lot of people just look at ICH E6 or ICH whatever, GMP, GOP—this is not a general guide on how to conduct research. These are the very specific documents to give guidance on what the research has to do if you intend to take the results at some stage to a regulatory authority which is part of the ICH consortium. [ID# 08]

A second participant suggested that the 13 principles could be **c**onsolidated to three—data quality, patient safety, and ethics—with the remaining principles viewed as actionable subcategories that support these 3 concepts. Reorganizing the principles in this way might lead to each of these sections having a greater impact:

I think some of it can be consolidated a bit. I talked about there's 13 principles, but really there's three. One of them is data quality, one is patient safety, and one is about ethics. Then the rest are a little bit of how you achieve those things… I understand why they have them broken up like this, because there's a certain point that they wanted to make, but I wondered if they could be categorized as patient safety or ethics or the number of 2.1 that's going to be conducted in accordance to ethics and Declaration of Helsinki. Then what other principles that are maybe 2.1.1 that really emphasize that or kind of lead up to some of that?… My biggest, I guess if I want to call it "complaint," is that I think these could be layered. Not that they're not all good, but maybe it's having a bigger bang or bigger effect if you actually kind of group them and saw them as layers and as those three things: ethics, safety, and quality. [ID# 12]

Finally, one participant expressed support for using the GCP principles as the basis for investigator training, stating that in their experience, sites do not always follow what is written in the GCP and need frequent reminders. This participant suggested that while a training program covering all the sections of the ICH E6 GCP guidance might ultimately be beneficial, the section outlining the 13 GCP principles would be a good place to start; training effectiveness could then be gauged and the program scaled up from there.

2.1.2.3 Section 3: Institutional Review Board/Independent Ethics Committee

Four participants described aspirations for revising the guidance on IRBs/IECs. Of these, two suggested adding guidelines that would make the operations of ethics committees more transparent, such as describing IRB/IEC procedures and publishing membership rosters and voting records. Another noted the importance of thoroughly reviewing the existing IRB/IEC guidance as part of the renovation and updating any information that is out of date:

> *Then I think what also could help is to set some transparency rules on IRBs/IECs, so that they really need to publish their procedures. That we need to know who voted in a meeting, things like that. This could be—so, we have clear guidance on that. [ID# 23]*

A participant also suggested that the ICH think through how to incorporate the role of patient advocacy into the guidelines, noting that it is important to incorporate the patient voice in study design to help ensure more robust and feasible trials. This participant was unsure of the best location for guidance about working with the patient community on design and implementation but thought that the proper location was probably the E8 document. However, they suggested cross-referencing any such new guidance in E6 as well. Within E6, the participant stated that the best location for the guidance was probably within the section on IRB/IEC, as ethics committees would need have oversight over the interaction with patient advocacy representatives so as to ensure that no coercion or undue inducement occurred (see also Appendix B, reference B37).

2.1.2.4 Section 4: Investigator

Thirteen participants named aspirations they had for the ICH E6 GCP renovation of the Investigator section, with several suggesting revisions to multiple components of this guidance. The aspects of investigator guidance mentioned most commonly for revision were investigator responsibilities (n=5), informed consent (n=4), safety reporting (n=3), and adequate resources (n=2).

2.1.2.4.1 Investigator responsibilities

Two of the five participants who spoke about investigator responsibilities indicated that it would be important to update the investigator guidance to bring it into alignment with current regulations. Two discrepancies were noted. The first discrepancy was that the existing guidance implies that the

investigator is responsible for reporting SAEs, whereas current regulations now indicate that this is the sponsor's responsibility:

> *There's also stuff in there which is not in alignment with current regulations. It's not the investigator who is reporting serious adverse events to everybody. That's done by the sponsor. So, there needs to be some fine-tuning there. [ID# 05]*

The second discrepancy was that the investigator guidelines, as currently written, are US- or FDA-centric in assuming that tasks such as submitting to an ethics committee are conducted. A participant described that while some of this discrepancy can be resolved by following country-specific legal requirements (eg, in Europe, the sponsor is legally required to submit to the ethics committee, not the investigator), it would be helpful if the guidance were to incorporate more flexible wording (eg, "the party who submits") to account for such regional differences (see also Appendix B, reference B38).

Two other participants requested that the process of investigator oversight in remote trials be clarified. Two specific points of confusion were described. First, one participant expressed uncertainty about how physician oversight should take place for trials in which the investigational product is shipped to people at home, noting that both the frequency and route of monitoring in such situations are unclear:

> *So, to what extent does that oversight meet? Under that oversight, can they go in once a year? Can they have a video conference? As we come up with sensors and other things, does it just mean that the sensors do their thing and the physician reviews and signs off? I don't know. [ID# 16]*

Second, the other participant expressed confusion about who should fill the role of principal investigator (PI) for remote trials:

> *The other situation, there are more and more trials which are run remotely. But, there again, this notion of PI and what it means in this context, doesn't fit. So, for me, this is another thing that needs to be, kind of, understood better. In the types of trials we are running now, what is this role of PI? With whom sits the responsibility? [ID# 19]*

A participant also described that the ICH E6 GCP guidance on investigator oversight is inadequate for multisite or multimodality trials and should be clarified in the renovation. The current ICH guidance does not adequately correspond to real-life situations in which health systems in different countries may not be legally able to assign PI oversight to physicians either outside of the institution or in a different department within the same institution. Similarly, for multimodality trials—for example, when oncologists from different specialties coordinate a search for a biomarker across multiple types of cancer—it is unreasonable to suppose that one specialty should be given oversight over the other(s),

which is what the current notion of PI in such a situation requires (see also Appendix C, reference C7).

Finally, one participant suggested that the ICH guidance be updated to specify that the investigator should have greater familiarity with the profile of the investigational product.

2.1.2.4.2 Informed consent

Of the four participants who described that the section on informed consent should be updated, three stated that the guidance should indicate whether and how ICH E6 GCP applies to different forms of consent (eg, e-consent, delayed consent, waiver of consent, opt-out consent). One participant indicated that not taking circumstances that may call for such alternate forms of consent into account could cause harm by impeding research progress, as it may have the effect of removing choice from patients who might have otherwise elected to participate (eg, a registry that does not include patients from the very sick or very healthy end of the spectrum, as such patients may die or be discharged before full consent can be obtained; a waiver of consent would be preferred in this situation) (see also Appendix C, reference C8).

Regarding alternate forms of consent, a participant further noted that different regions have different regulations regarding consent, so it is possible to rely on local guidance when ICH could establish a global standard both for consent and for data privacy, since ICH E6 GCP is viewed by many as the ultimate guideline.

Participants also raised a number of individual aspirations related to the guidance on informed consent. One participant noted that with certain cultures or populations, such as indigenous populations, consenting processes need to be more flexible, as more culturally appropriate methods of obtaining consent may need to be used with these groups:

> *No one's arguing about informed consent, but the methods by which you obtain it are antiquated within the documents and culturally inappropriate in certain places. So, one has to recognize that there's variation internationally and even variation within countries. So, for example, our indigenous people, you don't obtain consent in that way. You have to talk to elders and go to people. So, I think what we need to do is allow people the flexibility to develop approaches that are appropriate for the population in question and really for today's times. [ID# 13]*

Another participant said the revised guidance should allow more flexibility in who obtains consent, as the most appropriate person may vary depending on the circumstances of the study:

> *The other part, I guess, is who obtains consent when it is necessary on an individual basis. Who is the most appropriate person to obtain consent? As you know, some countries say it*

should never be the investigator. Some countries say it should always be the investigator. And then there's all these wonderful things on the in-between. You see, they could make the case based on the situation. If a doctor's making $25,000 off of every patient, maybe they're not the right person to get consent. But if there is an issue that requires medical knowledge to that level and knowledge of the patient's history in order to interpret the information, maybe the physician is the most appropriate. So, no longer do I think there should be rules, but there should be areas to consider and rely on the investigators to make the cogent argument. [ID# 13]

This same participant argued that consent itself could be broken down into 3 main components: how consent is delivered, the unit of study to which the participant is consenting, and the criteria for waiving consent. This would move the process of building a consent form away from a checklist exercise and toward a more conceptual approach, in which the 3 key hallmarks of informed consent are incorporated into the consent process but research participants are no longer faced with consent elements that are not truly necessary for the type of study in which they are participating (see also Appendix B, reference B39):

One participant spoke about shortening or simplifying consent, given that consents are becoming so long and complex that they cannot easily be understood by many trial participants. Simplifying the consent process could also ease burden on trial staff:

…so for the patient, they need to understand what we are doing, and at the present time, the type of informed consent that they have, they cannot understand what they are doing. It's too complex for them, they cannot read 20 pages, long list of these names they don't understand, and we have to review this process with them, with the conductor, company, regulator, and patient. It's not a task for only one person. [ID# 22]

2.1.2.4.3 Safety reporting

Three participants raised safety reporting as an aspect of ICH E6 GCP guidance that could be improved. Two described that the safety reporting process could be streamlined, particularly with regard to postmarketing activities and adverse event [AE] grading. The first participant was concerned about the current ICH guidelines related to postmarketing safety reporting, citing that the availability of funds to effectively conduct such reporting is a barrier:

And postmarketing safety reporting is ridiculous. We can't do registries and look at specific drug names because if we don't pay sites, they will not have the time to actually collect the information that Health Canada is saying according to ICH is required. [ID# 13]

Another participant indicated that grading AEs involves administrative burden and time, then suggested that instituting global reports might serve as a solution to this issue:

…if I go back to serious adverse events, quite often they are not regular graded, they are floating different parts or you have to sign one form for one adverse event, another one, another one, and it's not a medical statement. And so, the follow up is very difficult for the paperwork, and we're spending most of our time signing forms and we very often even don't remember what was before. So, we need more global reports for that. I think that that's one problem, in fact, the most difficult one. [ID# 22]

A participant also described a need for greater flexibility in safety reporting, commenting that when an event has been reported by someone who is an expert in their field, having another person adjudicate that event is not going to improve the information that was provided. They also noted that safety and study populations look different in many parts of the world and that we risk continuing to exclude marginalized populations from research by applying universal safety reporting criteria to regions such as low-resource settings, where required information cannot be readily obtained and where it can be challenging to go back to confirm that outlier results are truly outliers (see also Appendix B, reference B40). This participant also provided an example of a situation in which ICH E6 GCP criteria on safety reporting were misapplied, resulting in partially halted data collection, because the ICH criteria would have required full safety reporting in an observational study (see also Appendix C, reference C9).

Finally, two participants suggested updates to the section on safety reporting, with one proposing to modernize the language by endorsing the use of e-signatures on safety reports, and the other requesting addition of the phrase "important medical events," which does not otherwise appear in the guidance.

2.1.2.4.4 Adequate resources

Two participants suggested changes to the information about adequate resources. Both participants indicated that greater flexibility in medical oversight should be permitted, depending on the situation. For example, for studies being conducted in family medical practices, usual medical care may mean that triage is performed by someone other than a doctor, particularly for well-person visits in which there are no issues. This participant felt that, when the usual standard of care does not require a doctor to be present at all visits, this should be permissible for research as well, provided the doctor is made aware if an issue arises. Furthermore, certain health care professions have risen to greater prominence since the guidance was written, so the renovation should reflect the rise of nurse practitioners and physician assistants, both in terms of a site being able to provide adequate resources and in terms of being able to demonstrate investigator qualification:

I think about when ICH first came out in around '96, there were a number of health care professional careers that didn't exist then. So, if you think about the statement around medical care and medical decisions need to be made by a qualified physician or dentist, could it be a physician assistant? Could it be a nurse practitioner? [ID# 16]

One participant also indicated that it should be made acceptable, per the revised guidelines, for certain staff members to have only limited knowledge of the study, depending on their role. If someone's only task for the study is to draw blood, then they should not need to have a full understanding of study objectives and end points in order to do that job:

> *Adequate resources. It's an obvious section. The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol. We've had people take that to task, and when we do blood collection, have gone and asked those in the lab, "Tell us about the study." Well, they're involved in the trial to collect the blood. We need nothing from them beyond what they do on a usual basis every day of their lives. They're involved in the trial in that they provide a service to the trial, but they aren't involved in the usual conduct of the trial. When you have big study groups, they'll organize their teams into the screening team, the follow-up team, the closeout team. Well, does the closeout team have to know how to screen? Probably not. That's already been a done deal. So, again, it's recognizing that we need more flexibility to determine the adequate resources. [ID# 13]*

2.1.2.4.5 Documentation

One participant requested clarifications to the ICH E6 GCP wording about documentation. Specifically, they suggested clarifying requirements for source documentation, for documentation of the informed consent process, and for investigator oversight documentation. They explained that clearly defining in ICH E6 GCP the requirements for source documents (for example, noting the content, date, and time of any conversations that research staff have with patients) would help greatly with audit success, as auditors are looking to tell a story of how the study is run, and they use source documents to do so (see also Appendix C, reference C10). ICH E6 GCP should make clear that documenting the informed consent process is a part of this too, since from the monitor's perspective, it does not suffice to have a statement in the notes that the patient agreed to be in the study; the process for obtaining consent and allowing the patient to ask questions should also be described. Likewise, having documentation of investigator oversight (for example, minutes from meetings between investigators and staff about the study) helps with auditing of study conduct and helps the monitors document the elements that they in turn need to report back to the companies that have contracted with them. Thus, it would also be useful to make this clear in the renovation (see also Appendix B, reference B41).

2.1.2.4.6 Information to add to Section 4

In addition to the suggested updates to subsections of the ICH E6 GCP Investigator guidance noted above, participants provided a wish list of general information to add to Section 4 as part of the renovation.

Two commented that, while study staff pay a lot of attention to the ICH guidelines, investigators are far less likely to have the time to thoroughly familiarize themselves with ICH GCP. Thus, it would be helpful if ICH could provide a cheat sheet or standard operating procedure for busy investigators that provides investigators with an overview of their responsibilities. Training materials or a summary introduction for new PIs (consisting of a general overview of investigator responsibilities and a checklist of steps to follow) were also requested. The Investigator section already contains the information, but the section is lengthy and verbose as currently presented (see also Appendix B, reference B42). Finally, one participant requested that the guidance be updated to include information about how to address noncompliance by the investigator.

2.1.2.5 Section 5: Sponsor

Seventeen participants described aspirations they held for the ICH E6 GCP renovation of the Sponsor section, with several discussing suggested changes to more than one aspect of the guidance. The elements mentioned most frequently for revision were quality management using a risk-based approach (n=11), study roles (n=4), sponsor responsibilities (n=4), safety reporting (n= 3), documentation (n=3), and new technologies and processes (n=2).

2.1.2.5.1 Quality management using a risk-based approach

Eleven participants described aspirations related to quality management using a risk-based approach. More than half of these participants requested that a risk-based approach be emphasized throughout the guidance. Participants described that they liked the new sections on quality management and the risk-based approach but suggested that it would be more helpful if ICH E6 GCP provided more specific guidance on implementing quality management systems (see also Appendix B, reference B43 and B44), particularly in terms of clarifying what is meant by some of the terms that were left open to interpretation in the last revision.

> *I hope for clarification. I think that ICH GCP is really a core fundamental of clinical research, and I was happy of the last revision. There are two where we got some clarification on some of the oversight topics and risk-based elements; however, what I'm still missing is decisive guidance or – I'm really struggling in interpreting what is in some pieces when there is reference given to oversight or risk-based approaches what is meant by that. What is really meant by risk-management plan and we have some delay until we see the first audit – inspections from regulatory bodies who then interpret ICH GCP, so that's always a gap or a lack of uptake until we get the read out of the regulators. Because ultimately we want to satisfy not only ICH, but we do on our interpretation once the new guidance comes out, comes into effectiveness, but also, of course, regulatory expectations and this is then – might be a different interpretation of the same text that is provided. [ID# 21]*

A participant said it would also be helpful for demonstrating best practices of implementation if the revised guidance could provide concrete examples, case studies, and scenarios (see also Appendix B, reference B45):

> *I think in general with, let's say, ICH E6 (R2)—how it was rolled out, I think it's really a very helpful renovation to the ICH guidelines. I think it's more the challenge of the implementation, so I think that it's really not a lot of guidance out to the industry how to actually realize let's say a risk-based approach to clinical trial management, etc. I think there's a lot of experience in the industry and everybody, I think, tries to really figure it out and tries to find solutions, but I think I would appreciate a little bit more guidance from the ICH E6—how this ICH Committee—how this actually could look like with different examples, case studies, etc… I definitely like the way the ICH is going. I think it's definitely beneficial because it's definitely a step into the right direction. They're aligning GCP more to what GMP is already doing since quite a while, and really contemplating it, really asking for a more risk-based approach to working. [ID# 15]*

One participant stated that providing more clarification and guidance related to a risk-based approach could enable sites to manage resources more efficiently by focusing mostly on critical areas rather than wasting time and funds by attempting to focus on everything to the same degree. It could also serve to reduce investigator burden by cutting down the number of things that sponsors ask for:

> *I personally think, internally, it would really have an impact in the way that people can really more efficiently manage their resource, meaning really paying attention to the critical areas, it's better than their wasting a lot of time really focused, trying to focus on everything. I think that's the one advantage. There could be better guidance. On the other hand, I think also knowing that a lot of let's say investigator sites feel the burden of sponsors asking for a lot or using a ton of different systems and technologies. I think with a better guidance in terms of how oversight needs to look like. That could also really take a lot of burden from investigators and sites. [ID# 15]*

Three participants suggesting that the revised guidance should be clear that it is not prescriptive, or a law, but should be read as the "spirit of risk management." One participant described that legal teams at sponsor organizations and CROs are over-engineering training programs, protocols, and study documents based on their interpretation of the E6 guidance. This overemphasis on audit readiness is resulting in such a high degree of complexity for clinical trials that potential investigators are choosing not to involve themselves or their patients in trials, thus limiting accrual (see also Appendix C, reference C11). Another participant who also felt that regulators have transformed the E6 guidance into a "law" suggested that the guidance be updated to state that, while it contains elements that *may* be used for trials, depending on the specifics of the study, there is no expectation that all of them necessarily *will* or *need to be* used within a single project. Instead, sponsors should decide what is relevant for each study based on the estimated risk and choose those elements accordingly (see also

Appendix B, reference B46).

Two participants suggested that the Sponsor section should be clear that the guidance allows for flexibility. For example, a participant noted that, in low-resource settings or in specific situations such as vaccine trials during an Ebola epidemic, it may not be possible to bring a monitor to the site, due to considerations of time and the monitor's personal safety. In such cases, it would be helpful if the guidance encouraged the people involved with a trial to consider the context and relative risk of research, rather than strictly abiding by a checklist (see also Appendix B, reference B47) A participant also noted that the revision should make clear that, when sponsors are creating study plans, those plans should be written in such a way as to make the type of study and the resulting level of GCP that is required readily understood. The participant further cautioned that such a flexible approach to ICH E6 GCP needs to include all types of studies, not just regulated studies:

> *I just think that it's really, really important that either it's very, very clear that it's only applicable to regulated studies or that there's enough flexibility that when people interpret it including the regulators and the inspectors at the site, they're able to identify that type of study it is and therefore the degree or the level to which the GCP should be applied and some of that onus is on sponsors in terms of how we're going to write that plan or whatever it is a regulator or an inspector can understand that, "I'm going to look at this study through this lens."…I'm going to be cautious and say it can't really only be about regulated studies because then suddenly everything else gets left out with nothing, which we don't want, but I do believe that that risk assessment in chapter five, if they can work that—so it basically brings in some of the concepts of E8 and this is how you're going to evaluate your study, and therefore everyone can easily recognize it, it falls, it lands in one of these kind of categories. So that's my vision of it. There might be other ways to kind of look at it, but I do believe that that risk assessment will definitely help to put them in buckets or categories in terms of the type of research it is and therefore the risk to the patient whether it's safety or ethics or whatever. [ID# 12]*

Participants also raised a number of aspirations related to the guidance on quality management. First, a participant who described that there can be a tendency to over-manage vendors based on interpretations of ICH E6 (R2), indicated that it would be beneficial for oversight to be more differentiated, such that the mechanism and degree of oversight depends on sponsor size, capacity, and degree of expertise. This participant stated that it would be helpful for the GCP guidelines to acknowledge that differences between sponsors exist and to make recommendations for implementation of a risk-based approach (see also Appendix B, reference B48).

Second, a participant described that they found the new section on quality management and risk management in the E6 guidelines to be too generic and recommended cross-referencing other E documents such as E8 and E9 when building a risk profile, as the guidance contained within the other E documents contains helpful information that should be used when designing a study and evaluating

risk (see also Appendix B, reference B49). Third, a participant who indicated there has not yet been a full-scale inspection on the basis of the R2 revision, described that, as a result, there is uncertainty related to whether the revised guidelines have been implemented correctly. This participant expressed two-fold reservations: (1) Was their company's interpretation of the revision accurate? (2) If it is determined during the course of a future inspection that their implementation of risk-based monitoring was not what ICH had in mind, what are the consequences of an incorrect implementation? Based on years of experience with inspections and protocol deviations, the participant is familiar with things that should be avoided during trials, but it is still unknown how seriously a deviation from the revised guidelines would be treated, if the company took an approach in good faith that ended up not being in alignment with the ICH intent (see also Appendix B, reference B50). Fourth, the same participant requested that the revised guidelines clarify the scope and format needed to meet the requirement of documenting quality management activities, such as what is needed to document that certain study team members received a communication about quality management and whether there are consequences if a new team member is not communicated to when they come on board:

> *I mean you look at a section on risk communication, where it says the sponsor should communicate quality management activities to those who are involved with the activities. Okay, now do we need to have this written out, all the people that were involved in the communication of the risk activities? If somebody joins midway through a trial and they were not communicated to, is that a finding? …Study teams turn over. And in some ways if you didn't communicate some of these quality management activities, is it a risk to patients' rights, safety, welfare, and data integrity? Maybe not. [ID# 16]*

2.1.2.5.2 Sponsor responsibilities

Four participants expressed a number of aspirations for the renovation to the ICH E6 GCP guidance on sponsor responsibilities. One participant, as previously noted in the section on investigator responsibilities, indicated that the existing guidance implies that the investigator is responsible for reporting SAEs, while current regulations indicate this is the sponsor's responsibility. Thus, in the renovation, the guidance should be updated to align sponsor responsibilities with current regulations.

A participant called for updates to the Sponsor section to reflect changes in sponsor responsibilities arising from advances in technology, such as systems that are now being put in place at trial sites by the sponsor rather than being implemented by the sites themselves:

> *I'd say it needs to respect the principles of ICH and the Declaration of Helsinki and key data protections of subject data and all of that imposes restrictions. But I think that there's much more emphasis now on systems that are being put in place by the sponsor or on behalf of the sponsor, being utilized at the trial sites rather than being the sites, specifically, being*

responsible for record forms and so on. I think that there needs to be more recognition, I think, of the overall responsibilities of the sponsor and how that interacts with the sites to ensure that the respective obligations of the investigator and the sponsor are compliant. [ID# 11]

As previously noted in the context of situational flexibility being an important aspect of quality management using a risk-based approach, a participant described that sponsors are responsible for creating a study plan that clearly specifies the degree to which ICH E6 GCP should be applied to a study. Another participant suggested that sponsors should focus less on regulatory readiness and more on creating the best protocol for a study. They described that, in their previous work, sponsor overemphasis on the potential for not having everything that would be required for an audit or inspection has resulted in sites in more challenging parts of the world not being considered for inclusion in a trial when, in fact, those regions of the world would stand to benefit most from the product being developed. This participant further explained that, when they have had success in activating sites in more challenging areas, the sites have evidenced both a willingness to learn ICH E6 GCP procedures and an understanding of GCP principles (see also Appendix C, reference C12).

The same participant suggested that the sponsor guidance on monitoring responsibilities should recognize the challenges of handling investigational products in remote trials and under-resourced countries, where there may be temperature control or humidity challenges (see also Appendix C, reference C13).

2.1.2.5.3 Clarify study roles

Three participants asked that the revised guidance further clarify certain study roles. One participant described that the role of the CRO in the sponsor-CRO relationship should be clarified so that it is clear what can and cannot be delegated by the sponsor to the CRO:

The other things, again, there is wrong way of the relation between the sponsor, the investigator, and the CRO. We think that the sponsor cannot delegate everything to the CRO, especially for the safety. They have to be responsible for that because in the CRO, you have limited medical expertise. If you put medical expertise first, and so they have to be very careful in what they delegate and keep the medical expertise with the investigator directly on the serious adverse event. So, of course, they cannot look at all adverse event Grade 1, 2, at least for the serious of adverse event, which would do that. [ID# 22]

One participant noted that new sponsor oversight roles have arisen since the R2 revision of the ICH E6 guidance, related to the reinforced role of sponsors in clinical research oversight. With the renovation, the guidance should acknowledge and define these new roles, including CRA oversight and sponsor liaison (see also Appendix B, reference B51). Another participant noted that, in some

cases, the concept of sponsorship and what constitutes sponsorship should be defined, given that the role an organization plays may change from study to study:

> *Today, academic trials are slightly different. Sometimes we're coordinating site and sometimes we're the sponsor. Sometimes the other legal person is actually at the CRO. So—but almost—keeping to those broad—to know if it needs to be a subcategory of defining the sponsorship in a little bit more detail in there. And I guess, going through [the guideline]…just to see what concepts there are questions. [ID# 01]*

2.1.2.5.4 Safety reporting

One participant noted that the revised guidance should clearly state that ICH E6 GCP requires reporting to local agencies, as there has been pushback in this participant's experience from local agencies in certain countries, which do not request or even want to receive safety reports. Having this requirement clearly specified in the ICH guidelines would help sponsors make clear to local agencies that they are following proper ICH procedures in making such reports (see also Appendix C, reference C14). Another participant requested that the ICH clarify the timeline for SAE reporting in digital trials, as the field is evolving rapidly and ICH ideally should provide guidance for trials conducted in digital environments:

> *…and then you think of SAE reporting and the immediately reporting. If you do that, it's like something in an—when does the clock start for the reporting timelines? [ID# 21]*

One participant described that the renovated guidance should revise the definitions of SAEs and SUSARs so that expected AEs are not miscategorized as unexpected:

> *…if we focus on the event and the safety for treatment and for the study, you have to revise some of the definition. For example, at the present time, you have a definition of SAE and SUSAR and now when you don't know what it is, the company or the CRO will say, "Well, that's a SUSAR." And so expected toxicity, especially that we know very well—in hematology are terrified are SUSAR and at that time, you have a lot of burden of paper for that to be clear it when it's something completely expected. In the ICH, it's clearly written that you can have a risk-adapted position, but it's not done in most of the protocols controlled by company and in academic study, you're under the pressure of following, more or less, the same rules even if you cannot reduce all the paper. And so, it does—and we have to go back to the first definition of SUSAR and serious adverse event and stop adding other things you don't understand. You didn't know that's a SUSAR. [ID# 22]*

As previously noted under clarification of the sponsor-CRO study relationship, one participant noted that, when sponsors delegate to CROs, the reporting of AEs should be conducted by the sponsor and

the grading of AEs should be conducted by an investigator, not the CRO in this situation, as CROs have limited medical expertise.

2.1.2.5.5 Documentation

Three participants addressed the ICH E6 GCP sponsor guidance on documentation. Of these participants, two suggested that the ICH should allow for flexibility of training requirements and documentation of training, including documentation of GCP training. One participant indicated that physician licensure in a specialty should cover most of what clinicians need to know in order to conduct a pragmatic trial, aside from possibly requiring specialized training in trial-specific data capture systems (see also Appendix B, reference B52). Another commented that the ICH renovation should explicitly give permission for GCP recertification to be conducted as a brief refresher course:

> *I think that in the GCP document, some kind of a statement that says that GCP training should be documented by physicians and other practitioners participating in research, but that ICH thinks that recertification can be a briefer refresher course or something like that. Something that gives them permission to design it that way. You're not saying that it has to be that way; you're more or less giving permission because then that gives them cover. From the point of view of the sponsor and their clinical trial, if they do a clinical trial and then it comes back that the GCP training that was required in the trial does not meet the requirements as stated in the ICH E6 document, then that's going to kill the trial. That's a billion-dollar problem for the sponsor. [ID# 18]*

A participant also suggested that the ICH E6 GCP renovation clarify requirements for source documentation in digital trials, as well as who owns the digital source data:

> *I don't know if we're going too far when we ask for a clarification of the whole environment of digital trials [inaudible] trials and how to properly rephrase, for example, source data, source documents in a digital trial environment. The owner of the source data… [ID# 21]*

2.1.2.5.6 Update to accommodate new technologies/processes

Two participants requested that the ICH E6 GCP sponsor guidance be updated to accommodate new technologies and processes by describing best practices for ensuring data quality and integrity in digital environments. One participant noted that technology has progressed since the ICH E6 GCP guidance was first issued and that a change in approach is needed to accommodate new technologies and a move from paper-based to electronic systems:

> *Well, I think, clearly, since the guideline was first produced, there's been a tremendous advance in the way clinical trials are conducted now. Again, a lot of the approach within the guideline seems to be very much based on the traditional way of managing trials with paper,*

whereas we're obviously moving to a much more electronic environment now. Huge differences. And I think while respecting the principles, there needs to be quite a change in approach to accommodate the new technology. [ID# 11]

The other participant discussed the need to update the sponsor guidance to accommodate process changes in trials arising from new technology:

This is something that derived from ICH E6, but I see some topics and the field is so fast evolving that I do not even know if I think the ICH E6 R2 had some great new stuff with regard to certified copy and presentation of computerized systems. However, it is quite on a high level and the field is evolving in such a speed that probably ICH cannot keep up with the speed of which the technical capabilities evolve. How can that be covered properly and give guidance for the future on how to conduct a trial in a digital environment according to GCP? [ID# 21]

2.1.2.5.7 Investigator brochure

One participant commented that sponsors could do more to help investigators understand the information contained in the investigator brochure, and that the renovation of the ICH guidance provides an opportunity to formalize this for sponsors. Specifically, they noted that to increase comprehension of the guideline, sponsors should tailor the information in the investigator brochure to physician-investigators, as many of these investigators come from clinical practice and not scientific backgrounds:

But I still think many investigators are not totally familiar with investigator brochures. I think there's an opportunity there to improve that, improve that from implementation, which is what I do every day when I work. But also, how can the guideline help? So, I wrote many investigators working for sponsors need to be better educated about both investigator brochure information and potential foreseeable risks in products and research. Many are not coming from scientific background. We see the industry needs the patients; they need the investigators. Many are physicians that became investigators. And they—there's a lot of hard scientific information in the brochure that maybe is not always easy for them to read and digest. And I think sponsors could support them better in this education activity of explaining more and working with them in the understanding of the investigator brochure. [ID# 03]

The participant further suggested that the sponsor role could encompass providing support staff for investigator education about the investigational product, such as clinical science liaisons and medical monitors, whose role is to advise investigators and work with them to explain the product and its safety profile. Information about this aspect of the sponsor's role in investigator education should be added to the Sponsor section of the guidance:

There is a role called clinical science liaison, which I think has to do with taking the science [to

the] investigator on behalf of the sponsor. There is a role of medical monitor in 5.3. And it says the sponsor should have a medical support information available for investigators at all times. They should advise them and work with them in understanding the product and potential safety profile they need to be familiar with. But I think maybe the wording can be stronger. And maybe a little emphasis can be put on the sponsor should educate the investigators in the safety profile and the information of the safety brochure. [ID# 03]

2.1.2.5.8 Information to add to Section 5

In addition to the suggested updates to subsections of the ICH E6 GCP Sponsor guidance noted above, participants provided a wish list of general information to add to Section 5 as part of the renovation.

One participant requested that both the Investigator and Sponsor sections of the guidance include information about how to address noncompliance by the investigator, and what steps the sponsor should take to analyze and prevent recurrence of noncompliance:

Compliance responsibility and quality management in section four, investigator. And section five, sponsor. I don't have any specific place. But I can see we don't have guidelines about noncompliance management by investigator. What should sponsor do? What should investigator do? There's nothing about noncompliance by investigator in the guidelines. I would like to see some wording. I thought it would be good to clarify that sponsor is responsible for taking actions to analyze noncompliance and prevent recurrence of noncompliance. Stopping recruitment, closing clinical sites as needed. And I think it would be good to have some wording. [ID# 03]

Another participant commented that the guidelines should include collaborative research such as cosponsorship and codevelopment, as the priorities mentioned in the current guidelines may not be sufficient. Finally, a participant stated that the revised sponsor guidance should include information about which subcontracted or vendor services are subject to GCP. The participant noted that, in the absence of definitive guidance, sponsors are left to their own devices in figuring out whether vendor services are GCP-relevant or not, which leads to ambiguity and confusion, as different sponsors may interpret and thus act upon the existing guidelines differently:

When we talk about, for example, vendor oversight and subcontractor oversight, I think it would be helpful if we had such an addendum where there is a definition from ICH what kind of services are considered to be GCP relevant or not. Because from vendor-management perspective I'm specifically interested in the vendor management and then the oversight piece, and also about trial-related duties that can be given to clinical research organizations or to supply us and their subcontractors. However, I'm often struggling with, is this service really a

GCP relevant service or not? If the printing—the source printing without adapting the content, for example—of an informed consent form a GCP task or not? We are left alone to decide this on our own and I think also regulators are given the freedom to decide, often their inspections, if this is a GCP activity or not. This freedom to decide leads to ambiguity in the interpretation and it leads also maybe to different approach. And for us as a whole industry of people who are doing clinical research, it leads to unnecessary confusion that we could improve the process for all of us. If we go through a list of basic tasks and justify in a consensual—or mutual agreement that these tasks are to be considered in the basket of taken care of within the remit of GCP and some not, just out of it. These are day-to-day operational activities with which we are struggling. I see that the [inaudible] of ICH is not giving you an answer. [ID# 21]

2.1.2.6 Section 6: Clinical Trial Protocol and Protocol Amendment(s)

Only one participant commented about the section on clinical trial protocol and amendments when describing aspirations for the ICH E6 GCP renovation. They expressed uncertainty about whether this section belongs in the E6 guidance or whether it would be better suited for the ICH M guidelines:

Then, if we go ahead, there's stuff in there like clinical trial protocols or IDs. Does that still belong in ICH E6, or should that go in one of the multiple or the ICH M guidelines, where they're even discussing the electronic setup and data format for protocols in ICH, and the same for trial master size? [ID# 05]

2.1.2.7 Section 7: Investigator's Brochure

One participant described an aspiration for the Investigator's Brochure section of the guidance. This participant briefly commented that the section is the only guidance they have for how to write an investigator's brochure, and thus it could use some updates.

2.1.2.8 Section 8: Essential Documents for the Conduct of a Clinical Trial

Five participants described aspirations specific to renovating the Essential Documents section of the E6 guidance, two of which were points for clarification. First, one participant explained that duplication or triplication of documentation may occur, based on the way in which the guidance describes required documents as being needed before the trial, on an ongoing basis, or at the end of the trial, and also based on the split between whether documents are located on the investigator side or the sponsor side. This participant noted that since all documents have to be available at the end of the study for the regulatory file, one fix might be for the Essential Documents section to simply note those documents that have to also be present at the beginning:

…sometimes, weird separation in documents needed before, documents on an ongoing basis, documents at the end. Actually, we must have all these documents at the end and must have a

clear contrast documentation regarding this, but I've realized sometime in my earlier career that some companies split up the documentation before, ongoing, and at the end, and had a couple of threefold documentation. So, my recommendation would be rather which documents are necessary, which of those should be at the sponsor, which of those should be at the investigator, and just adding marking the documents which should be present already up front, because all the rest have to be present at the end. [ID# 06]

Second, the other participant recommended clarification related to the need to take local regulations into account when considering essential documents. The participant described confusion resulting from a misconception that the Essential Documents section serves as a complete list of all of the documents that need to be retained for a trial, when in actuality, local regulations may specify that additional documents are needed as well. The suggested fix for this was to add language to the section clarifying that the associated list represents core documents only and that local regulations may mandate additional materials:

I think the list of essential documents, while it's been very helpful, definitely created a lot of confusion as well. A number of organizations have taken—initially, at least. I think the situation's become a bit clearer now. Initially, a lot of organizations took that as just being the documents that need to be retained for the trial. Of course, it's actually much more than that and varies depending on local regulations as well. …I think it almost needs introductory statements to make clear that the trial master file needs to contain all of the information that's required to successfully reconstruct the trial and that the list that follows are, essentially, core documents. [It] would need to be supplemented so that the appropriate decision making is recorded and being aligned with local regulations—something along those lines. [ID# 11]

Two other participants called for introducing flexibility into the Essential Documents guidance. One participant noted that the section as currently presented has a prescriptive tone and could easily be used as a checklist for whether given documents have been obtained. This participant further noted, however, that checklists tend to result in people following them blindly rather than thinking about the elements they contain (eg, thinking about types of documents rather than specific documents). This participant also mentioned medical licensure documents for investigators as an example, pointing out that most major medical institutions would not allow physicians to practice without an active license. Thus, if an investigator is active at a hospital, it can be assumed that their licensure is up to date and that it would be a duplication of effort to obtain as additional verification. More flexibility in the ICH E6 GCP guidance would allow local factors such as institutional certification requirements to be considered when essential documents are being collected:

The curriculum vitae of all the—I understand how that's important because it identifies their qualifications, but for a medical physician, for a physician, the medical license, it's very important in some aspect if that is in a large institution, and you can prove that that institution

would not allow them to practice without a medical license, it's almost redundant. I think again you have to look at the setting in terms of where your investigator site is because the requirements that are already imposed to them just through normal clinical care or the infrastructure of that institution they're in…I totally agree with and support that you have to be able to show that that's already a requirement, but not necessarily collect every single license if you can prove that this institution is a recognized institution in whatever country it is and that that institution requires A, B, and C for anyone to practice and those qualifications are the same as what we need. [ID# 12]

The other participant who called for flexibility in the guidance described the necessity of allowing for situational variation in requirements. For example, in a study in which patients take the investigational product home and store it in their refrigerators, it makes no sense to require monitoring of temperature logs in that setting, compared with a study in which investigational product is stored in a lab under tightly controlled temperature conditions (Appendix C, reference C15). Providing examples or case studies in the guidance would be helpful for clarifying this section.

Finally, one participant suggested an addition to Section 8, proposing that "conversation notes" documenting what was discussed during patient interviews be explicitly added to the definition of source documents in Section 8, to be considered source data in the same way that lab and surgical results and medical chart notes are:

I'm just looking for the section on source documentation, records and reports, section 4.9, where it says—should maintain adequate and accurate source documents including pertinent conversations. And they do define what it should be and completeness and how to make changes. But it would be good—you know how at the back of the document they have that listing of regulatory authorities, the appendix? In that section of the appendix where it says during the trial, and I think it says 8.3.13. A further definition of that could include—they talk about x-rays. They talk about chart notes. They talk about lab results. They talk about surgical. I call them conversation notes but just a little definition about—during interviews with patients, please document the information provided to you, and make sure that this information is initialed and dated on the date that the conversation took place. [ID# 14]

2.2 Helpful aspects of ICH E6 GCP

Provided below is a summary of participants' narratives on the helpful aspects of ICH E6 GCP. Appendix D provides additional participant quotations on the helpfulness of ICH E6 GCP. Appendix E lists examples participants gave related to the helpfulness of ICH E6 GCP. We provide references in the sections below to link the summary information with participant quotations and examples in Appendices D and E.

More than half of participants (n=14) provided overall commentary about how ICH E6 GCP is helpful. Many of these participants also commented on specific parts of the guidance. We fist describe participants' general comments on the helpfulness of ICH E6 GCP, followed by participants' aspirations for each section of ICH E6 GCP.

2.2.1 General comments on the helpful aspects of ICH E6 GCP

2.2.1.1 Overall helpfulness

Nine participants stated that ICH E6 GCP (n=9) was helpful overall. Participants who elaborated further stated that they find all sections of ICH E6 GCP to be useful and that the information contained in it is clear. Participants also commented on the utility of ICH E6 GCP for training purposes (see also Appendix D, reference D1 and D2:

> *My personal feedback is that I think going the route the ICH is going and how it's already reflected in R2 is really a very good way moving forward because of the change in how research meanwhile is done. And also I think the ICH very well recognizes the challenges that global trial conduct really offers. So, I think in general, really only very positive and encouraging feedback from my side. [ID# 15]*

> *I can't say there's any section that I don't refer back to; it's all very important. [ID# 16]*

2.2.1.2 ICH E6 GCP principles apply globally

Five participants pointed out that ICH E6 GCP is helpful because the principles of GCP set forth in the document apply globally. Many of these participants elaborated that ICH E6 GCP serves as a common standard for research worldwide, unifying researchers and ethics committees across different countries, who nevertheless work within the same set of rules (see also Appendix E, reference E1). ICH E6 GCP also provides a framework for research in countries where legislation to support a clinical trial application cannot be identified; the basic documentation required by ICH E6 GCP may serve as a starting point for setting up a trial in that case (see also Appendix E, reference E2). ICH E6 GCP is also helpful in situations where legislation exists but may be less detailed in one region than in another; for example, between North America and Europe:

> *I would say the other chapters, they are even helpful in all countries because the laws don't go to so much detail like we have here. The US law is much more detailed than European law. You find obligations and/or monitors, what they do or think like that. We don't have that in Europe on that level in the law, so I would say it's a good supplement of the laws, and that I think that is also what it should be, such a guideline. We want to have more detailed requirements in this guideline and don't want to have everything in a law, but the laws have different levels of detail, and with this guideline I think this is the goal. [ID# 23]*

Participants also raised a number of points regarding the global applicability of GCP, including that ICH E6 GCP is the only globally agreed guidance and that it provides a framework for conducting clinical trials in countries with less developed ethical and/or regulatory requirements, thereby ensuring that the data produced in a trial will be meaningful to marketing organization applications:

> *Because of the work that I've undertaken, it's always been with CROs, the expectation has always been the data generated in these countries would be GCP-compliant, and that's necessary in order to support product registration in the EU at the very least. And so, for that reason, when we've been working with the sponsors, obviously, they've been wanting to recruit patients in these countries, but they've also been wanting to ensure that patients provide data that's meaningful to their ultimate marketing organization application. So, for that reason, we would ultimately have to follow ICH anyway given the fact that we do have to perform applications to these countries, and often the regulatory requirements and the ethics requirements in these countries are quite sketchy, at best. [ID# 10]*

Participants also pointed out that most countries are willing to work with the ICH E6 GCP guidelines and that, in some countries, ICH E6 GCP has even been codified into law (see also Appendix D, reference D3):

> *The ICH GCP guidelines certainly gave a very good harmonized approach that we were able to take forward and regulate it, and most countries would work with that. Where I think there are issues—it wasn't so much with the guideline itself as with the way it was sometimes interpreted in countries. [ID# 11]*

2.2.1.3 ICH E6 GCP is a guideline for conducting trials

Three participants described that ICH E6 GCP is helpful because it serves as a guideline for conducting trials. These participants raised a number of points, including that having clear guidance that designates strict research processes is important for establishing an evidence base in trials, as well as that clear guidance about required documentation in trials is important. One participant uses ICH E6 GCP to establish SOPs and metrics to use for the conduct of trials, viewing this as the most effective way to protect participants' rights, safety, and welfare. However, another participant noted that they consider ICH E6 GCP to be helpful because they are able to use it as a general roadmap for working with regulators, and not as a specific list of tasks. In this regard, they view ICH E6 GCP as a general framework from which they are able to pull out the pieces they need (see also Appendix D, reference D4):

> *I'm going to say I have taken ICH E6 throughout my career as a quality professional and even now in terms of operations and some of the principles, and then each of the chapters, they're valuable. It's an absolutely perfect roadmap for me. I understand what regulators want and*

where we're going to have to show evidence of their requirements of what they want to see. So, it's a nice roadmap per se, but I have shied away from actually looking at this as a task. I try not to do tasks…in terms of taking this away from being a very specific people or group and tasks to more of what I call "the frame" and talk about pulled out from each of those chapters the theme that kind of ran through it. So when I talk… about having qualified personnel working at it… I always talk about, "What's your organization and personnel look like?" For any given organization, if you look at that as the broad theme, then that's where you're going to show qualifications and that's where you're going to show if you determined you need licenses, etc. [ID# 12]

2.2.1.4 Provides useful information on human subjects protections

Three participants described that they find the information on human subjects protections in ICH E6 GCP to be helpful. Specifically, all three liked that the document clearly lays out the roles and responsibilities of ethics committees, investigators, and sponsors. One also appreciated the background information on human subjects protections that is provided, stating that this is useful to give trainees an understanding of why many of the formalities of GCP are necessary (see also Appendix D, reference D5):

What I've found very helpful in ICH E6 are definitely the chapters on patient and subject protection because Declaration of Helsinki gives you a good baseline, but ICH E6 goes far beyond that by introducing the roles and responsibilities of ethics committees, of sponsors and investigators. It doesn't specify too much the role of the health authority, which could possibly also be added. [ID# 05]

2.2.1.5 Other areas of helpfulness

One participant commented on data integrity, noting that the guidance provides good ideas in that regard:

The guideline also gives you some very good ideas about data integrity, what is the baseline, how to achieve it, either if you record the data in paper form or, now, electronics, starting with validation, starting with making corrections, starting with following the ALCOA principles. [ID# 05]

2.2.2 Helpful aspects of the specific sections of ICH E6 GCP

2.2.2.1 Section 1: Glossary

Three participants described the glossary of the ICH E6 GCP guidance as particularly helpful. Of these, two noted that the glossary was useful for training and served as a good starting point for

beginners to be able to define terms such as “protocol” and “source document.” Another commented that they used the glossary in their work as a helpful reference during the course of a trial, for example, by consulting the definitions to determine whether an event met the criteria for AE or SAE (see also Appendix D, reference D6):

> *One thing which I think is super helpful is the glossary at the beginning. I think it's really good to have somewhere, the glossary, you have somewhere also a definition of different terms…and it has to be in my mind very often, in discussions with the study team who really has the data to say if someone was hospitalized and was that an AE or SAE… It's a hospitalization, it's an SAE, whether they were because the patient felt dizzy after taking the drug or was run over as a pedestrian crossing by a car, it doesn't matter at the beginning. That's the next step in the definition whether this is probably or possibly related to the study drug or to the intervention. So, this is for me as a starting point. The definition of terms is very, very helpful. [ID# 08]*

2.2.2.2 Section 2: ICH E6 GCP Principles

Six participants discussed the ways in which the principles of GCP were helpful in their work. Almost all of these participants noted that this section establishes a set of fundamental concepts that all research should strive for, with one participant describing the principles as a standard for all types of clinical research, both drug and device, and another commenting that the principles serve as a checklist for essential elements of GCP that should be incorporated into the research (see also Appendix E, reference E3):

> *…again that's where we really use the spirit of GCP. I know that I'll start by saying for all of our clinical work, the 13 principles are pretty important. It doesn't matter whether it's for a drug application or a device application. The principles, in general, are very good and that north star for clinical research. [ID# 12]*

In addition to describing the GCP principles as foundational, participants commented on utility of the principles for a variety of purposes and groups, including auditors and inspectors. One participant engaged in a lengthy discussion of how the GCP principles were used at their institution to determine whether a particular trial design would pose sufficient benefit to patients to justify the increased risk (see also Appendix E, reference E4). Another participant discussed that the principles are both helpful for GCP training and serve to establish a foundation for research in other countries:

> *One section that I really like is probably one of the shortest sections of ICH. It's the actual section which is called “Principles.” This is something when I train people internally. Currently, ICH is the guidance, and, then I'm going back again to this introductory phrase that the principles of ICH can be applied to other types of research. What most people conclude is they*

understand principles as a kind of essence of the whole document, while I interpret principles as being a chapter with 13 points…which basically translates some of the principles of Helsinki declaration and some other, kind of, more ethical types of documents. And I think this is a very useful section. It's really something which can be used for all types of research without any danger, whatsoever. And, it really needs to be kept, and it's the one that we are very frequently using because it's true that, even though the ICH—the full document is heavy and not always easy to comply with, but if you go in some other types of research, which may be regulated in some countries but not regulated in other countries, you still want to have some documents to refer to as a something that you would like to comply with. And, they are the principles, the actual chapter on principles, is the one we have very, very frequently referring to. [ID# 19]

However, while the participant noted that the section on GCP principles translated the principles from the Declaration of Helsinki, another commented that more work could be done to clarify whether there is a distinction between GCP principles and the Declaration of Helsinki, or whether the GCP principles should also encompass the Declaration. In particular, this participant noted confusion about which of these sets of principles research should follow, in the event of slight differences between them:

I think it's really helpful to say these are the principles we all need to strive toward. Then, sometimes where it gets confused is what is the difference and what is the conflict between GCP and the Declaration of Helsinki. For me especially whether I was supervising protocols myself or offering it, why should we have GCP and Declaration of Helsinki? That might be one thing moving forward. I know that it's two different bodies. One is for regulatory agencies and the other one is for assembly of medical practitioners, so it's not easy to get both of them, but at least to remove any conflict between the two statements… I propose if we have the principles of GCP, should that not encompass all the GCP, should that not encompass the Declaration of Helsinki and the principles of the Declaration of Helsinki? Somewhere have one common source of what are the principles on how simple research should be conducted. …You have two different things which are almost the same, but not quite. And then, you start getting into discussions. Which one is—if there is a slight difference—what is the now applicable thing we have to follow? Which of these do we adhere to? [ID# 08]

2.2.2.3 Section 3: IRB/IEC

Four participants said the guidance pertaining to IRBs/IECs was helpful to them. Two of these participants noted that the ICH E6 GCP guidance about ethics committee review was particularly helpful when they are working in countries where either IECs were not established or no legal framework for ethics review existed. Having guidance on IRBs/IECs in these situations established an internationally recognized standard by which they could ensure that good research was conducted, even in the absence of a formal regulatory framework (see also Appendix E, reference E5):

And, again, when this was first introduced, a lot of countries did not have ethics committees that actually met this criteria, and I think the whole move towards compliance with this one has been great, really strengthened that aspect of clinical trials… take the ethics committee review issue that there were a number of countries where ethics committees were not established in this way, and there would be problems, then, inspected around ethical review. And so, their own regulatory authorities were also raising this with the governments and would need to bring their ethical committee procedures into line with this international requirement. [ID# 11]

Participants also commented that they found the details about IRB composition, function, and operations to be useful, that the information on IRB member responsibilities contained was helpful for training new IRB members, and that the information contained in the IRB/IEC section was clear and easy to find:

I feel like it's very clear, and I would say it's very easy to pull out the information you needed. [ID# 17]

2.2.2.4 Section 4: Investigator

Thirteen participants described the ICH E6 GCP section on investigators as useful, with several commenting on multiple aspects of this guidance. The most commonly mentioned helpful elements of investigator guidance dealt with investigator responsibilities (n=8), informed consent (n=6), source documentation (n=3), and safety reporting (n=2).

2.2.2.4.1 Investigator responsibilities

Eight participants felt that having clear guidelines for investigator responsibilities was helpful. More specifically, five participants said they appreciated the guidance on investigator oversight, noting that this clarified that investigators are responsible for overseeing qualified study staff (eg, coordinators), but also that investigator oversight extends to personnel outside the immediate study team (eg, lab techs, radiology) and even to subcontracted services. One participant stated that the guidance should clarify that investigators in investigator-initiated multisite studies are responsible for ensuring qualified personnel and a qualified investigator at the other sites (see also Appendix D, reference D7):

[For] section four about investigator…that they should guarantee adequate number of qualified staff. That there should be documented trail of investigator supervision. We use this all the time when we are working, all the time. [ID# 03]

To communicate that they are responsible for the services that they subcontract was an amendment in the R2 to complete study procedures. This has been hard to put across. Many investigators think they can subcontract in our facility, but then they are not responsible anymore. I think that's the reason why the wording was put there originally. So, we are working

to communicate this. [ID# 03]

Three participants noted that description of investigator responsibility for ensuring adequate resources was helpful, as investigators should understand from the guidance that they are responsible for ensuring that there is sufficient staff time (both investigator and other staff) to cover the work of the study, as well as ensuring adequate staff training, a sufficient patient population, and the physical resources necessary to conduct the study. For investigator-initiated multisite studies, this responsibility extends to ensuring adequate resources at the other study sites.

> *I also talk about the resources because oftentimes I see physicians not allocating their own time. They've often way over-allocated. And I go through and say, per these guidelines, it is your responsibility to make sure that you have enough time to be able to adequately dedicate to this trial and your staff that you have staff that are qualified and trained to be able to do this. So, those are the big things. [ID# 17]*

One participant commented on the necessity of the investigator's understanding that they are also still responsible for the medical care of the patient, in addition to the study intervention. Another described that the investigator section of the guidance can also be useful for clarifying how CROs are supposed to interact with investigators.

2.2.2.4.2 Informed consent

Of the six participants who commented on the informed consent guidance in the investigator section, five noted that having clear guidelines for informed consent is helpful. Participants described using the informed consent section as a reference to ensure that all required information is included in a consent form, with one elaborating that the section sets a minimum standard for what should go into an informed consent document. Two participants indicated that they find this section to be a helpful template for building an informed consent document, and another noted that future revisions of E6 should include an option for e-consent (see also Appendix E, reference E6):

> *In chapter 4 regarding investigator, it also states pretty clearly all the information that has to go to, for example, an informed consent form. These parts are pretty helpful because it's a minimum consent or minimum standard what all of us must have, for example, with trial protocol and in informed consent form. [ID# 06]*

> *And, of course, essentially, informed consent as well, very, very helpful and, I think, have greatly improved that process. Naturally, as companies have been starting to look more at e-consent, it's becoming a little more tricky. I think that's probably one area that needs to be looked at now by you guys. [Interviewer: So, the GCP guidelines, should it include a section about e-consent?] It would be really helpful if they did. [ID# 11]*

One participant further described that having standard expectations for informed consent laid out by ICH E6 GCP enabled consent documents written in accordance with the E6 guidelines to gain wider applicability, such that they could be used across regions. This, in turn would allow the data generated to be used outside of the country in which it was collected:

> *…and, for example, through the effects of the informed consent form requirements laid out in ICH E6, those are particularly useful. They provide a template, in essence, for how the documents should be written and they make it easier for us to prepare a standard document that can be used across regions, which is a huge advantage, particularly when you're working in countries or regions where requirements aren't completely outlined. For example, regions outside of ICH. Although ICH members don't include necessarily all countries, what we do find is that most countries will follow recommendations laid out in ICH, particularly when it comes to ICH E6 …This is the benefit generally if you write a master informed consent form that complies with ICH requirements—adding in country-specific requirements afterwards is quite straightforward and generally won't result in a document that's unacceptable. And in countries where requirements aren't available, even those outside of ICH regions, the ICH template really becomes a gold standard there to ensure that you're conducting the research in a manner that would—permit that data to be acceptable for use outside of that particular country… [ID# 10]*

2.2.2.4.3 Source documentation

Three participants indicated that they find the language on source documentation in the investigator section of the guidance to be helpful, particularly in the context of training investigators on requirements, where it serves as a useful reference. One participant also commented, in relation to the previous note about investigator oversight of external personnel such as lab technicians or radiology staff, that although they consider this section of ICH E6 GCP very important, documentation of such investigator oversight is often lacking, possibly because investigators do not see the importance of generating the documentation, and obtaining the records is not reliably enforced (see also Appendix E, reference E7):

> *We are always using ICH combined with the local regulatory and legal. And then the source documents, of course. I think it was also a great incorporation of the R2 that more details what we are expecting for source documents. We are still having challenges with all this electronic source documents and the validation—the checking they are robust enough to be used as a source for research. Many investigators are not understanding what requirements should be met. And we end up talking directly to the ITB for at the hospitals and there are still a lot of training and learning to take place there. [ID# 03]*

2.2.2.4.4 Safety reporting

Two participants described helpful elements of the investigator guidance related to safety reporting. One placed the usefulness of this section in the context of training, noting that the guidance was helpful for explaining the safety reporting scope of responsibility and the difference between safety surveillance and safety reporting to investigators and clinical research associates. The other described referencing this guidance in the context of needing to review additional ICH procedures for AE reporting, in addition to following procedures prescribed by the local ethics committee and local laws.

2.2.2.4.5 Other

Three other participants commented briefly on helpful elements of the investigator section. One of these again noted that this portion of the guidance is useful for training, while another commented that the guidance contains useful considerations for both investigators and sponsors to keep in mind when setting up a trial. Finally, the third noted that in areas such as academia, where concepts like investigator qualification may not be well defined, ICH E6 GCP makes a clear statement on this topic (specifically, mandating that investigators be selected for trials based on qualification).

2.2.2.5 Section 5: Sponsor

Twenty participants commented on one or more aspects of the ICH E6 GCP guidance on sponsors that they found helpful. The most frequently mentioned helpful aspects of sponsor guidance dealt with sponsor responsibilities (n=13), quality management using a risk-based approach (n=8), quality assurance and quality control (n=5), and trial design (n=2). Two participants also commented generally that they like this section of the guidance, describing that all of the subsections are helpful and that the guidance is clear.

2.2.2.5.1 Sponsor responsibilities

Twelve participants said they appreciated that the guidance establishes clear guidelines for sponsor responsibilities. They said this has been helpful both in defining the roles of the various parties involved in a trial, including defining the role of the sponsor, and for helping to protect the rights, safety, and welfare of research participants (see also Appendix D, reference D8).

The most helpful guidance around sponsor responsibilities appeared to be that on sponsor oversight. Within the topic of oversight, participants described that the guidance specifies that the sponsor is ultimately responsible for all study oversight, including oversight of subcontracted and CRO activities, a clause that participants found to be a helpful addition. Separately, a participant noted that the guidance was helpful in defining that any activities not transferred to the CRO remain the responsibility of the sponsor (see also Appendix D, reference D9 and D10):

Yeah, I don't think the responsibility has changed. It's just that GCP became stronger in making sponsors responsible for the delegations of CROs. I've been in research for more than 20 years, and I've seen sponsors delegate entire CROs everything. And without being very engaged in what they were doing. And it comes from there. You still need to know what they are doing. You still need to check they are compliant, and everything is okay. And I see these roles, these oversight roles, not only being done more and more. And I think because it's—either it should be incorporated or GCP should be looking at how universal they become. Maybe CTTI can help with this. [ID# 03]

Actually, this section on sponsor responsibility has also been very helpful, particularly coming at it from the point of view of a CRO. We really appreciated the statement that any duties which are not transferred to the CRO remain responsibility of the sponsor. That was very clear. [ID# 11]

Two other aspects of sponsor oversight were also discussed. One participant described their internal organizational process for ensuring that site investigators follow GCP guidelines, based on the sponsor oversight guidance delineating sponsor responsibility for investigator adherence to GCP. Another participant noted that ICH E6 GCP language on sponsor oversight formed the basis for their organization's creation of a set of flexible study oversight SOPs, which can be adapted on a study-by-study basis depending on the study team's assessment of risk (see also Appendix E, reference E8):

Certainly Section 5, sponsor responsibilities, I'm deep into. Referring back to safety reporting and so on, it's good to be aligned between vendor and an investigator's site. The monitoring section we've done line by line assessments to make sure that we are doing that properly. We used it in our conversations with our potential partners or CROs, "Show us how you're adhering to the guidelines. What is your quality management system?" [ID# 16]

Additional comments on helpful aspects of the sponsor responsibilities section referenced guidance related to ensuring that site investigators are qualified to conduct the research and are not simply well-known opinion leaders, as well as guidance addressing how sponsors should handle voluntary or negligent noncompliance by investigators. A participant also described that the sponsor section of the guidance is helpful for supporting communication with investigators and sites, both by clearly defining study roles so that all parties know what they and others are working on and by encouraging between-site communication:

And explaining what these people do; especially on the oversight staff. Because it helps—when you are working in research, everyone has a role. And I think many times I work in studies where one CRO is always doing something, another CRO is doing something else. A sponsor is doing something else. There are several vendors involved. For me, it's critical to understand who is doing what, who to communicate with for what. And who's responsible for

what. And this helps the team work well because everyone knows what they are supposed to do. When these definitions of roles are not clear, then maybe the relationship becomes strained because it's not very clear or transparent what you are there to do. … 5.23 reminds the sponsor and CRO role for supporting communication between investigators. It talks about multi-center studies. And it says that sponsors should promote or encourage the communication of the study progress between investigators…But what it says is it's good to have this—encourage this conversation so people see part of a study of our global team. And they can also grow and learn from others in what they're doing and how they're dealing with protocol deviations and this type of thing. I think this is key to engagement in a successful study and motivation. [ID# 03]

2.2.2.5.2 Quality management using a risk-based approach

Eight participants discussed how the guidance on quality management using a risk-based approach as set forth in the sponsor section of the ICH E6 GCP guidelines has been useful to their work. Four of these participants especially liked the shift to risk-based monitoring established as part of the R2 revision, commenting that it was clear and helpful:

I think that kind of the move to the risk-based monitoring has been very helpful…And it means that you're not wasting a lot of time looking at data… And you can concentrate on the things that really are important like safety outcomes, primary outcomes. You're not spending two hours going to a site, looking at everyone's height or something that probably isn't that relevant unless you're doing a study on a growth hormone or something. So, I think that whole idea of being able to pick and choose and to concentrate, the whole risk-based elements say well what's important to look at here, where do the problems arise, I think that's really, really good. [ID# 07]

I definitely believe that the sections which speak about how to really assess risk, monitor risk, and really control risk is really a good—it's definitely an improvement to the ICH guidelines. Because on the one hand, previously there wasn't really a lot of talking about—offering around risk management, but I think it's really well spelled out and how to theoretically do it. That's what I really like about it. [ID# 15]

Several comments focused on helpful aspects of the ICH E6 GCP guidance related to monitoring. Two participants appreciated that the guidance includes an explicit statement about monitoring or auditing not always being necessary, and one participant noted the importance of defining the role of monitoring. Another participant found the guidance that monitoring can be centralized, and not always on-site, to be useful (see also Appendix D, reference D11):

I like the fact that they put monitoring in that you don't have to do it because remaining silent

on an issue indicated to people 100% at all times. [ID# 13]

Sometimes I use summary information to say that "Hey, you're going a little too far." …When we deal with QA and their auditing, I remind them that the section of audit says "if or when you perform an audit." There's actually no requirement to perform an audit. Now, we all do it as part of quality management, but sometimes they say—I could say, "Hey look, did you go a little overboard?" That's when we get mad at each other. [ID# 16]

Finally, a participant commented that one benefit of the sponsor guidance on risk-based management has been to force sponsors to foresee potential risks, such as a lack of study participants, during the trial planning phase and to take steps to mitigate them. Another participant liked that the R2 revision defines quality management systems and describes how they should be implemented (see also Appendix D, reference D12):

I think if I go directly to what I do and what is most important to me is of course, the quality management section where we had for the first time now with R2– the definition of quality management systems and how that should be implemented. The definition of critical processes, risk identification, risk evaluation, and also risk control… [ID# 21]

2.2.2.5.3 Quality assurance and quality control

Five participants commented on the helpfulness of guidance related to QA/QC, with each participant making a different point. One participant merely indicated that the information in this section was clear, and another praised the greater emphasis on quality management and quality assurance. Another participant pointed out that the ICH E6 GCP makes the need for a protocol clear by describing basic elements of high-quality research:

The aspect about quality assurance and quality control. It's the sponsor who is responsible for implementing quality control and quality assurance and it gives some more specific guidance in terms of SOPs and protocol…It gives us guidance. It tells us we have to have a protocol. If there wasn't a GCP, who tells us we need a study protocol? Is there any legal or is there any obligation? I mean, we would do a correct study, for sure, and if we don't have a protocol, but yeah, it's good that there is a protocol. It helped me in this sense because it gives me some base, guidance, and principles in how to do proper research. [ID# 09]

Two other participants provided more focused commentary related to QA/QC. One noted that any partners in the trial, such as CROs, are held to the same high standards the sponsor organization would use for themselves. The other participant expressed a need for guidance on quality indicators for other types of data, such as registry data, explaining that existing regulations may be too strict with regard to alternate sources of data (see also Appendix E, reference E9):

I also see that some things now might be a bit too strict when we go to a different kind of data. This is what we're seeing now. That we go to the more pragmatic trials, noninterventional studies, things like that. Then you cannot require every detail. Sometimes it might not be helpful, and it's been perceived also from the investigator side as too bureaucratic. So, we need to find the right balance of generating high-quality data, but then taking into consideration where is the data coming from. Of course, if we are using registry data, for example, they will not be as complete and as clean as when they are primary data collection, and we do it all for the study only, or for the trial only. But we need guidance. When can we use such registry data, and what are the quality sectors we need in this study? In a regulatory environment, we are talking here of maybe generating a comparator arm this data of secondary use, so data which are already entered in a database, in a registry. Can we use this data? What are the factors so we can decide yes, the quality is good enough, we can use this data? [ID# 23]

2.2.2.5.4 Other

Three other participants commented briefly on helpful elements of the sponsor section. One of these participants noted that this portion of the guidance is a useful framework for training PIs on investigator-initiated studies, in which the PI serves in both the investigator and sponsor role. While these PIs may have many years of experience in an investigator role, many have never taken on sponsor responsibilities and may be unaware of some requirements. Another participant pointed to training, this time on source documentation, commenting that the guidance is useful for educating clinical research associates and investigators on the maintenance and minimally requested site-level documents in the trial master files. Finally, the third participant noted that the guidance is helpful by encouraging a move toward electronic records, which may ultimately lead to wider acceptance of electronic documentation and e-signatures (see also Appendix E, reference E10).

2.2.2.6 Section 6: Clinical trial protocol and protocol amendment(s)

Four participants provided comments related to the clinical trial protocol and protocol amendments. Of these, two participants noted that this section is helpful because it provides a template for writing protocols. Another participant states that the section serves as a reference point for them in reviewing protocol documents for development partners. Finally, a participant commented that this section is helpful in focusing data collection activities according to study objectives—for example, when working in a phase 1 vs a phase 2 study (see also Appendix D, reference D13):

Pretty helpful, of course, is, for example, chapter 6, regarding the protocol that clearly states the different parts for clinical trial protocol. This is pretty clear, and you can build a template or so regarding all these paragraphs assigned to write clinical trial protocols. [ID# 06]

2.2.2.7 Section 7: Investigator's brochure

Four participants described aspects of the section on Investigator's Brochure as helpful. One participant reiterated their comment from the protocol section, noting that they also use the investigator's brochure guidance as a reference when reviewing documents for development partners. Another noted that this section is helpful because it is the only guidance they have for writing an investigator's brochure, but also called for it to be updated. An additional suggestion for improvement came from a participant who described this section of the guidance in positive terms but noted that the guidance could be expanded to improve investigator familiarity with investigator's brochure content (see also Appendix D, reference D14):

> *Yes, number three is to strengthen the role of the medical monitor and the decoding of the investigator brochure to clinical investigators. I like this section of the investigator brochure. But I still think many investigators are not totally familiar with investigator brochures. I think there's an opportunity there to improve that; improve that from implementation which is what I do every day when I work. But also, how can the guideline help. I wrote many investigators working for sponsors need to be better educated about both investigator brochure information and potential foreseeable risks in products and research. [ID# 03]*

2.2.2.8 Section 8: Essential documents for the conduct of a clinical trial

Seven participants described the Essential Documents section of the guidance as helpful. Of these, three noted the utility of having a complete list of potentially required documentation collected in one place. Two participants further described that, while the list of essential documents provided is exhaustive, the section also notes the basic or core documents that must be obtained during the trial and allows for flexibility. For example, while it specifies that curriculum vitae (CVs) must be obtained, it does not specify that they must be obtained every year, though it is often interpreted as such. A participant noted that examples would be helpful for avoiding incorrect interpretation of this section (see also Appendix D, reference D15):

> *And, of course, pretty helpful is chapter 8, with all the listings of all the documents. It should be in a better-ordered way, I think, as I just mentioned before. [ID# 06]*

> *I've complained about the essential documents list, but some of my younger colleagues would come back and say, "We've collected CVs annually," and I'll think, "Because their medical degree expired?" No, they're fine. If you need a license, a medical license to perform, and that is an annual renewal, then sure, collect that. And the nice thing about the Section 8 is it doesn't say we need a CV every year. But I think that examples really would've helped because people need to see the continuum. [ID# 13]*

Participants also commented on other aspects of the guidance on essential documents, noting variously that the requirements to retain and show previous versions of documents (version control) and to document investigator training ensure transparency in the conduct of a trial; that the section serves as a checklist to follow prior to investigational product release; and that trial processes are defined based on when essential documents are collected in the course of the trial (see also Appendix D, reference D16):

> *"Section Eight: Essential Documents for the Conduct of A Clinical Trial," that formed the basis of a checklist that we would use for IP release at my previous organization, and I imagine, here as well... And so, what we would do is we would use that to confirm that everything was available, that the package from the site was complete. And then, that would allow us to release the drug for use in a clinical study. [ID# 10]*

> *No. 1 is section eight, which is essential documents. I use that all the time to make sure that the investigator site binder—that documents are collected at the right time, that our processes are defined based on when we collect those documents, and how they impact the rest of the study. So, that's a really important part of what I look at. [ID# 14]*

2.3 Unhelpful aspects of ICH E6 GCP

Provided below is a summary of participants' narratives on unhelpful aspects of ICH E6 GCP and recommendations for renovation. Appendix F provides additional participant quotations on the unhelpful aspects of ICH E6 GCP. Appendix G lists examples participants gave related to the unhelpful aspects of ICH E6 GCP. We provide references in the sections below to link the summary information with participant quotations and examples in Appendices F and G.

All 23 participants discussed one or more unhelpful aspects of ICH E6 GCP. Thirteen participants provided overall commentary about how ICH E6 GCP has been unhelpful. Many of these participants also commented on specific parts of the guidance. We describe participants' general comments on unhelpful aspects of ICH E6 GCP, followed by participants' aspirations for each section of ICH E6 GCP.

2.3.1 General comments on the unhelpful aspects of ICH E6 GCP

General comments on unhelpful aspects of ICH E6 GCP consisted primarily of observations about the interpretation and implementation of ICH E6 GCP, including questions or concerns about its applicability for different types of clinical trials and challenges related to complying with the guidelines. Some participants framed their comments in terms of distinguishing between the strict application of ICH E6 GCP and the spirit of GCP, that is, recognizing that the principles of GCP are valuable guidance for conducting clinical research but that the guidelines may need to be adapted to particular circumstances or contexts.

2.3.1.1 Need flexibility to accommodate different types of research and address applicability to nonclinical trials

Six participants made general comments about unhelpful aspects of GCP, indicating that the guidelines should be flexible enough to accommodate different types of clinical research. Two participants pointed out that not all clinical trials involve drug development and/or improvement:

> *Because remember that many things that you do in clinical trials have nothing to do with drug improvement. If you want to do surgery, open surgery, versus laparoscopic surgery and robotic surgery, they've got nothing to do with drugs. [ID# 02]*

This participant also said that the application of GCP to different types of trials needs to be fit for purpose and that clinical trialists, sponsors, and regulators need to collectively decide on the best approach (see also Appendix F, reference F1).

Another participant noted that they use the spirit of GCP for observational studies because it provides a strong foundation for any type of clinical trial:

> *I definitely separate what I call "observational studies" from interventional studies. Intervention is when there is some kind of intervention. Observational… that's where we really use the spirit of GCP. I know that I'll start by saying for all of our clinical work, the 13 principles are pretty important. It doesn't matter whether it's for a drug application or a device application. The principles, in general, are very good and that north star for clinical research. [ID# 12]*

This participant also described the importance of flexibility in the application of GCP to different types of trials while focusing on what matters most—patient safety, quality conduct, and quality data (see Appendix G, reference G1).

On a similar note, two participants raised questions about the scope of ICH E6 GCP and noted the need for clarification about whether and how ICH E6 GCP applies to different types of trials beyond regulatory drug trials. Participants raised questions about when full compliance is mandatory and to what extent GCP applies to diagnostic research, device trials, cluster randomized trials, epidemiological research, or behavioral studies (See Appendix G, reference G2).

One participant stressed the importance of recognizing that it may not be possible to meet all ICH E6 GCP guidelines in clinical trials conducted during global health emergencies (eg, Ebola vaccine trials). Full compliance is the goal, but compromises may have to be made based on an appropriate allocation of resources while striving to maintain the highest quality standards (see Appendix G, reference G3).

Another participant noted the importance of recognizing that the size, capacity, and/or expertise of a sponsor affects their ability to interpret and implement ICH E6 GCP guidelines. In this regard, it would be helpful to provide guidance, examples, and best practices in interpreting and implementing GCP for small and medium-sized companies. This participant commented that the guidance and best practices or examples would not need to be written into the ICH guidelines and become mandatory:

> *I think it would be really helpful to have a more robust guideline or guidance available for direction how interpretation of certain sections really should look like. Not in a way that it's mandatory, but as I said initially, I think with some examples. It doesn't really need to be written into the ICH guidelines itself, but in a company kind of pamphlet with case studies or examples would be really helpful so that there is a broader understanding on how good can look like. [ID# 15]*

2.3.1.2 Clarify implementation of guidance

Two participants commented that the ICH E6 GCP guidelines are too open to interpretation based on research role. For example, investigators and clinical operations personnel may have different interpretations of how to implement the guidelines. One of these participants said that clarifying how to implement the guidelines could consist of adding information to describe the minimum structure and framework to meet GCP standards. While providing clarification would help stakeholders meet the minimum standard for GCP in clinical trials, this participant felt it is not necessary to mandate it as a requirement; rather, the guideline serves as a process guide for GCP in trial implementation. Clarifying roles and requirements—whether for investigators, sponsors, or CROs—would enable stakeholders to know what is expected of them to prevent inspection findings and facilitate marketing approval.

2.3.1.3 General recommendations

One participant provided a general recommendation for updating ICH E6 GCP: acknowledge changes in drug development, different types of studies, and data sources. This participant explained that the guideline has worked well over the past decade and that it is important to have a common standard; however, the guideline needs to be modernized because drug development is changing. They acknowledged the challenge of providing this guidance and appreciated the approach of providing guidance about different types of clinical trials in separate annexes. Such guidance would, for example, clarify whether registry data can be used as a comparator arm in a clinical trial (see Appendix F, reference F2).

Another participant recommended that the ICH E6 GCP revision include explicit recognition of other stakeholder groups, such as communities and patient associations, who should be involved in the process of designing and conducting clinical studies:

…it's incredible that the community and the patient association, but also communities, as such, are not even mentioned as research stakeholders who should be involved in the process of designing and conducting the studies. And, this is, after 25 years of research in the HIV and tuberculosis researchers from these disciplines, they even wrote some good participatory practices to help people to navigate the collaboration with the researcher—with research communities…I find this quite strange. [ID# 04]

2.3.1.4 Miscellaneous unhelpful general aspects

One participant said that, while ICH E6 GCP does not mandate repeated GCP trainings, sponsors in the United States interpret the guideline as requiring GCP training for each of their sponsored trials (see Appendix F, reference F3).

2.3.2 Unhelpful aspects of specific sections of ICH E6 GCP

2.3.2.1 Section 1: Glossary

Four participants identified unhelpful aspects of the glossary section, and some offered recommended revisions. One participant said the glossary's definition of a clinical trial is not consistent with the World Health Organization (WHO) definition (see also Appendix F, reference F4).

Another participant noted that the definition of "vulnerability" could be expanded to include information about social and economic vulnerability. The glossary's definition of "certified copy" needed some clarification, according to another participant (see also Appendix G, reference G4)

I could tell you that there was a lot of confusion around the certified copy. I got so many questions about this and it took me a long time to get my head around this. Do you know the whole thing of having a certified copy? I think even the wording of that could be possibly clarified because it basically says that it has to be verified. So, say if you're printing out lab results from a computer. You have to then sign and date to say yes, what's on the page is exactly what was on the computer database. That's our understanding of it, but it's taken a while to get here. The same with if you photocopy a document, make sure it exactly matches the original. There's no pages missing and all that. There's no data cut out of it. So, in a way, it's quite simple. But it did seem to cause a lot of confusion initially...Because it talks about paper media, which I suppose is the easier one, but also it talks about any media – any other type of media. [ID #07]

One participant needed clarification of the term "validation of computerized system," specifically how system environments should look when used to generate clinical research data for an authorization application (see Appendix F, reference F5).

2.3.2.2 Section 2: The Principles of ICH GCP

Eight participants discussed revisions of one or more of the 13 GCP principles. Their comments ranged from principles in need of additional guidance or clarification, to updating the informed consent principle to reflect different forms of informed consent, to challenges of following certain principles given global variations in privacy rules, to a concern about the principles being used as a checklist during inspections. Comments on each principle are described below.

Principle 2.9: Freely given informed consent should be obtained from every subject prior to clinical trial participation

Two participants commented on the need for revisions of this principle. One participant said the principle should be updated to reflect different types of informed consent, such as delayed consent, opt-out consent, waiver of consent, and e-consent. Elaboration of these different kinds of consent could be provided in the appropriate sections of the guideline (see Appendix G, reference G5). Another participant stressed that the guideline should clarify that informed consent must be fit for purpose based on the type of trial (eg, experimental first-in-human studies vs labeling or repurposing an existing drug, comparing two types of surgery). This participant also discussed the need to simplify and streamline consent forms as part of the process of making informed consent fit for purpose (see Appendix G, reference G6).

Principle 2.10: All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification

Two participants provided feedback on this principle. One participant recommended clarification of the meaning of clinical trial information:

> *I think I was focusing on this [Principle 2.10] because clinical trial information is, on one hand, patient data, on the other hand, all this metadata—for example, information regarding ethical approvals, health authority approvals, additional documentations or so, to make it clear that all these things are mentioned. On the one hand, we have data, and in the data, we have these principles of auditors, so the data must have data integrity, nobody can change data, but we must also have concise documentation information regarding all these other issues to prove that all these data are also collected properly, handled properly, and so on. [ID# 06]*

The other participant said it would be helpful to clarify the meaning of retention requirements for the length of storage and the retention of different types of media (see also Appendix G, reference G7).

Principle 2.2: Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks

According to one participant, analysis of benefits and risks is often not done in trials and adding guidance about how to quantify the risks outweighing the benefits may be helpful (see also Appendix G, reference G8).

Principle 2.3: The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society

One participant described that in their field, trial patients may be sick to begin with, thus the goal of treatment is improvement or cure:

> *…we have to be careful when you say we just want that the patient—we expect that the patient have been well. Within several disease, especially in my field, the patient are sick to begin with, so their wellbeing will be either a cured or improved. [ID# 22]*

Principle 2.4: The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial

One participant commented on the need to define the meaning of "adequate" in this principle.

Principle 2.11: The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s)

One participant discussed the challenges of sponsors ensuring the privacy and confidentiality of records given regional and national variations in privacy rules and suggested that further guidance is needed, along with guidance on how to re-consent patients for follow-up research without having direct access to patient contact information (see Appendix G, reference G9).

Miscellaneous recommendations

One participant noted that the principles are high-level and are being used as a reference point for inspections, which was not their intended use (see Appendix F, reference F6).

2.3.2.3 Section 3: IRB/IEC

Ten participants discussed concerns and difficulties they have experienced in implementing Section 3, with many of these participants offering recommendations for revisions. Their comments generally focused on the need for additional guidance or clarification, including guidance on the oversight of ethics committees to ensure they are following GCP, allocation of responsibility for monitoring site compliance between IRBs and sponsors, addressing the challenge of composing and training IRBs in countries with low study density, and standards for conducting research in public health emergencies.

Participants also commented on the need to update this section to reflect variation in the composition and responsibilities of ethics committees by country, changes in technology that affect trial conduct, and data privacy. Concerns were also raised about multiple ethical reviews, the independence of commercial IRBs, and the potential for GCP requirements for IRB review of safety reporting to discourage people from volunteering to serve on ethics boards.

Two participants suggested the IRB/IEC section be updated to recognize variation in ethics committee requirement by country. These variations include differences in who submits to the IRB (eg, investigators vs CROs), countries with central IRBs, and differences in requirements for the frequency of reports to the IRB/IEC. A recommended update to the guidelines would involve specifying the necessity of checking with the local/regional ethics committee each time an IRB/IEC issue arises (see Appendix F, reference F7). Additional suggested updates to this section include adding a chapter on the responsibilities of IRB/IECs versus the responsibilities of health authorities, since health authorities are also involved in efforts to ensure patient safety and data integrity. The same participant noted a need to update the section to reflect changes in technology affect trial conduct and additional guidance on data privacy, particularly with regard to long-term sample storage for future research (see also Appendix F, reference F8).

One participant discussed problems with multiple ethical reviews, with each IRB making changes along the way, and argued that ethics reviews should be fit for purpose (see Appendix F, reference F9). Another participant drew upon their experiences conducting clinical trials in Latin America to discuss the challenge of composing and maintaining IRBs in countries with low study density, noting that these countries may not have pools of qualified and experienced people to draw upon in developing IRBs. Their recommendations included developing guidelines for the type of training needed to serve on an IRB, considering collaborative or remote reviews, and providing best practices (see also Appendix G, reference G10).

Another participant stated that, while this section includes good information about IRB composition, functions, and operations, there is a need for clarification of IRB and sponsor responsibility for monitoring site compliance, suggesting that this responsibility may be better suited for sponsors than for IRBs (see also Appendix G, reference G11).

One participant commented that ethics committees sometimes instruct investigators to do something that directly contradicts GCP. The participant suggested that it may be helpful for ICH to consider adding guidance about the need for oversight of ethics committees to ensure they are following GCP (see Appendix G, reference G12). Another participant observed that the public's trust of for-profit commercial IRBs in the United States may be undermined by concerns about their independence (see Appendix G, reference G13). Another participant described that the burden of ICH E6 GCP requirements for IRB review of safety reporting is a disincentive for volunteering on ethics boards,

and another participant stated that, although their country's laws supersede the IRB/IEC guidelines, it is still an important section to include in the guidelines.

2.3.2.4 Section 4: Investigator

Fourteen participants commented on one or more unhelpful aspects of the investigator section. Most of these participants discussed multiple challenges and experiences they have encountered in implementing the guidelines in this section and also provided suggestions for improvement.

2.3.2.4.1 Investigator responsibilities

Five participants discussed issues and concerns related to investigator responsibilities, and most of their comments focused on reassessing and reallocating some of the responsibilities assigned to investigators. Two recommended more clarity around the meaning of the paired term "investigator/institution," which is used throughout this section. While separating the combined term may not be feasible in the guideline, participants said it would be helpful to document the respective responsibilities of investigators and institutions (see Appendix F, reference F10). Two participants questioned whether investigators should bear responsibility for submitting reports to the IRB/IEC and final reports, one of whom mentioned that sponsors are also identified as responsible for report submission. Allowing flexibility at the local level to determine whether the investigator or sponsor submits these reports and recognizing that there may be variations in reporting requirements and submitters were offered as suggestions (see Appendix F, references F11 and F12).

Another participant commented that there is a lack of clarity about the required content of the investigator's report and how the investigator's report relates to the final report. One participant noted that investigators should be responsible for medical care and decision making in remote trials to ensure trial participants' safety (see Appendix F, reference F13). Given sponsors' access to greater resources to audit individual service providers, another participant observed that sponsors, rather than investigators, should be responsible for ensuring service providers' qualifications (see Appendix F, reference F14).

2.3.2.4.2 Update to accommodate new technologies/processes

Specific suggestions for updates included a concern about the environmental impact of archiving paper copies and a suggestion that the ICH provide guidance on what can be archived digitally and what must be archived in paper form (see Appendix F, reference F15), rules for recording and documenting remote trial data, and guidance on defining source data in the era of electronic case report forms (eCRFs) (see also Appendix G, reference G14).

One participant suggested updating this section to include the need for human oversight of data collected by artificial intelligence, specifically guidance about apps, data transfer, and remote data collection (see Appendix F, reference F16).

2.3.2.4.3 Safety reporting

Two participants commented on how the safety reporting requirements contribute to investigator burden. They explained that investigators often complete multiple forms for the same SAE and that the timeline for immediately reporting individual SAEs means that investigators are often unable to get a sense of SAEs in the aggregate. This requirement, combined with the volume of AE reports that investigators must review, lack of differentiation in AE reporting between known and well-documented side effects of a study drug and other AEs, makes it difficult for investigators to get a sense of the big picture related to AEs that are related to the study drug. Streamlining the safety reporting requirements would increase efficiency and investigators' understanding of investigational product-related AEs and decrease investigator burden (see Appendix G, reference G15). Another suggestion for streamlining safety requirements and reducing investigator burden involved drawing upon electronic health records or hospital records rather than completing multiple forms for the same SAE.

2.3.2.4.4 Adequate resources

Two participants said that guidelines about investigators having adequate resources to carry out the trial are either not fully understood or are not respected by investigators. One of these participants explained that investigators may not fully understand the implications of having the potential to enroll enough patients to meet sample size requirements. While investigators may downplay smaller than intended sample size as a function of slow enrollment, they may not fully grasp the consequences of under-enrollment. These consequences include inability to complete the trial, patients taking investigational drugs "for no good reason," and inability to use the data from the trial. This participant stated that explaining the importance of having adequate resources to meet sample size requirements would not necessarily have to be incorporated into the ICH guidelines but could be addressed in a white paper (see Appendix F, reference F17). The other participant commented that the requirement for the PI to have adequate resources is often not respected. This can take the form of the PI having inadequate time available to meet their responsibilities, such as being unavailable when contacted by the CRO, which then must deal with a sub-investigator. It can also take the form of a PI who delegates the responsibility of following patients in a trial to a sub-investigator, even though the PI is responsible for signing CRFs. This participant recommended that the ICH E6 GCP guidelines emphasize PIs' responsibility to be available for study-related communication or meetings on a regular basis. In addition, the guidelines could be amended to state that, in cases where the PI is not following patients, it is allowable for sub-investigator who is following patients to sign off on CRFs and attest to the completeness and accuracy of the data (see Appendix G, reference G16

2.3.2.4.5 Clarify language

Two participants raised concerns about some of the language in the investigator section, one of whom pointed out that the meaning of "adequate and accurate source documentation" is too open to interpretation and should be clarified. Providing examples of source documentation that meets the criteria would be helpful, including a statement indicating what such documentation should look like (see Appendix G, reference G17). The other participant noted that additional guidance about which types of data can be recorded on a CRF would be helpful (see also Appendix F, reference F18).

Five participants provided comments about various other unhelpful aspects of the investigator guidelines, including one participant who offered several recommendations for revisions related to informed consent in lower- and middle-income countries or countries with low literacy levels. Suggestions included adding guidance on consenting minors, specifically, allowing for culturally appropriate ways to consent orphans in lower-and middle-income countries when a legal tutor is not available:

> *There a number of things which are—or something on the consent of minor people. There is only a request of legally acceptable representative, but in many lower/middle-income countries, there is not legally acceptable representatives, so what should we do in such case? …With children, I've seen it myself that if you followed ICH guidelines, you can only accept informed consent for an orphan from a legal tutor but the reality is that in many lower-/middle-income countries in rural areas, people do not go to the tribune or to the capital to be endorsed, and there is a kind of tutor which is recognized by customary law. So, what should we do there? Should we just refuse those kids in research and this would be unfair? Or, should we violate GCP, or maybe, GCP could consider other culturally adapted way to check that the tutor or the person is tutor is acting in the best interest of the minor, or not? That's completely not clear. [ID# 04]*

The participant also described that the ICH guidelines do not address the question of whether, in the case of a long-term clinical trial or sample storage, someone who was consented as a minor should be re-consented when they come of age. Thus, guidance is also needed about re-consenting for long-term sample storage if someone was consented while a minor and comes of age.

The same participant said that the ICH guidelines do not mention the potential benefit of using audiovisual and video tools for informed consent in lower- and middle-income countries with low literacy or no written language (see also Appendix G, reference G18)

Based on their own experiences, this participant also commented on the importance of recognizing how the decision about whether to participate in clinical trials is shaped by lack of access to health care among socially vulnerable or excluded populations:

We have to acknowledge there is nothing that much that we can do for that because we should solve out the problem of poverty, but we should acknowledge that these people are vulnerable in research because their capacity to freely decide is hampered. It's not only small children and old people with Alzheimer's who are vulnerable, but also socially excluded people, people without access to healthcare are really vulnerable [ID# 04] (see also Appendix G, reference G19).

One participant commented on the need to simplify documentation of investigator qualifications, particularly the administrative process related to site selection. Another participant recommended reducing the complexity of monitoring, reporting, and consenting requirements to make them more fit for purpose and less time-consuming for investigators. The randomization and unblinding procedures section of the guideline is general, and one participant stressed that it would be helpful to indicate that randomization and unblinding procedures are protocol-specific.

2.3.2.4.6 Make process-oriented

One participant highlighted what they view as the need to reorient the guideline from a prescriptive to process-oriented approach on how to implement the central components of GCP:

I think the investigator chapter is quite good for the investigator, but again it's too prescriptive. If someone just follows this without thinking, it can get them in trouble I think.

[Follow-up question: So how would you fix that?]

I think there has to be – I think the investigator themselves has to make sure that there's enough ownership in terms of that… how are we going to implement the principles, not just telling them they have to have a document here and how they have to have a document there or whatever. They have to have qualified personnel. So…bringing it to an ultimate objective, which is patient safety or quality data or personnel that are qualified to do the job right [ID #12].

2.3.2.4.7 Miscellaneous concerns

One participant voiced concern from a sponsor's perspective about the investigator section, because they have the least amount of control over it, noting that they fear that something will be missed in a trial that can dramatically change the assessment of a study drug's efficacy (*see Appendix G,* reference G20).

2.3.2.5 Section 5: Sponsor

Eighteen participants commented on unhelpful aspects of the sponsor guidelines. Most of these participants discussed multiple challenges and experiences they have encountered in implementing the guidelines and also provided suggestions for improvement. The three most frequently mentioned

problem areas of the sponsor guidelines related to monitoring (n=7), quality management using a risk-based approach (n=5), and trial management, data handling, and record keeping (n=5).

2.3.2.5.1 Monitoring

Participants mentioned the following challenges with implementing the guidelines in the sponsor section together with recommendations for renovation:

- Noncommercial sponsors lack financial resources to cover costs of external monitors. ICH should consider developing guidance allowing flexible approaches to monitoring for low-risk studies conducted by noncommercial sponsors (see Appendix G, reference G21).
- The guidelines do not address confidentiality and privacy issues in decentralized trials. Guidance on how to implement monitoring in home-based decentralized trials to address confidentiality and privacy issues is needed (see Appendix G, reference G22).
- Implementing a quality-by-design approach to risk-based monitoring involves a shift from a retrospective monitoring approach to a proactive approach that "means that you have to think about things which could happen, but have not happened" to ensure that you do not have any issues during a trial (see Appendix G, reference G23).
- Monitoring roles and responsibilities have changed. The guideline should be updated to reflect changes in monitors' responsibilities and should include information about new roles and tasks (see Appendix G, reference G24).
- Clarification needed about the different types of monitoring, particularly how they relate to remote clinical trials (see Appendix G, reference G25).
- Monitoring of every detail in medical record is time consuming and may be irrelevant to the trial's research questions.

One participant expressed concerns about the adequacy of using a centralized monitoring approach and its implications for inspections. They recommended clarifying that, if centralized monitoring is based on an adequate risk-based monitoring plan, it will be considered appropriate. They suggested that sponsors and CROs should agree upfront to a monitoring plan based on a risk-based assessment approach to avoid problems with audits (see Appendix G, reference G26).

Another participant stated that a risk-based monitoring approach can be taken to the extreme, with minor deviations from the risk-based approach viewed as major protocol deviations. They recommended that GCP allow for flexibility in the risk-based approach based on a recognition that there are differences in the global standard of care, particularly in low-resource settings and/or the Global South (see Appendix G, reference G27).

2.3.2.5.2 Quality management using a risk-based approach

Five participants described a lack of clarity about the meaning of quality risk management and quality tolerance limits and their implementation. They noted that ICH E6 GCP does not mandate a risk management approach, but that industry's interpretation of GCP becomes the required standard. Participants explained that lack of understanding about these key concepts has resulted in individual sponsors overcompensating to ensure GCP compliance, leading to complex documentation requirements that have made trials more difficult rather than easier to conduct. They expressed that sponsors' misinterpretation of a risk-based approach results in over-resourcing both low- and high-impact risks.

Participants also described that the term "quality tolerance limits" is still misunderstood three years after the release of ICH E6 GCP, creating problems with implementation. Part of the confusion, according to one participant, is that the concept is borrowed from manufacturing practice and refers to upper and lower limits. This participant described that the concept is inappropriate for pharmaceutical studies because these studies are not based on planning to set a lower limit of, for example, too few SAEs or the lowest level of inappropriately randomized patients that will be considered acceptable. Since one goal in quality clinical trials is to aim for no deviations, the participant stated that it raises the question of why sponsors would want to aim for a lower limit of deviations. This participant suggested that "set thresholds for action" would be a better, more understandable concept than quality tolerance limits (see also Appendix F, reference F19). Participant suggestions for addressing these concerns include clarifying the meanings of quality risk management and quality tolerance limits and reinforcing the guidance that sponsors should decide which risks to accept.

Participants also said that the quality assurance/quality control guidelines increase complexity and burden and are a disincentive for conducting clinical research. They stated that this may especially be the case for researchers conducting smaller, investigator-initiated, and/or noncommercial studies, who may not find it feasible to continue conducting clinical trials. As a result, the pharmaceutical industry may also be less likely to fund smaller, postapproval, hypothesis-testing drug studies. Participants felt that, overall, the guidelines make pharmaceutical sponsors wary about investing in anything but simple, innovative, decentralized trials (see Appendix G references, G28—G32).

Three participants raised concerns that inspections are still based largely on ICH E6 (R1). They described that sponsors have implemented a risk-based approach to quality management, but inspections based on R2 are rare and sponsors have not yet received feedback about whether their approach to risk-based monitoring is acceptable. Participants suggested that inspectors use the current guidelines in inspections (rather than R1) so sponsors will know whether they are implementing a risk-based management approach correctly. In addition, these participants voiced uncertainty about what revising the guideline again will mean for inspections, since inspectors are still relying on R1 (see Appendix G, references G33—G34).

2.3.2.5.3 Trial management, data handling, and record keeping

Five participants commented on a lack of clarity on data handling and record keeping. One participant recommended a number of revisions to improve the data handling and record keeping guidelines, including:

- Providing more guidance on computer validation systems, particularly with regard to electronic health records
- Clarifying how inspectors are monitoring based on the guideline
- Specifying that the site and the sponsor are responsible for validating systems under their control
- Considering requiring vendors who are transferring hospital records to electronic systems to be GCP-compliant (see Appendix G, reference G35).

Other participants' recommendations included:

- Clarifying that data handling and record keeping should be fit for purpose and identifying requirements for regulatory versus nonregulatory trials
- Clarifying why, in e-based studies, sites must keep backup CDs of the data archive when sponsors are responsible for maintaining the archive
- Clarifying how long records must be retained and whether retention requirements vary by type of media (see Appendix G reference G36)
- Clarifying that data protection guidelines vary based on local requirements and that the ICH guidelines may need to be adapted
- Adding guidance about following the General Data Protection Regulation, which is enforced in Europe (see Appendix G, reference G37)

2.3.2.5.4 Need for greater clarity in this section and throughout the guideline

Two participants commented on the need for greater clarity in this section and throughout the guideline in general. One participant suggested changing "may" language to "should" language, because the GCP guidelines are an international document and there are varied interpretations of these terms. Some people may interpret "may" as optional, whereas others may interpret it as a requirement. The participant said that nuances in the meanings of these terms (eg, between American and British English) may lead to different interpretations. This participant also suggested that ICH consider being clear about when the guidelines must be implemented as opposed to when

implementation is optional (see Appendix G, reference G38). The other participant stated that the document is not specific enough and recommended that ICH provide more guidance on how to implement the guidelines.

2.3.2.5.5 Safety Reporting

Two participants spoke of the need to revise the safety reporting subsection of the sponsor guidelines. One participant said there is a need to take more of a risk-based approach to safety reporting. In other words, it needs to be "adapted to the level of knowledge already available, and it's not working like this." They described that adapting the timeline and frequency of safety reporting for known AEs, other than SAEs or unexpected AEs, would help to address this issue. In addition, one of these participants noted that the ICH E6 GCP guidelines are premised on a model of single drug development and single drug use, yet treatments may consist of a cocktail of drugs or may be multimodal, including the use of devices. They stated that this can create difficulties for allocating AEs to a specific drug or modality. They recommended updating the approach to safety reporting from its current focus on single drug development and trials to multimodality and/or device trials. They stated that it is also important to involve stakeholders from multimodality and device trials in the ICH E6 GCP revision process to refocus on patient safety over the current focus on product development (see Appendix G, reference G39).

The other participant said there is a need to reduce investigator burden related to reporting AEs and suggested that ICH provide guidance on the use of statistics in AE reporting to give investigators an overall picture of AEs on a regular basis (see Appendix G, reference G40).

2.3.2.5.6 Shipping, manufacturing, and labeling investigational product(s)

One participant stated that problems with ensuring the quality of investigational products in lower-/middle-income countries without stringent regulatory authority can create challenges for following GCP and recommended that the ICH address this issue in the revised guidelines (see also Appendix F, reference F20). Another participant observed that the interaction between local and ICH E6 GCP guidelines with regard to shipping, manufacturing, and labeling drugs, particularly in Europe, makes "things very complicated" and increases sponsors' work. They also noted, however, that this is "probably not an ICH issue, but probably a European issue" (see Appendix F, reference F21).

2.3.2.5.7 Sponsor responsibilities

One participant recommended defining sponsor responsibility for investigator-sponsored studies (see Appendix F, reference F22). Another participant noted that the ICH guidelines do not distinguish between commercial and noncommercial sponsors, leaving open the question about implications for the allocation of responsibilities by sponsor type (see Appendix F, reference F23).

2.3.2.5.8 Guidelines need to be updated to accommodate new technologies and processes

Two participants described the need to update the guidelines to accommodate new technologies and processes. Both participants suggested adding guidance on data sharing and compliance, including examples of implementation and updates to the data privacy and record keeping guidelines (see Appendix G, reference G41) and to the guidance on sample sharing (see Appendix F, reference F24).

Four participants provided information about various other unhelpful aspects of the sponsor guidelines:

- Laboratory quality management: One participant noted that using accredited labs is not always feasible in lower-/middle-income countries (see Appendix G reference G43).
- Obtaining IRB/IEC approval: One participant noted that the guidelines are missing information about multiple ethics reviews. Recommendations included adding clarification about obtaining ethics review for multicenter, externally sponsored, and multinational clinical trials, as well as adding information about multiple ethics reviews of trials conducted in the Global South by sponsors from the Global North (see Appendix F, reference F25).
- Investigator qualification: One participant noted that the guidance about a qualified physician providing medical oversight may limit the pace of enrollment and that the pool of potential study participants might increase if nurse practitioners and physician assistants were allowed to be responsible for providing medical care (see Appendix G, reference G44).
- Investigator selection: One participant stated that the sponsor guidance is not specific enough about how to determine investigator qualification and suggested that a standardized tool to assess whether an investigator is qualified and competent to conduct a trial would be helpful (see Appendix G, reference G45).
- Contract research organizations: One participant mentioned that they found the CRO section in the current revision of the ICH E6 GCP guidelines to be helpful, particularly with regard to Section 5.22 about sponsor oversight of trial-related duties delegated to CROs or their subcontractors. The participant suggested that the ICH define “trial related duties” within the realm of ICH E6 GCP to facilitate the delegation and monitoring of those tasks (see also Appendix G, reference G46).

Two participants discussed the need to expand stakeholders’ involvement in the revision process, one of whom provided information about several resources that interpret the guidelines. They recommended that the ICH consider adding a separate document listing resources for interpreting ICH E6 (see Appendix F, reference F26).

Two participants commented on other concerns related to the sponsor guidelines. One said that the choice of whether to follow GCP for noninvestigational medical product trials is left up to the sponsor, sometimes they choose to follow GCP and other times they may not follow GCP and believe that having consent from patients is sufficient. The other participant described that, while ICH E6 GCP provides a harmonized approach, problems can arise in how countries interpret the guidelines. They gave the example of sponsors' control over electronic data capture systems in Europe and the risks for sponsors to potentially "interfere with that data" (see Appendix F, reference F27).

2.3.2.6 Section 6: Clinical Trial Protocol and Protocol Amendment(s)

Six participants raised concerns about the usefulness of this section for protocol development and the vagueness of the section leaving it too open to interpretation. Four of these participants provided recommendations that ranged from developing an interactive tool about protocol development to including a GCP-compliant protocol template in the guidelines, emphasizing the importance of conducting a quality control check on protocols, defining key concepts, and stressing the importance of tracking versions of the protocol and their impact on other study documents.

Section is not very helpful for protocol development

One participant commented that this section was not helpful in providing information about how to write a GCP-compliant protocol and suggested that the ICH consider incorporating interactive tools about protocol development into the guidelines as an addendum, an annex, or an online tool (see Appendix G, reference G47).

Another participant stated that this section provides minimal content and needs to be updated. They recommended that the ICH provide additional guidance on how to make protocols simpler, more feasible, and more operational, along with more guidance about what should not be included in a protocol (see also Appendix F, reference F28).

Another participant observed that other ICH guidelines (eg, E9) provide better guidance for protocol development. They also noted that Section 6 of ICH E6 GCP provides only basic information and that it reads like a checklist of items to include in a protocol rather than providing substantive guidance about protocol development (see also Appendix G, reference G48).

Another participant observed that the protocol section is too vague and open to interpretation. They elaborated that different interpretations and implementation of protocol guidelines in multisite trials can result in poor-quality data. They suggested that having a GCP-compliant template and adding guidance about the importance of conducting a quality control check on protocols to ensure that they have all the required elements would help to address this issue (see also Appendix G, reference G49).

The same participant suggested that the subsection on quality control and quality assurance be expanded to include definitions of the meaning of quality control and quality assurance of the data (see also Appendix F, reference F29).

Finally, one participant mentioned information to add to Section 6, which included guidance on version tracking and the impact of protocol version changes on other study documents (see also Appendix G, reference G50).

This participant also said it would be helpful to add guidance on how to distinguish between substantial and nonsubstantial changes in the protocol.

2.3.2.7 Section 7: Investigator's Brochure

Seven participants commented on unhelpful aspects of the investigator's brochure guidelines. Some of these participants offered suggestions for improving this section. One participant said that the section is not helpful because they rely on the investigator's brochure from the manufacturer or pharmacy that produces the investigational product. One participant recommended clarification about whether it is necessary to rewrite an investigator's brochure if the trial is using an old drug for a new purpose. Another participant pointed out that companies in Europe struggle with an EU requirement that the investigator's brochure include a section about investigational product safety that provides information about whether an AE is known or new. They suggested that there may be a need for guidance about the impact of local regulations on the content of the investigator's brochure (see also Appendix G, reference G51).

A participant observed that many physician-investigators may not have the scientific background to fully understand the investigator's brochure. Their concern about investigators' full comprehension of the safety profile of the investigational product and information in the investigator's brochure prompted a recommendation that this section of the GCP guideline emphasize the need for sponsors to better educate investigators about the investigational product (see Appendix G, reference G52).

Another participant noted that this section is brief and broad, considering the complex content of investigator's brochures. They suggested adding a standalone document that expands upon the content and purpose of the investigator's brochure [ID #06] (see also Appendix F, reference F30).

Lastly, one participant recommended adding guidance in this section that emphasizes the importance of version tracking the investigator's brochure and the need (as appropriate) to update other study documents (such as informed consent documents) when changes in the brochure occur (see Appendix F, reference F31).

2.3.2.8 Section 8: Essential Documents for the Conduct of a Clinical Trial

Eight participants commented on difficulties related to guidance about the trial master file, the ways that various interpretations of GCP affect the essential documents that are collected, the need for clarification or additional guidance about the required frequency for updating CVs and the purpose of the insurance statement, and the utility of collecting all essential documents. Recommendations related to improving the shipping records for the IP and trial-related materials subsection were also provided.

One participant commented on the challenges of creating a trial master file in under-resourced countries, specifically nothing that "you're trying to create an entire infrastructure that doesn't exist nor is not necessary in these settings or will never be sustained." Another participant spoke of the need to recognize that challenges to archiving data in lower-/middle-income countries may limit an investigator's access to clinical data and documentation of AEs:

> *I think it is the whole issue not about data capture and record capturing and TMF and more about the archiving of TMFs and in some of these hospitals, there is no archive, this is then acceptable if the documentations archives are hundreds of kilometers away in the capital where there is the climate control archive facility and then it means that the investigator doesn't have easy access to the documentation in case there is some later AE or something where he needs to go back. So, I think that's something very, very difficult. Yes, we can organize an archive somewhere in the capital, but is that really still in the spirit why you need to archive at the site or close to the site the site records? While the clinical data and everything for this is archived on the sponsor's side somewhere. [ID# 08]*

Another participant stated that the trial master file guideline is "too exhaustive" and that researchers may not understand that it can be adapted:

> *But, other than this, the TMF is too exhaustive. Not all of it is applicable to all situations, and again, it's not necessarily completely clear to everyone that the actual TMF can be adapted. [ID# 19]*

Two other participants stated that the interpretation of GCP influences the types of essential documents collected. One of these participants observed that, while GCP does not require that the FDA 1572 be updated every time there is a change in investigators, the sponsors' interpretations of GCP affect the frequency of having to update these forms (see Appendix G, reference G53). The other participant noted that interpretation of GCP has resulted in the addition of many types of plans that are now part of the essential documents section (eg, data validation, data verification, and data reconciliation plans).

Two participants discussed that further clarification was needed in the essential documents section, including clarification about the required frequency of updating CVs and the purpose of the insurance statement. They suggested that the ICH may want to consider adding an appendix with country-specific examples of insurance statements (see also Appendix F, reference F32).

Another participant raised the question of the utility of requiring all the documents in this section:

> *If you practice medicine, why do we need these documents? I'm telling you, I don't understand why we need them. We have the clinical trial protocol, it can be long or short, it needs to be fit to purpose, right? It needs to describe adequately what you're going to do and why you're doing it and how it's going occur. Having a preferable trial protocol that's been approved by the IIB and you're including the patient. What do you really need to know? You need to know that the patient consented and you need to know that they were given a study treatment or what treatment they were given and then you need to know what the outcomes were. Then, if I treat somebody with bowel cancer, I'm an oncologist and I treat them, and nothing to do with clinical trial, I need to know that they consented to treatment, anyone looking at that record needs to know what I gave them and anyone needs to know what happened to them. That's no different than clinical medicine and yet there's an enormous amount of extra work required. [ID# 02]*

Commenting on the ecological impact of clinical trials "using too much paper," and associated space requirements to archive documentation, one participant requested that ICH provide guidance about whether electronic site investigation files are consistent with GCP (see also Appendix G, reference G54).

Finally, another participant recommended that the subsection on shipping records for investigational product(s) and trial-related materials would be improved by defining the meaning of "accountability" as it pertains to this subsection and by clarifying the meaning of shipping conditions (eg, temperature monitoring and condition of the boxes). The participant said that the value of adding this information would be that researchers conducting clinical trials would be able to use ICH E6 GCP as their only reference if they had questions, rather than having to search the internet for answers to their questions (see Appendix G, reference G55).

3. METHODS

3.1 Recruitment

At the end of the CTTI survey on ICH E6, participants provided their contact information if they were interested in participating in an interview to share their experiences with implementing ICH E6 GCP. We purposefully selected interested survey participants to ensure a sample diverse in the geographic employment of participants, countries where the participants conducted research, the participant's role in research (eg, investigator, clinical operations, quality assurance), and the participant's type of institution (eg, university/academic center, pharmaceutical company, contract research organization). Selected individuals were sent an email invitation to participate in the in-depth interviews.

3.2 Data collection

The purpose of the interviews was for survey participants to share detailed information about their experiences with implementing ICH E6 GCP and their renovation preferences. During the interview, participants described the following:

1. What they hope the revision to ICH E6 GCP will achieve overall
2. The sections of ICH E6 GCP that have been most helpful to them and why, including examples in applying the guidance
3. The sections of ICH E6 GCP that have been least helpful to them and why, including examples of difficulties in applying the guidance
4. How the ICH E6 GCP guidance could be improved, including how the conduct of trials could be improved if their suggestion was incorporated into the guidance

We did not design the interview for participants to reflect specifically on their survey responses. However, we did describe to a few participants the sections of ICH E6 GCP that they reported needed renovation when requested by the participant or when the participant needed encouragement to respond to the interview questions.

The qualitative interviews were conducted from September 15 to November 29, 2019.

3.3 Participant eligibility

Individuals were eligible to participate if they (1) completed the survey, (2) reference ICH E6 GCP to implement their research, (3) conduct research for registrational purposes, and (4) are willing to have the information they provided in the in-depth interview be linked to their name and organization.

3.4 Data analysis

We used descriptive statistics to summarize the demographic data. All interviews were transcribed verbatim following a transcription protocol. We used NVivo 12, a qualitative data analysis software program, to apply codes to the transcripts. Participants' narratives were analyzed using a two-stage deductive and inductive approach. First two analysts developed structural codes based upon the three primary research questions: (1) aspirations for renovation of ICH GCP; (2) helpful sections; and (3) unhelpful sections and suggested revisions. These primary codes were further segmented into subcodes for (1) each of the eight sections of ICH GCP, and (2) general comments about each of the research questions. The analysts then independently applied the structural codes. Intercoder agreement was assessed on five interviews (22% of the transcripts). Discrepancies in code application were resolved through discussion between the two analysts, and edits were subsequently made to the codebook and the transcripts were recoded accordingly.

Analysts then inductively identified content codes in each structural coding report that reflected participants' aspirations for the ICH E6 GCP renovation, experiences in implementing ICH GCP, and views on renovating the guideline. We used the subsections of ICH E6 GCP to categorize these content codes, while coding general comments separately. Analysts also inductively identified content codes that emerged across numerous sub-sections of ICH E6 GCP. The content-driven coding reports were then reviewed to identify participants' main experiences and suggestions based on their frequency. While we identified several overarching themes, as described in the executive summary, many experiences and suggestions were made by one or a few participants. Because we believe participants had valuable information to share based on their unique experiences and insights, we describe most of participants' comments in this report. Data summary reports were produced summarizing the participants' narratives, together with illustrative quotes and examples.

3.5 Ethics

The Duke University Health System Institutional Review Board (IRB) determined that the research is exempt from further IRB review.

4. PARTICIPANT CHARACTERISTICS

Of the 327 individuals who completed the survey, 75 agreed to be contacted for the follow-up, in-depth interviews. We conducted interviews with a total of 23 stakeholders who were diverse in their geographic location of employment, the countries where they conducted research, their role in research, and their type of institution. Appendix A describes each participant's individual information and provides their ID#, which can be used below to reference participant quotations.

Participants' places of employment were geographically located in 10 different countries (**Table 1**). Similar to the survey population, most interview participants were from Europe and North America.

Table 1. Interview participants' geographic location of employment (n=23)

Region/Country	n (%)
East Asia and Pacific	**2 (8.7)**
Australia	2 (8.7)
Europe and Central Asia	**13 (56.5)**
Belgium	2 (8.7)
France	2 (8.7)
Germany	4 (17.4)
Ireland	1 (4.3)
Switzerland	2 (8.7)
United Kingdom	2 (8.7)
Latin America and Caribbean	**1 (4.3)**
Argentina	1 (4.3)
North America	**7 (30.4)**
Canada	3 (13.0)
United States of America	4 (17.4)

Participants conducted research in 124 countries worldwide (**Table 2**).

Table 2. Geographic location of participants' research

Region/ Country	n (%)
East Asia and Pacific	**17 (73.9)**
Australia	13 (56.5)
Cambodia	2 (8.7)

Region/ Country	n (%)
China	7 (30.4)
Indonesia	5 (21.7)
Japan	6 (26.1)
Malaysia	6 (26.1)
New Zealand	10 (43.5)
Philippines	6 (26.1)
Singapore	8 (34.8)
South Korea	10 (43.5)
Taiwan	8 (34.8)
Thailand	6 (26.1)
Vietnam	3 (13.0)
Europe and Central Asia	**21 (91.3)**
Albania	1 (4.35)
Andorra	1 (4.35)
Armenia	1 (4.35)
Austria	14 (60.9)
Azerbaijan	1 (4.35)
Belarus	5 (21.7)
Belgium	19 (82.6)
Bosnia and Herzegovina	2 (8.7)
Bulgaria	7 (30.4)
Croatia	7 (30.4)
Cyprus	2 (8.7)
Czechia (Czech Republic)	12 (52.2)
Denmark	13 (56.5)
Estonia	5 (21.7)
Finland	13 (56.5)
France	17 (73.9)
Georgia	3 (13.0)
Germany	20 (87.0)
Greece	10 (43.5)

Region/ Country	n (%)
Greenland	1 (4.35)
Hungary	9 (39.13)
Iceland	3 (13.0)
Ireland	15 (65.2)
Italy	18 (78.3)
Kosovo	1 (4.35)
Latvia	7 (30.4)
Liechtenstein	1 (4.35)
Lithuania	8 (34.8)
Luxembourg	4 (17.4)
Malta	2 (8.7)
Moldova	4 (17.4)
Montenegro	1 (4.35)
Netherlands	16 (69.6)
North Macedonia (Formerly Macedonia)	1 (4.35)
Norway	13 (56.5)
Poland	13 (56.5)
Portugal	9 (39.13)
Romania	8 (34.8)
Russia	11 (47.8)
Serbia	6 (26.1)
Slovakia	8 (34.8)
Slovenia	8 (34.8)
Spain	17 (73.9)
Sweden	14 (60.9)
Switzerland	13 (56.5)
Turkey	8 (34.8)
Ukraine	8 (34.8)
United Kingdom	20 (87.0)
Latin America and Caribbean	**13 (56.5)**
Argentina	10 (43.5)

Region/ Country	n (%)
Brazil	9 (39.13)
Chile	8 (34.8)
Colombia	6 (26.1)
Costa Rica	2 (8.7)
Cuba	1 (4.35)
Dominican Republic	2 (8.7)
Ecuador	3 (13.0)
El Salvador	1 (4.35)
Guatemala	3 (13.0)
Jamaica	1 (4.35)
Mexico	7 (30.4)
Panama	3 (13.0)
Paraguay	2 (8.7)
Peru	5 (21.7)
Uruguay	3 (13.0)
Venezuela	5 (21.7)
Middle East and North Africa	**9 (39.13)**
Bahrain	1 (4.35)
Egypt	4 (17.4)
Iran	1 (4.35)
Israel	6 (26.1)
Jordan	1 (4.35)
Kuwait	1 (4.35)
Lebanon	3 (13.0)
Oman	1 (4.35)
Qatar	1 (4.35)
Saudi Arabia	2 (8.7)
Tunisia	3 (13.0)
United Arab Emirates	2 (8.7)
Yemen	1 (4.35)
North America	**18 (78.3)**

Region/ Country	n (%)
Canada	14 (60.9)
United States of America	18 (78.3)
South Asia	**8 (34.8)**
Bangladesh	3 (13.0)
India	8 (34.8)
Nepal	1 (4.35)
Pakistan	1 (4.35)
Sri Lanka	1 (4.35)
Sub-Saharan Africa	**13 (56.5)**
Benin	2 (8.7)
Botswana	1 (4.35)
Burkina Faso	1 (4.35)
Cameroon	1 (4.35)
Congo, Democratic Republic of the	1 (4.35)
Cote d'Ivoire	1 (4.35)
Ethiopia	2 (8.7)
Gabon	1 (4.35)
Gambia	2 (8.7)
Ghana	1 (4.35)
Guinea	1 (4.35)
Kenya	3 (13.0)
Malawi	3 (13.0)
Mozambique	3 (13.0)
Namibia	1 (4.35)
Nigeria	1 (4.35)
Rwanda	3 (13.0)
Senegal	1 (4.35)
Seychelles	1 (4.35)
Sierra Leone	2 (8.7)
South Africa	11 (47.8)
Sudan	1 (4.35)

Region/ Country	n (%)
Tanzania	5 (21.7)
Uganda	4 (17.4)
Zambia	3 (13.0)
Zimbabwe	3 (13.0)

[a] The regional headers represent the total number of participants and percentage of the study population who conduct research in one of the countries in that region. The country subheaders represent the total number of participants and percentage of the study population who conduct research in that country.

Participants also had various research roles (**Table 3**) and represented different types of institutions (**Table 4**).

Table 3. Interview participants' main role in research (n=23)

Research role	n (%)
Clinical operations personnel	7 (30.4)
Principal investigator, coinvestigator, subinvestigator, site investigator	5 (21.7)
Quality assurance/quality control personnel	5 (21.7)
Regulatory affairs personnel	4 (17.4)
Clinical research associate/research coordinator/study nurse	1 (4.3)
Data analyst	1 (4.3)

Table 4. Interview participants' place of employment (n=23)

Type of institution	n (%)
University/academic research center affiliated with a hospital/medical center	8 (34.8)
Contract research organization (commercial/for profit)	5 (21.7)
Pharmaceutical company or biotechnology company	4 (17.4)
Non-governmental organization or not-for-profit organization	3 (13.0)
Hospital/medical center not affiliated with a university/academic research center	2 (8.7)
Trade/professional organization	1 (4.3)

5. STUDY TEAM

- **Principal Investigator**: Amy Corneli, PhD, MPH, CTTI Lead Social Scientist; Associate Professor, Departments of Population Health Sciences and Medicine, Duke University School of Medicine
- **Team Leads**:
  - Annemarie Forrest, RN, MS, MPH, CTTI Director of Projects
  - Pamela Tenaerts, MD, MBA, CTTI Executive Director
  - Teresa Swezey, PhD, MA, CTTI Assistant Social Scientist; Clinical Trials Project Leader, Department of Population Health Sciences, Duke University School of Medicine
- **Interviewer**: Teresa Swezey, PhD, MA
- **Qualitative Data Analysts**:
  - Teresa Swezey, PhD, MA
  - Carrie Dombeck, MA, CTTI Research Associate; Research Program Leader, Department of Population Health Sciences, Duke University School of Medicine
- **Statistician**: Li Lin, MS, Senior Biostatistician, Department of Population Health Sciences, Duke University School of Medicine
- **Research Assistant**: Adora Nsonwu, Clinical Research Specialist, Department of Population Health Sciences, Duke University School of Medicine

Appendix A. List of interview participants

Participant ID#	Country of employment	Type of organization	Research role	Geographic location(s) of research
ID# 01	Australia	Non-governmental organization or not-for-profit organization	Clinical operations personnel	Australia; China; Malaysia; New Zealand; France; Germany; Ireland; Italy; United Kingdom; Argentina; Brazil; Chile; Saudi Arabia; Canada; United States; India; South Africa
ID# 02	Australia	University/academic research center affiliated with a hospital/medical center	Principal investigator; co-investigator; sub-investigator; site investigator	Australia; Japan; New Zealand; Singapore; South Korea; Taiwan; Belgium; Finland; France; Germany; Ireland; Italy; Netherlands; Norway; Poland; Russia; Spain; Sweden; United Kingdom; Canada; United States
ID# 03	Argentina	Contract research organization (commercial/for profit)	Clinical operations personnel	Argentina
ID# 04	Belgium	University/academic research center affiliated with a hospital/medical center	Clinical research associate/research coordinator/study nurse	Cambodia; Belgium; Italy; Benin; Burkina Faso; Congo; Democratic Republic of the; Ethiopia; Gambia; Malawi; Mozambique; Rwanda; South Africa; Uganda; Zambia
ID# 05	Germany	Pharmaceutical company or biotechnology company	Quality assurance/quality control personnel	Australia; China; Indonesia; Japan; Malaysia; New Zealand; Philippines; Singapore; South Korea; Taiwan; Thailand; Vietnam; Armenia; Austria; Belarus; Belgium; Bosnia and Herzegovina; Bulgaria; Denmark; Estonia; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Latvia; Lithuania; Netherlands; Norway; Poland; Portugal; Romania; Russia; Serbia; Slovakia; Slovenia; Spain; Sweden; Switzerland; Turkey; Ukraine; United Kingdom; Argentina; Brazil; Chile; Colombia; Costa Rica; Guatemala; Peru; Uruguay; Egypt; Israel; Jordan; Canada; United States; India; Cote d'Ivoire; Kenya; South Africa; Tanzania
ID# 06	Germany	University/academic research center affiliated with a hospital/medical center	Clinical operations personnel	Australia; New Zealand; Singapore; Taiwan; Austria; Belgium; Bulgaria; Croatia; Czechia (Czech Republic); Denmark; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Latvia; Lithuania; Netherlands; Norway; Poland; Portugal; Romania; Russia; Slovakia; Slovenia; Spain; Sweden; Switzerland; Turkey; Ukraine; United Kingdom; Canada; United States
ID# 07	Ireland	University/academic research center affiliated with a hospital/medical center	Regulatory affairs personnel	Austria; Belgium; Denmark; Finland; France; Germany; Ireland; Italy; Netherlands; Norway; Spain; Sweden; Switzerland; United Kingdom

Participant ID#	Country of employment	Type of organization	Research role	Geographic location(s) of research
ID# 08	Switzerland	Non-governmental organization or not-for-profit organization	Data analyst	Australia; Cambodia; Indonesia; Thailand; Belgium; Croatia; Germany; Netherlands; Norway; Russia; Serbia; Spain; Switzerland; United Kingdom; Argentina; Brazil; Peru; Canada; United States; Bangladesh; India; Gabon; Malawi; Mozambique; South Africa; Tanzania; Uganda
ID# 09	Switzerland	University/academic research center affiliated with a hospital/medical center	Principal investigator; co-investigator; sub-investigator; site investigator	Austria; Belgium; Denmark; Finland; France; Germany; Greece; Ireland; Italy; Netherlands; Norway; Slovenia; Spain; Switzerland; United Kingdom; Guinea; Tanzania; Zambia; Zimbabwe
ID# 10	United Kingdom	Contract research organization (commercial/for profit)	Regulatory affairs personnel	Australia; Malaysia; New Zealand; Philippines; Singapore; South Korea; Taiwan; Thailand; Vietnam; Austria; Belarus; Belgium; Bulgaria; Croatia; Cyprus; Czechia (Czech Republic); Denmark; Estonia; Finland; France; Georgia; Germany; Greece; Hungary; Iceland; Ireland; Italy; Latvia; Lithuania; Luxembourg; Malta; Moldova; Netherlands; Norway; Poland; Portugal; Romania; Russia; Slovakia; Slovenia; Spain; Sweden; Switzerland; Turkey; Ukraine; United Kingdom; Argentina; Brazil; Ecuador; Mexico; Paraguay; Peru; Venezuela; Israel; Lebanon; Canada; United States; India; South Africa
ID# 11	United Kingdom	Trade/professional organization	Regulatory affairs personnel	Australia; China; Indonesia; Japan; Malaysia; New Zealand; Philippines; Singapore; South Korea; Taiwan; Thailand; Albania; Andorra; Austria; Azerbaijan; Belarus; Belgium; Bosnia and Herzegovina; Bulgaria; Croatia; Cyprus; Czechia (Czech Republic); Denmark; Estonia; Finland; France; Georgia; Germany; Greece; Hungary; Iceland; Ireland; Italy; Latvia; Liechtenstein; Lithuania; Luxembourg; Malta; Moldova; Montenegro; Netherlands; Norway; Poland; Portugal; Romania; Russia; Serbia; Slovakia; Slovenia; Spain; Sweden; Switzerland; Turkey; Ukraine; United Kingdom; Argentina; Brazil; Chile; Colombia; Mexico; Panama; Uruguay; Venezuela; Canada; India; South Africa
ID# 12	Canada	University/academic research center affiliated with a hospital/medical center	Clinical operations personnel	Australia; China; Indonesia; Japan; Malaysia; New Zealand; Philippines; Singapore; South Korea; Taiwan; Thailand; Austria; Belarus; Belgium; Bulgaria; Croatia; Czechia (Czech Republic); Denmark; Estonia; Finland; France; Germany; Greece; Hungary; Iceland; Ireland; Italy; Latvia; Lithuania; Netherlands; Norway; Poland; Portugal; Romania; Russia; Serbia; Slovakia; Slovenia; Spain; Sweden; Switzerland; Turkey; Ukraine; United Kingdom; Argentina; Brazil; Chile; Colombia; Cuba; Ecuador; El Salvador; Guatemala; Jamaica;

Participant ID#	Country of employment	Type of organization	Research role	Geographic location(s) of research
				Mexico; Paraguay; Peru; Uruguay; Venezuela; Bahrain; Egypt; Iran; Israel; Kuwait; Lebanon; Oman; Qatar; Saudi Arabia; Tunisia; United Arab Emirates; Yemen; Canada; United States; Bangladesh; India; Nepal; Pakistan; Sri Lanka; Benin; Botswana; Cameroon; Ethiopia; Ghana; Kenya; Malawi; Mozambique; Namibia; Nigeria; Rwanda; Senegal; Seychelles; Sierra Leone; South Africa; Sudan; Tanzania; Uganda; Zambia; Zimbabwe
ID# 13	Canada	University/academic research center affiliated with a hospital/medical center	Principal investigator; co-investigator; sub-investigator; site investigator	Australia; China; Japan; Malaysia; Philippines; South Korea; Austria; Belgium; Czechia (Czech Republic); Denmark; Finland; France; Germany; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Romania; Russia; Slovakia; Spain; Sweden; Switzerland; Ukraine; United Kingdom; Argentina; Brazil; Chile; Colombia; Ecuador; Mexico; Venezuela; Tunisia; Canada; United States; Bangladesh; India; Rwanda; Sierra Leone; South Africa; Uganda; Zimbabwe
ID# 14	Canada	Contract research organization (commercial/for profit)	Clinical operations personnel	Austria; Belgium; Czechia (Czech Republic); Germany; Ireland; Italy; Netherlands; Poland; Spain; Sweden; United Kingdom; Mexico; Canada; United States
ID# 15	United States	Pharmaceutical company or biotechnology company	Quality assurance/quality control personnel	China; South Korea; Austria; Belgium; Czechia (Czech Republic); France; Germany; Italy; Poland; Spain; United Kingdom; Argentina; Israel; Canada; United States; South Africa
ID# 16	United States	Pharmaceutical company or biotechnology company	Quality assurance/quality control personnel	Australia; China; Indonesia; Japan; New Zealand; Philippines; Singapore; South Korea; Taiwan; Thailand; Vietnam; Austria; Belarus; Belgium; Bulgaria; Croatia; Czechia (Czech Republic); Denmark; Estonia; Finland; France; Germany; Greece; Greenland; Hungary; Ireland; Italy; Kosovo; Latvia; Lithuania; Luxembourg; Netherlands; Norway; Poland; Portugal; Romania; Russia; Serbia; Slovakia; Slovenia; Spain; Sweden; Switzerland; Turkey; Ukraine; United Kingdom; Argentina; Brazil; Chile; Colombia; Costa Rica; Dominican Republic; Mexico; Panama; Peru; Venezuela; Egypt; Israel; Canada; United States; India; Kenya; South Africa
ID# 17	United States	Hospital/medical center not affiliated with a university/academic research center	Quality assurance/quality control personnel	Australia; Finland; Germany; United Kingdom; United States
ID# 18	United States	Hospital/medical center not affiliated with a university/acad	Principal investigator; co-investigator;	United States

Participant ID#	Country of employment	Type of organization	Research role	Geographic location(s) of research
		emic research center	sub-investigator; site investigator	
ID# 19	Belgium	Non-governmental organization or not-for-profit organization	Regulatory affairs personnel	Austria; Belgium; Croatia; Czechia (Czech Republic); Denmark; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Latvia; Lithuania; Luxembourg; Netherlands; Poland; Portugal; Slovakia; Slovenia; Spain; Sweden; Switzerland; Turkey; United Kingdom
ID# 20	France	Contract research organization (commercial/for profit)	Clinical operations personnel	Australia; New Zealand; Austria; Belgium; Bulgaria; Czechia (Czech Republic); Denmark; France; Georgia; Germany; Greece; Hungary; Ireland; Italy; Moldova; Netherlands; Norway; Poland; Romania; Russia; Serbia; Spain; Sweden; United Kingdom; Israel; Lebanon; Canada; United States
ID# 21	Germany	Pharmaceutical company or biotechnology company	Clinical operations personnel	Singapore; South Korea; Taiwan; Belgium; Denmark; France; Germany; Greece; Italy; Moldova; Netherlands; Portugal; Spain; Sweden; Switzerland; Turkey; United Kingdom; Brazil; Chile; Mexico; Egypt; Tunisia; United Arab Emirates; Canada; United States; South Africa
ID# 22	France	University/academic research center affiliated with a hospital/medical center	Principal investigator; co-investigator; sub-investigator; site investigator	Australia; New Zealand; Belgium; Czechia (Czech Republic); France; Germany; Ireland; Portugal; Spain; Switzerland; United Kingdom; United States
ID# 23	Germany	Contract research organization (commercial/for profit)	Quality assurance/quality control personnel	South Korea; Austria; Belgium; Czechia (Czech Republic); Denmark; Finland; France; Germany; Italy; Lithuania; Netherlands; North Macedonia (Formerly Macedonia); Norway; Poland; Russia; Sweden; Ukraine; United Kingdom; Chile; Colombia; Dominican Republic; Guatemala; Panama; United States; Gambia; Tanzania

Appendix B. Additional Participant Quotations Related to Aspirations for ICH E6 GCP

Aspiration	Reference #	Illustrative Quotations
General Aspirations for ICH E6 GCP		
Clarify whether/how ICH E6 GCP applies to non-regulatory drug trials	B1	So, I do hope that this time, the ICH GCP, or ICH as the regulators behind, will realize that this guidance is actually touching much larger amount of clinical research than its initial intent. Now, its initial intent is there to support clinical trials, which are run in the scope of submission of the field for registration of new drugs. That's the initial think of the ICH, in order to also harmonize the requirements between the regions. But, with time, this guidance imposes itself as a key standard in a much more diverse series of clinical research, which are not only for putting drugs on the market, but which are also for even post-marketing surveillance, which would be also applying to the work that the academic organizations will do with drugs already on the market and are registered either to enlarge the indication – not necessarily the label because they are not marketing authorization holders – but actually enlarge slightly the indication in the clinical practice. Or, not even that. They would simply work on the adjustment of the dose, schedule, the way to give this, maybe, in combination with other treatment modalities. I'm working in the field of oncology, so mixture of modalities and the sequencing, like, if you first give the chemo and then the surgery, or the other way around, can there be improvements and can be a valuable subject for research with the proper methodology. And so, this has nothing to do with the initial remit of the registration dossier. And though, we are not at all pleading for different exigency of the quality, but it can be understood that the intensity of surveillance, and monitoring, and safeguards to be put in place in case of a very new drug, where little is known about this drug, and then a drug which is already well-described. And so, what is being the subject of research is not adding, or is unlikely, to make us learn additional things about the drug's safety. It's about how to better use it. So, it's not enough proportionate. And though, in the latest addendum, there is some notions of the risk-adapted approach, and it's a little bit more flexibility, which is introduced, it's still not enough adapted, really. Also, the introduction of GCP states that the principles of GCP can be, as appropriate, applied to different types of research. **[ID# 19]**
Provide flexibility to accommodate different types of research	B2	I am coming from academia. 95% of the things we are doing are academic trials, a lot of pharmaceuticals, but others, also, that we use still to guide our practice also for the non-pharmaceutical trials. I mean, for example, for the data management, why should it be different? I don't see – why shouldn't we have the same responsibility split in the trial that evaluates surgery as compared to a pharmaceutical trial?…The principles, for sure.. not the topics that are specific to investigational medicine or products, but all the rest…I wouldn't see why not… a lot of things are actually the same... when you have a multicenter surgical trial, why you wouldn't have the same kind of concepts and responsibilities that you have for a pharmaceutical trial. [ID# 09]
Make clear that the guidance is only for regulatory drug studies	B3	It must be made very clear that this is for medicinal products, so for drugs, because we have sort of a blurry sentence in the introduction that it could be also used somewhere else. And then sometimes ICH is quoted in a medical device environment, and that would not be correct. I mean, yes, the principles can be used also in other studies where there is no specific guideline available. For example, for medical devices, we have other GCP guidelines, so it should be clear that this should not be used everywhere. [ID# 23]
"Spirit of GCP" – not every trial	B4	And, obviously, also tailoring for different types of research. Sometimes a different aspect of the ICH GCP doesn't relate to all type of research. And would be good if that could be part of the revision itself, [outlined what is] sometimes is applicable and sometimes it's

Aspiration	Reference #	Illustrative Quotations
needs to fully implement all aspects of ICH GCP		not. [ID# 01]
"Spirit of GCP" – not every trial needs to fully implement all aspects of ICH GCP	B5	[Question: And so, if the guidance was revised to make clear that this is the minimum that you have to do to conduct a trial, following GCP to high standards, and these are the other things that you have to do, and the rest of this is for regulatory purposes, do you – in terms of the global guidance that that would provide, would that meet kind of global standards. Do you think that that would work better for global standards of conducting clinical trials?] Yeah. I think it would. And that's probably not because what ICH originally intended this. These are the standards we want to see when you come with a package for approval. But it is also to say if a Gates Foundation or Wellcome Trust or Rockefeller Foundation or Swiss Government or USAID are giving money for these kind of trials that they don't automatically implemented that these trials have to be conducted according to ICH GCP. Because that's – I think it's not the intent, or I hope it wasn't the intent of the regulators that everything has to be one size fits all and that size unfortunately is a very large size. But to define the standards, they need to see to approve a drug or reject a drug. While a lot of the – I wouldn't say peripherally – but other people involved in regulating clinical trials that may be supporting and financing clinical trials, use now ICH E6 as the standard, although it's not appropriate as a standard. It's a bit like if regulatory authorities were car approvals in the US or in Europe – defined something that needs to be met for a school bus, and suddenly the same standards are applied for a 4-seat private car and the 2-seater motorbike and a bicycle. Wouldn't work. It would make it impossible that you can buy a normal car for a family, makes unaffordable trials. …It's the gold standard and it's almost enforced across the board. [Follow-up question about being enforced inappropriately Yes. That's my [inaudible]. [Follow-up question: Right. And always with the caveat here that you said a couple of times that you're not saying – you don't take issue with GCP at all, but it's the application of the ICH E6 GCP E6 principles to trials for which it was not intended to be used. Is that correct?] Yeah. **[ID# 08]**
Identify the minimum requirements of GCP necessary for different types of trials	B6	And if I look back to the Tuskegee issue and the issues of World War II that caused us to have to create things like the Declaration of Helsinki, we're not there anymore, and we've got enough people watching. And so, I think we should be allowed to have more flexibility and creativity. So, what should ICH do? They should require people to complete each of the sections, naming the three fundamental, four fundamental components that need to be considered and how you will address it. … Flexible, international, considerate, and put the onus on the investigators to recognize what's needed in a trial. [ID# 13]
Guidelines may be translated into local law and/or procedures, as needed	B7	GCP provides the framework, right? It's a guideline, and it should remain a guideline. It is not a law, and to us, it's interpreted or implemented as a law – the laws within the country. And punishable laws differ by country, as you know. Leave it to the country, in Canada, it's provincial, and perhaps a local level to decide what's most appropriate for the situation. [ID# 13]
Clarify language to	B8	I hope that actually the whole text will be revised and not only another addendum will be written because of this – the addendum we now have some inconsistencies in

Aspiration	Reference #	Illustrative Quotations
ensure consistent terminology		terminologies, and we need to have this explanation in the introduction that if there is a conflict, then this version takes priority or something like this. I think this as GCP requires consistency throughout the document of a clinical trial. I think the guideline first becomes a stencil, so I have hope for a revision which actually goes through the full text and makes it more consistent. …Yeah, so we have two levels here. The first level is the consistency within the document, and Revision 2, we have some inconsistencies in the document and this is why in the introduction they say, "If there is such a situation of a conflict, then the Revision 2 takes priority." So, that is something how this will solve because they did not touch the old text of Revision 1. And I can give you an example. For example, the old text, which is also the new text because the old text is also the text of Revision 2, so the Revision 1 text says – the Chapter 8, the table of essential documents, this is the minimum list of documents. Whereas Revision 2 says you can take a risk-based approach and there might be situations where you don't need all the documents. So, we have within the guideline as it is now, we do have some inconsistencies which only can be solved with this explanation in the introduction that R2 takes priority over R1. So, we know then that – but for somebody who is not following this over many years and is just starting, this is very confusing. …And I have to say, I mean, it's really I would almost say surprising how good this document was written such a long time ago and has really served us very well, but now I think it is time to revisit. And I was, to be honest, very disappointed that with R2, this was only an addendum, and that the authors did not go back to the expert group or whoever was working on it – did not go back and rewrote the whole thing. So, it was a bit – we do it a bit quick and dirty. We add what we need to add, but we don't go back to the basic text, and I think now with R3, I think it should really happen now. [Follow-up question: In the R2 it says, as you mentioned that the way that they dealt with things, if there's a conflict between what's written here and what appears are R2 addendum information, R2 is always the one referred to, but they didn't go back and revise the entire thing.] Yeah, and the R1 text or the original text was not really – this did not really fulfill the expectations of people who are working in a quality environment, you know. I mean, if we go out and check documents of clinical trials, and when we find the least inconsistency we give a finding, we as audit [inaudible], and here we have a document which from the very beginning has discrepancies. This is not a good role model thing. **[ID# 23]**
Clarify aspects of the guidance	B9	And so, what's interesting about GCP is it's a globally harmonized guideline that everybody's looking at. So, you know I work in Latin America, and I know that apart from my own regulations if I'm looking at a good implementation and I'm complying with ICH GCP, then the result of the research studies can be used internationally for submissions or for publications. It's like international rules for research sort of thing. And I think best practices – if you break them down at the corporate level, companies may have their own ways of doing it. But I think they all agree on following the GCPs. So, GCPs are all on top of the best practices, but are instructing the world. And for many companies that do not have the resources to develop their own best practices or are not the ones that have the volume of research or the resources to set up quality systems that are super sophisticated or get to conclusions because they don't have the critical mass of research going on. Then GCP can use this information to share with the world and maybe this experience can be used for better research. [ID# 03]
Clarify aspects of the guidance	B10	I think, actually, it's quite what I've been seeing. I think ICH has done a good job because, in general, the E6 guideline is very good, and it's clear in many areas.. And, honestly, there, there simply has to be a compromise because the regulations are going to be different in different companies, so you've got to look through all of that. [ID# 11]

Aspiration	Reference #	Illustrative Quotations
Clarify aspects of the guidance	B11	So, what I see is a lot –in my experience as a monitor and auditing at sites in the U.S. and outside the U.S., I see such a huge variation in the quality of research done. Maybe you have a site in a small town that a physician just has one research coordinator and they're new to research versus somebody that is at a large academic institution where they have a very large training program, standardized processes. There can be such an enormous difference in the quality of the work provided. So, that's where my desire – when you're talking about improving the quality, if we could have more standardization that hopefully would inherently improve the quality, that's the lens that I'm really looking at just because I've just seen such a wide variation in the quality of different sites. [ID# 17]
Clarify aspects of the guidance	B12	If the guideline is revised, I also think that ICH needs to put some effort in developing training materials, doing stakeholder meetings, and really informing the audience who has to work according to this guideline in a better way. [ID# 05]
Clarify aspects of the guidance	B13	I mean, one other thing I might say, perhaps, it goes back to this issue of interpretation of the guidelines, and this isn't, particularly, an issue for the guidelines, but whether ICH would consider establishing some sort of a process whereby organizations could seek advice on a consistent interpretation. I mean, it might not be so the advice they'd want, but at least it was something that was adopted on a global level. Then, they'd only have to put one process in place. [ID# 11]
Make more user-friend and operationally feasible	B14	I think the ICH, the GCP guidelines are – it's a rather long document for people to go through. And so, part of it – on the one hand, I would say if there is any way to make it shorter or maybe at the beginning have the key points and some highlights, something – I liken it to our patients who have an informed consent document. They now can be 20 - 30 pages long. And there's evidence to say that patients don't even read them anyway. It would be nice if we could somehow – I know for example, with the new common rule revisions that became effective in January, I think the intent was to try to – they required one consent document to highlight the key information first with the intent of hopefully that would improve the patients being more informed about participating in research. I guess with the ICH guidelines, I'm not sure how that would be done. If it was really focused, to make it short enough so that the people that really need to pay attention to this would pay attention to it rather than looking at the document and going, oh, this is 66 pages. I'm not going to go through every little detail of it. So, if there was some way to – when you say how to improve it – I wish there was a way to make it shorter. [ID# 17]
Make more user-friend and operationally feasible	B15	Frankly, I think that most of us who are in the field doing research have felt the crush of clinical trial complexity and all of the documentation, framing, and all of that. So I hope in some way that at least for this part of the GCP that this is able to be translated with practitioners and also through them to the patient in a more streamlined way than it is now. I guess I'm trying to say I'd like to preserve all of the goals of GCP and yet have it be so it happens in a more transparent action. It's not that GCP is onerous anymore; it's that everything is onerous. Cutting the time and effort requirement down of any part of the research effort is a good thing in my view. … basically for all of the physicians – mid-levels, coordinators, etc. – who are working at clinical trials, there are these requirements for documentation of GCP training and that's fine, but the GCP training itself can be pretty tedious and kind of repetitive. You end up doing it every two years. I think that the first time you certify it, I think that there's certainly room for that to be a more rigorous course, but as you're recertifying every two years for – I think that there's room to create a more streamlined recertification process. …so I guess that's what I'm saying is I think that when you recertify, that should be a quicker process that kind of hits the main points of GCP and yet is something that hopefully could be completed in a few minutes rather than an hour or two, which I think it is now. [ID# 18]

Aspiration	Reference #	Illustrative Quotations
Make more user-friend and operationally feasible	B16	Well, I think it's very important to start evaluating the clinical study around the world, as we have more and more country and it evolve more and more. Investigator – from the point of view of an investigator, we make clear that we need to be able to [do an]academic study, as well as company-sponsored studies. And if the procedures are too complex, they are becoming too expensive, the investigators are not getting involved, so the data collected are no longer in the hand of doctor, then some other people in between. Because I think it's dangerous for the patient and for the quality of the data. [ID# 22]
Complexity of regulations is a disincentive for investigators	B17	And one point of particular interest to me was the fact that this would reflect on investigator-initiated studies. And recently I've been doing a lot of work trying to investigate some of the difficulties around those particular aspects, and I feel that these additional requirements perhaps will cause investigators additional difficulties when they're not being sponsored by large pharmaceutical companies. …And the requirements for the protocols as well are also useful, and the requirements of "Investigators Brochure." Again, it provides a template, and it allows us to standardize these documents, which is a great advantage. However, my understanding is that, from an investigator perspective, complying with all these requirements, although it was originally intended as being in the spirit of ICH GCP, what's actually happening is these requirements, as laid out in GCP, are becoming a checkbox. And so, what we are finding in feedback from investigators – that has been surveyed, that I'm aware of – various pieces of research discussing this – it seems the data gathered is overly prescriptive and it introduces a level of complexity that they can't necessarily comply with without the support of pharmaceutical funds funding their research. And I'm looking at the additional requirements. So, for example, talking about the acceptability of electronic records, etcetera, I wonder whether or not that will really be applicable and – to investigators, just moving forward, if they were wanting to initiate their own clinical studies. …You see, I think the very difficult today with the language we have, it perhaps comes back to what the problem is. We know it's a guideline, and from our perspective, we know that these are recommendations that should be followed. We are practical to do so. And where there's a deviation from a guideline it's acceptable to justify that deviation. However, I don't think it necessarily comes across that way ultimately with people who don't have the benefit of a large regulatory department or don't have access to additional support from project managers and clinical trial assistants to know that those necessarily can be deviated from. And I think that's exactly it; they view it as requirements rather than as guidance. Yeah, it's an interesting problem that I don't think this revision really tries to address. And to be honest, I was quite interested, actually, to discover recently that a number of investigators were complaining about – ICH becoming a burden on their research, and claiming that it would inhibit further clinical research that was sponsored by academic institutes. Because I had always, from the perspective of a CRO employee, regarded them as quite valuable, whereas they were regarding it as just another layer of bureaucracy. **[ID# 10]**
ICH E6 GCP needs to be fit for purpose	B18	I think it's got to be fit for purpose, I think the GCP have got to be risk adjusted and when we're talking about a trial which involves physiotherapy on Mondays and Wednesdays, rather than Tuesdays and Thursdays to use as an example, it has to be fit for purpose. And in terms of the process the clinicians have to go through, in this case the physiotherapist, the bureaucracy that has to be dealt with, the consent forms, patient interview, the monitoring the study and so on. All of those things have to be fit for purpose. So, I think the problem is that they're not.

Aspiration	Reference #	Illustrative Quotations
		… Like I said, I do not find it fit for purpose, I do not find that the 20 page consent form is helpful to the patient, but we give it to them. I do not find that the monitoring of every single thing that goes on in the medical record, much of which is not relevant to the trial, much of which is not relevant to the question, is helpful. And it's time consuming. I think the general idea that we protect the GCP is helping make sure that we protect the rights of patients and informed consent of course is very important. But I remind you that that's how medicine is – that's very different from clinical medicine, right? The rights of patients to be provided informed consent. And yet, why do we have a 20 page consent form for a chemotherapy trial and a one page consent form for chemotherapy when they're not on study? Which one do you think the patient understands? They probably understand neither of them, but that's what I mean. That's a piece of paper designed by lawyers or by sponsors to protect themselves. Not look after the needs of patients, they're not to consult the research. … I'm talking about sense of purpose, I'm not suggesting we should do things that are unethical. I'm not suggesting that we shouldn't have oversight, but what I'm suggesting is that it needs to be fit for purpose. And it needs to be designed in a way that encourages research at the same time as protecting the rights of individuals. And what we have now is a system that discourages research and maybe protects the rights of individuals but it does so in a way that is so – You know what happens, right? You get one protocol, you know is a 10 IRBs. How often does it get through all 10 without a change? Because they all think they know better. They all think they know better than anybody else, and they don't. And so, IRB is fine but why do we need 20 of them? Who do we need 100 of them? We've done them all over the country, you've got them too. You've got centralized IRB in the U.S. now, which is most helpful, but it goes to an IRB – One place goes to a different IRB, they change it. So, does that mean the first one was unethical? It doesn't mean that at all does it, right? It means that they've got a different view about this but in the end, we'll all try to do the same thing. So, we are definitely going to do research. We are definitely going to do research that protects the rights of participants and those doing the research. But at the same time, it needs to be fit for purpose. **[ID# 02]**
Include a variety of stakeholders in the revision process	B19	And even if we speak about patients, people who speak in these type of assemblies are not always patients themselves. Sometimes, they are patient advocates. But, they are an ear to patients and they are more defend their point of view because the other stakeholders, even though some doctors are extremely attentive to what patients tell them, just from their place, there is a kind of conflict of interest, if you wish, because a researcher, even listening to patients, but he is still a researcher. So, he will try to make research going, that's his primary interest. The primary interest of patients is to get involved in the healthcare because they need cures, but in a way which is acceptable to them, which is truly a different angle of view. And, so I think it's, actually, not only to bring their voice into the assembly, but I think – and we already have experiences of this – that actually brings, also, certain positions of the assembly into the patient community. And, then ultimately, that understanding of why certain things have to be done, despite the fact that the patient community may not spontaneously feel very comfortable with it. … And I think that the outcome of this is quite positive on both sides. [ID# 19]
Be mindful of length of revision process	B20	Okay, so whenever the next renovations are, they're still clearly three years out – confusion in the industry about E6 (R2) and what's required from it. And so, more broadly, whatever the renovations are, I hope that they do not lead to additional three years or more of confusion about how to address whatever the new changes are. [ID# 16]
Be mindful of length of	B21	There are a number of areas already in place where there are regulations and so on that could be used to develop the better system. That could be various groups around the world, so clinician groups, trials groups, the ICH and so on could come together and think

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revision process		about how this could be done in the short term as opposed to what's required in the longer term. I think that, as I say, I think that it's not going to be straight forward to do it as a how. You know, how are we going to fix this tomorrow when it's been ingrained with sponsors and CROs and by people for many, many years. But we have an urgent problem on our hands and that is the bureaucracy is getting worse. [ID# 02]
Highlight the purpose of ICH E6 GCP	B22	…I think that the thing that's missing here, is that it needs to be an understanding of why we're doing research in the first place. We're doing research to improve people's outcomes. Whether you're talking about pregnant women, whether you're talking about healthy babies and their development, or you're talking about people with advanced cancer. And doing this to improve people's outcomes and to understand their outcomes and to improve their outcomes, right? That's why we're doing this. Not just outcomes, but risk factors, you know, you can make that as broad as you like. And all I'm suggesting is, that this has to be consistent and to value add to the practice of medicine. Because that's all medicine is about, right? Medicine is about improving, understanding risks, you know, prevention treatment, diagnosis, treatment, to improve outcomes. …Isn't that what we want? Isn't that when you go to the doctor, right? That's what we do, right? We want them to get better. … It would be very presumptuous of me to assume that I actually have input directly about what ICH does, but I guess my plea is that we sit down and figure out why we're doing research in the first place. And what the major initiative is all about. It's not about making money for drug companies, it's about improving the outcomes of people. For our community, for our brothers and sisters and children and parents and so on. And if we don't do that, we've got to figure out a way of making it easier, because it's getting harder and harder and harder. [ID# 02]
Highlight the purpose of ICH E6 GCP	B23	And risk is measured by the sponsor's risk and those sort of issues rather than what's important to the patient and I think that we need to bring the community into this and we need to say, yes we want to avoid fraud and yes we want to avoid the terrible disasters. You know, that people don't know they're being experimented on and things like that. Terrible things did happen. But bad people do bad things, and no amount of regulation stops them. All you've got to do is design a system that allows the good people to do their work well. The communities, the beneficiary and that. [ID# 02]
Highlight the purpose of ICH E6 GCP	B24	Overarching, I'm hoping that it will improve the quality of the research done and the standards that we have to follow, that it will encourage people to continue to follow those standards. [ID# 17]
Highlight the purpose of ICH E6 GCP	B25	I think the most important take-home I had from my recent investigations was that some people do regard GCP perhaps as becoming quite onerous. And I think it's not the intention of GCP. I think the intention of the guideline is fair and just. It's just that perhaps the requirements are becoming a checkbox exercise. And so, I would recommend that perhaps that is considered, and then, the introduction steps are taken to make it clear that the ICH guidelines are recommendations for the most part, and not something that necessarily have to be adhered to with religious fervor. But, otherwise, I do appreciate the work that the ICH – and I particularly do like the ICH E6 guideline overall. I think it's a very useful – guidance document, which has international relevance that goes beyond the regions – which are currently members of the international committee. [ID# 10]
Reintegrate clinical research into clinical medicine	B26	I think what I have seen develop over time is that the bureaucracy and regs – So, the purpose of protecting the rights of patients in clinical research and the patient's rights to be involved or not and choice and so forth is of course a fundamental tenet of the way we practice medicine. The way I think about this from a contextual point of view, is that research should be an integral part of clinical medicine. There is a substantial amount of medicine that is not evidence based and we need to develop evidence in order to understand why we're doing things and how we're doing things. There is considerable risk and considerable harm inadvertently being done to

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		people because the practice of medicine is [inaudible] evidence based. And we don't even know we're doing harm some of the time. The problem is, that the current mechanisms of GCP and so on, which were set up appropriately to consider, particularly in the patient throughout, and develop a separate industry of clinical research and would separate it away from clinical medicine. …I think what we have to do is have a conceptual understanding that the purpose of GCP needs to bring research back into the practice of medicine. We owe it to the communities of the future to stop creating this separate industry of research which denies the vast majority of patients access to the opportunity to be involved in developing appropriate [inaudible]. It's in a high level, right. So, it's not about saying GCP will get rid of this rule or that rule. But it's really about saying why we created this whole thing in the first place. While I believe we should be creating it, we should be developing a system that forces, or at least allows or encourages the integration of clinical research into clinical medicine. **[ID# 02]**
Modernize to accommodate new technologies/ processes	B27	What about previous very good principles in the guidelines, like the informed consent process, which is a process between investigator and patient where the investigator informs the patient about the trial and what's going on, but we all know that even since the last 10-15 years, it was always the sponsor who provided the investigator with the template and the content of the informed consent form. Now, with the possibility of electronic informed consent form, you will possibly have a third party in there – another vendor – and the process will not be purely investigator/patient, so how do you make these kinds of situations possible? Even the data is possibly somewhere else. [ID# 05]
Modernize to accommodate new technologies/ processes	B28	Telemedicine as part of research practices our patient reported outcomes are being used more and more. And what are the challenges and how do we ensure through good guidelines that we are giving the right orientation to preserve quality and integrity of the data. [ID# 03]
Modernize to accommodate new technologies/ processes	B29	Well, I think artificial intelligence is being used for healthcare and has been approved for healthcare. And in itself, artificial intelligence could be studies to generate new – what we obtain from artificial intelligence could lead us to new information, to new research or to new artificial intelligence use. [ID# 03]
Modernize to accommodate new technologies/ processes	B30	I don't know what's going to happen when a subject is taking their drugs from home and the investigational product, perhaps if it's shipped there, perhaps they had a video conference with a healthcare provider. How does that get monitored? What is going to be acceptable to say that we have good data quality and patients' rights, safety and welfare were protected? I don't know. [ID# 16]
Update study roles	B31	It's nice that they updated as part of the overall renovation to introduce the new concept and also ensure that trials are not so complex anymore, that they are feasible, that the patients are much more heard, the patient was incorporated on all of that. Therefore, possibly, you also need a chapter in ICH E6 about patients or subjects…[This chapter would include] The role of the patient within the clinical trial –because currently, it's just small chapters in E8 and other documents, but overall, drug development needs to become patient-centric because we all do that for patients, but also for caregivers. [ID# 05]
Include study coordinator in study roles	B32	And I have this thing with the study coordinator because there is no mention of study coordinator in the GCP. And I think study coordinators are critical to clinical research. And they carry a critical role for the success of the studies. And I would like to see at least the study coordinator mentioned. It's different from study investigator because we

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		call the investigator someone who is doing a clinical judgement on the patient. Study coordinators not necessarily, it could be. But not necessarily. Study coordinator is always someone who is organizing visits, taking care of the logistics, looking at the overall compliance on the study, taking care of the – covering investigator's back in a way. He's responsible, but sometimes it's a very important decision with a job at university, seeing patients. So, the study coordinator is a very important person, and I think mentioning them in the GCPs would help give entity to the role. And establish the importance of administrating resources, logistics, people, coordinating, calling the patients. And all of this is super important for a clinical protocol. And recognizing that importance in a study allows for study coordinators to feel empowered to do a better job and recognized. I think without them our research would not be possible. And so, I think – I would suggest maybe in the glossary or I don't know somewhere in GCP it could be mentioned, the possibility of or the recommendation that there be study coordinator assisting the investigator in the organization of the study and the implementation of the study at the site level. **[ID# 03[**
Ensure transparency	B33	The last thing is really to be careful because even if a decision is taken to enlarge the group of stakeholders, I think it's very important to keep the full transparency with a pubic consultation, kind of, round. Not only in order to just be transparent, which is very important by itself, but also to be able, without necessarily getting out of control of the number of stakeholders, to expose the document to a larger number of experts, but account, maybe, for more marginal cases, which will improve the quality of the document. [ID# 19]
Restructure from a task/group orientation to a process based on principles	B34	[The chapters are]– task and person-specific, and I find it's hard – the principles that are stated right at the very beginning are not well-represented or well-demonstrated throughout. Then it gets very tactical as opposed to being able to say more and emphasize those principles. [Follow-up question on tactical versus focused on the 13 principles] That's right. …Why I responded that all chapters need to be revised: Because I think we should have chapters that are not specific to groups. So one of the examples I can give is in each of the chapters – for the IRB, for the investigator, for the sponsor, and for the monitor – they all have the section called records, and they all – "This is how you have to keep your records. This is what we want you to keep." The same is true for supervision or oversight. So I think the chapter should be on a principle, and this is how – so whether it's IRB or sponsor or investigator, they have to have records, and this is kind of the key principles in terms of recordkeeping. Same with the number of times. In each of these chapters, they talk about qualified personnel, right? So why can't they just – really, to focus on qualified personnel, it's not about the investigator or the IRB; it's about qualified personnel and how regardless of who you are, you're going to make sure you have qualified personnel. …I totally get it that ICH is trying to harmonize a bunch of national regulations, so it's a bit of a challenge. I do believe that this is 20 years old and it was the first – it was an amazing document 23 years ago or whatever because nobody really knew – everyone talked about GCP, but I was around back then and I remember thinking, "Now we actually have something that we can kind of refer to," because FDA had theirs and people kind of referred to it as GCP, but it wasn't really. EMA had stuff. So this was the first time that everyone could kind of focus on one thing and kind of understand. So I see this as totally this was a really good document 23 years ago. Maybe it should've been revised 10 years ago instead of – but I totally understand that the challenges in terms of bringing all the international regulations together and finding that common ground in terms of how best to articulate it because I am very much a process person, but other national cultures might – there's always going to be that challenge, and I do

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		believe that 23 years ago a task base was probably the best way to go. We just need to – now that everybody kind of has that under their belt and has some ideas and concepts, it's time to move on to something that's a little bit more process-oriented. **[ID# 12]**
Section 1: Glossary		
Have consistent definitions across regulations	B35	I think the definition of adverse drug reaction where we do have the sentence, "The relationship cannot be ruled out." I mean, then we have a reaction and not an event. This has changed over the years also, and it's more like there is evidence that there is a relation, then we'd talk of a reaction, but we have a little bit of a truth here in the safety area and I think this should be – actually, by deleting this half sentence, "The relationship cannot be ruled out," this would solve it already. We do have this discussion that's unlikely related or the relationship is unlikely or it isn't. According to ICH now, it would be related and according to other regulation it would be not related. So, we have a conflict here. …They should look at the definitions and find the consensus. And the consensus really, I think, really guides the author to deleting this half sentence here. …I'm a trainer. I'm a GCP trainer, and I suffer from having different definitions of course. …if you have newcomers to the area, you want to be as clear as possible on just the definitions, and if they have several, it's not good if they're not consistent. [ID# 23]
Section 2: The Principles of ICH GCP		
Complete compliance with ICH E6 GCP regulatory requirements should be reserved for regulatory trials with a marketing indication	B36	I think that in a lot of trials, especially single-center investigator-driven trials, when they are conducted by not necessarily investigative sponsor, but sponsored by industry or by organizations like MLG or MVI or DNVI, very often it's just a – if the ICH GCP had been done for everything, which then especially for smaller trials, for single clinical trials, various studies without thinking because a lot of people are just, it's ICH. We have to do the full IT validation whether a data capture system is now 100% CFR Part 11 compliant. Maybe a well-managed, normal computer system automatically might do the trick. And my understanding is that in GCP you don't need that, but in ICH GCP, this kind of quality control, quality assurance, IT validation – it's getting more and more important. And it might stifle scientific research and progress…And it is the case – for me, it is the case that a lot of funders now define GCP as the standard we have to adhere to – E6 R1 or E6 R2. But there's no flexibility. It has to be the full program. [ID# 08]
Section 3: Institutional Review Board/Independent Ethics Committee (IRB/IEC)		
IRB/IEC oversight of patient advocacy involvement in protocol development	B37	There's also the revision of the guide eight, number eight guideline; an important role to the patient advocacy group in giving an opinion about the design – this is you, social science. So, giving an opinion about the design of the study. In my experience, I've been working with patient organizations on how patients with GCPs in this specific country live. What access to healthcare they get? What are their problems? And what is the study design. How do they see it from their daily life as a patient? How do they see the protocol happening? Do they see it's feasible? So, guideline eight, the way it is being revised introduces this concept and invites sponsors to work more closely with patient advocacy groups to make designs more robust and to ensure the patient community eventually will be okay with participating. I think patient advocacy – I don't know if it should be part of E6 or another guideline. How to incorporate it to ICH? If it will be incorporated in E8, as part of the protocol design process, I think it needs to be mentioned. And I think it's sensitive the way that patient organizations communicate with sponsors. And there should be also best practices there. But how much do IRB participate or are looking at how this interaction is done to ensure there is no undue inducement you know, coercion, this kind of thing. And I think – I'm all for this happening, but it needs to be careful. And it needs to be protected so that no other thing is confused in these communications.

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		So, it should be either in E8, E6 or a new guideline – best practices for advocacy participation in the design and implementation of clinical studies. [Follow-up question if covered in E8, would be helpful having it cross referenced in E6] Yes, of course. I have been reviewing E8. And I saw it's there. It's there. But there is no mention of this – there's mention of the importance of the participation of the patient community. There's no mention of careful consideration for potential misconception, undue inducement, this type of thing. I think maybe it could be added here under IRB. IRB should be aware of this happening in the studies and review or give an opinion or maybe it should be another entity. I would leave it up to the ICH guys. **[ID# 03]**
Section 4: Investigator		
Update to align responsibilities with current regulations	B38	And I also hope that the revision would be a bit less FDA-oriented in the approach because, I mean, I fully understand when it was first written that the FDA regulations were already available for GCP, and of course, the impact was a big one. But for example, the investigator is the one submitting to an ethics committee and so forth. This does not apply in all countries and I find it a pity that there is not more flexibility built in this guideline. And I think with what we're trying now, that we see that many countries have followed and have also have their own legislation now in clinical trials. And of course, being in Europe, I mainly am thinking of Europe of course, but not only – but here, for example, we have in our law that the sponsor submits to an ethics committee, and so we have a conflict already. I mean, we know that a law which took priority over a guideline and we can live with it, but we know now that we have these situations, I think we should also take them into account and have a bit more flexibility and talk more of the party who submits, whoever that is. **[ID# 23]**
Informed Consent	B39	Well, I think what they need to do is instead of creating checklists – because really, ICH is a checklist in many ways, right? And they've got the whole appendix and all the things you have to collect. Instead, turn it around and say there's three hallmarks of informed consent for how you're going to provide the information, what the units of consent actually is because try doing a cluster randomized trial in ICH/GCP, and everyone thinks you're basically breaking laws. Then, the other part is when consent actually can be waived at an individual level. … We have three components: how we're gonna give the information to people, what's the most appropriate unit for consent, and then what basis should consent be waived. The GCP should say every protocol should contain a section describing. And that way, right, ethics boards are looking at it, people are looking at it, investigators are looking at it who are going to participate if it's a multisite trial. Of course, that has to translate to a consent process, but no longer do we have a 14-page form that talks about the stuff that people just can't even comprehend. [ID# 13]
Allow more flexible safety reporting	B40	– safety reporting. I spent a few hours this morning adjudicating events and thought, "I can't stand this." We have the rule – and it's in the discussion on what you should actually collect – we have this erroneous interpretation that having people review information makes it better. And you know, it's garbage in, garbage out. And in a way, I'm not saying that the information people are providing is garbage, but what happens on a local level is people actually take a look at the situation. Agreed, the people who do it have to have the proper training and qualifications. … any world-renown cardiologists, if she says it's an MI, I'm gonna say it's an MI. I might not completely agree with them, but its criteria are obviously quite sound. So, I think there are times when we have to look at safety. What's an outcome, what is a safety signal, and how best to implement the process. The day of the individual safety report is dead, and it should've died long ago, yet it continues, especially in the pharma world because they say that according to GCP – now, I know it's [inaudible] in particular, but E6 talks about the safety in SAE reporting. It's all part and parcel, and they say, "No,

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		it's not." And so, again, it's the lack of flexibility and in terms of understanding the key criteria required in safety. Do no harm – fundamental. How do you show that you do no harm? It's not by creating more case report forms. It's by actually counting the stuff that's important, understanding that which you can qualify and that which you can't. If it is supposed to be international, one has to recognize that safety and enrollees in those settings, looks very different than safety in Canada. And even Canada has some settings that are fairly scary in terms of what can be done. So, marginalized populations remain marginalized because the required information cannot be obtained. When we try to implement studies, especially with pharma, in anywhere that's a little unique, "Oh, the data can't be real." They're real, it's just not what you're going to need to be able to confirm whether the enzymes are 10 times the effort of when they're normal. If not, they go back and say, "Well, we have to have complete safety reporting because of ICH." And there's no doubt that we have extrapolated ICH beyond their original intent, but there is no doubt that they have to now catch up to the necessity of research or research needs, basically, in these key areas. **[ID# 13]**
Documentation	B41	Another area is the principal investigator oversight. We know that principal investigators often delegate a lot of responsibility to their staff. And that's fine, and that's documented well. But what we don't capture sometimes is the fact that principal investigators have regular meetings with their staff to discuss what's going on with the study, to see if the patients are compliant, if there's any questions about meeting criteria for inclusion/exclusion. And again, that's an area where the sites often tell us – "Oh, yeah, we have weekly meetings." But there's no document that shows that. So, then we have to write either a note at the end that says this is the process and get the investigator to sign off on it to acknowledge his oversight. And that's the thing that comes up in all the other files…And even if it's a note at the beginning of the binder that says this is our plan [for] meeting to discuss the study, and they have weekly meetings that we'll do this and ad hoc meetings to do this. And then it's signed and dated by the PI. At least that shows that we can ask the question. You document this after we did amendment X of the protocol. Where did you show the trainings? How did the PI –? And then at least we can document that we had that conversation based on this document, and the site confirmed to us during the monitoring visit. Because the monitoring report becomes part of the study document for the company that we work for. And we can say that we confirmed that – yes, the PI oversight was there as outlined in the binder by this document, and this is how we confirmed it during our conversation with the site. So, I've documented it in my monitoring report, so it's considered documented now. So, the circle is complete. [ID# 14]
Provide training materials/overview for new PIs	B42	Those of us who've been around for a long time, the way we learned how to be PIs is just doing it. One day you were a PI. Suddenly one day you were PI-ing this trial and you kind of signed the documents and you did the things you were supposed to do, but that has gotten a lot more complex. So in our organization, we're trying to recruit new, younger PIs to carry on. I think that it may not be in the scope of GCP here, and there are some areas that talk about the investigator responsibility, but we're interested in trying to figure out how to get our younger PIs, the ones who are just starting, to kind of be able to absorb everything that they have to do. When we came along, it kind of hit you all at once. When you become a PI now, suddenly you're getting all these documents and all of these things are happening that you don't really understand very well. That may not be in the scope of what you're looking for, but that's something that is a concern for us. [Follow-up question on addressing how to help new PIs] …I'm looking at page 13 of this where it's listed under section 4.1 that talks about investigator qualifications agreement, and it gives kind of a general overview that the person who is an investigator should be qualified to do what particularly what it says, and it should be aware that comply with GCP and those kind of things. What I have in mind is something where it says the investigator should be prepared to – I think it would be helpful at some point to go through what the investigator is responsible for. The

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		investigator is responsible for the delegation of authority. The investigator is responsible for certifying the information on the 1572 among all the people in the organization that are going to be involved in the trial and basically touching the patient and all of the locations where that's going to take place. The investigator needs to, in a timely fashion, review and sign off on the safety reports, and the investigator needs to review the deviations that occur on the trial. I'm just thinking off the top of my head the kind of things that you do when you're monitoring all of this. The investigator should periodically monitor the clinical course of the patients who are enrolled in this clinical trial. Something like that that kind of spells out and I guess in kind of a general way the things that an investigator should do. I don't know if you've – well, as I think about it, I'm not sure if ICH wants to put all of that in there because they don't want to conflict with specific protocol recommendations, but to me, that seems like it's kind of hitting the high points and helps, too. Particularly among I think the new investigator, you can just show, "This is in the GCP documents. Here's what you need to do," and it almost for them can even become a checklist of, "I haven't reviewed the safety reports this week," or whatever. That kind of thing. I think a document like that would be helpful. I guess I don't really know whether it should be in ICH or not in ethics or not. I guess what I'm thinking is kind of more of an introduction to section four. The investigator is saying, "Here's the overview and here's the shortlist. Once you understand what to do, here's the list of things you do need to do," and then following that would be the detail of the rest of this because this is kind of – I'll agree that a lot of what I talked about is in here, but it is kind of verbose and stretching over several, several pages here. **[ID# 18]**
Section 5: Sponsor		
Provide guidance on implementing quality management systems	B43	Specifically, I'm really interested in improving the quality of the work that is done in clinical research. So, I really like the new sections on quality management systems, things like that. … I do really like the risk-based approach. I wish there was a little bit more detail. And I know with the documents that it's supposed to be generalizable to everyone. It's hard to do that, so I'm not sure about the how. But that's with the risk management piece, I would like to see more detail. But then, on the one hand, I want it to be key information, too. So, it's kind of like you can't have one – you can't have both. …Have you ever heard of the AVOCA Group? So, they have established, it's an organization that's really focused on sponsors of studies. And they've come up with 12 components of implementing a quality management system. And the way that they have laid it out, I could maybe send you – I'm not sure that I have – I'd have to look and see. But anyway, as far as quality management, what I would like to see – the way that I see the way that information is in the ICH guidelines is very – it's general and there is some vagueness to it. So, if there is a way to make it, I guess what I'm kind of getting to is I would like to have more of the how you're supposed to do it versus just in reference to what you should do. [Follow-up question on being less prescriptive and more descriptive] Yeah. [Follow-up question on whether case studies would be helpful] Case studies, yes. Yeah, I could see that. It would be hard to put that in a document, though. **[ID# 17]**
Quality management using a risk-	B44	Well, again, I keep going back to the last revision. That was the introduction of the risk proportionate approach and risk management there, but again, linked to the essential documents. There are areas where some of the documentation has been reduced if you adopt a risk-based approach, and I don't think that comes through the current guidance.

Aspiration	Reference #	Illustrative Quotations
based approach		[ID# 11]
Provide examples, case studies, best practices for implementing a risk-based approach for quality management	B45	I would love to see an example. I said we know certain things that are really bad, and that was kind of tangent but it seems like no matter what you do every inspection is TMF. And the reason why I'm kind of concerned about things is a pharma company can come forward with a TMF that's 90% complete and accurate; an inspector will find something and they'll give you a finding. And more often than not, it's usually a major. And you're like "For goodness sake, we can't get perfection in some of these areas." And so, if there's this need for – we've been beaten up about perfection, what does that mean for these new guidelines? We don't know. [Follow-up question about the types of examples would be helpful] Yeah, I mean, so going back to the biggest change area, which is quality management. If a protocol team does their risk management planning, and they fail to identify a risk, and then that issue happens, what does that mean when you get inspected? Because generally if the issue happens we will certainly follow through; we'll do a root-cause analysis. We'll put a cap in place, all the things we normally would do. Does it really matter that we missed that one as part of our firm planning? **[ID# 16]**
"Spirit of risk management" – not a prescriptive checklist or a law	B46	You underlined yourself it's a guidance, and that's what it was in the beginning. But, then, different authorities and different regulators, basically, transformed it into the law. So, they just took this text as such, and they plugged in some legal documents, which is the case of EMA, and then you basically, need to justify the compliance of each individual line, which I think is not even the original intent. So, I think that one of the things which really needs to be, kind of, stipulated and reinforced, that basically, the guideline provides all different elements that may be used, but that no one would expect that they would be, eventually, all used in the same project. And that, somehow, initially, the sponsors, they're responsible for the project, would make an assessment on what's relevant and would pick up certain instruments while dropping the others depending on the risk assessment, reinforcing the elements of the trial with the most risk to data subjects and, maybe, lightening a bit on the documentation or requirements where, in this specific research, the risk is estimated less. So, the risk element is already in there, but not really with this idea that it's the sponsor who, kind of, decides on what's applicable and what's relevant, puts a plan together with justifications, and then implements its plan, which may apply certain elements of GCP, but not all of them at the same time, but with the proper justification. And then, those countries where there are mechanisms of formal approval of research prior to start, can appreciate this document, and can interact with the sponsor to discuss around things, to agree, disagree, whatever. Like, it's done on the basis of discussion of the protocol itself. **[ID# 19]**
Allow for flexibility, depending on situation	B47	I would think it's very important to try to keep it balanced between the risks and the advantages of being flexible because some people are saying, "If we keep the GCP standards, we will never be able to do research in lower/middle-income countries." Some people say, "We have to keep the highest possible GCP standards." And I think they're being very superb. I think that both of them are, kind of, wrong. I think the issue is principles are there, okay. The principles under the GCP are okay. You have to be sure that there is a good risk benefit before you bring intervention in human [inaudible]. You have to check your data, reliable too, etc., etc. Then the way you do it can be phased. So, if we are doing research and doing an Ebola epidemic research, maybe we will not have the time – we cannot even get the monitor at the site, it is pretty dangerous for the monitor. So, it's really a matter of can the principle and to be a little bit more flexible in the application of the principle, depending on the risk of the research and probably, I think,

Aspiration	Reference #	Illustrative Quotations
		the European regulation on clinical trials have tried to do something in that direction, trying to make a distinction between low-risk and high-risk clinical trials. But, the trouble is most people implementing GCP, in particular, auditor, inspector, and quality assurance, tend to have a checklist approach, without thinking too much about the context and the relative risk attached to the research and this is something that should be a little bit clearer. Implementers should be explained by the ICH guidelines that these are the rules, but there should be some room for contextualization, depending on context and the risks, provided that the principles are kept. **[ID# 04]**
	B48	It's really very difficult not to over-manage our vendors in the spirit of ICH E6 R2, although there is always a tendency to do. So, it's really very difficult to figure out what's the right kind of mechanisms and also the right kind of dose of oversight…I do think it would be beneficial to probably be more differentiated. Because I personally feel it really depends on what kind of outsourcing strategy you have – how a risk based approach needs to look like. So, I think if let's say, as a small biotech where most of the work is really outsourced, I think, and there is probably a lot of lack of internal expertise, I think you have got much better controls than for a bigger company where you outsource, but you also really have all the capabilities in-house, so you understand how good needs to look like. And I don't know – it's very difficult for me to verbalize it, but I think a better differentiation based on your operating model would be helpful. **[ID# 15]**
Include more cross-referencing of other E documents	B49	So my best example would be in chapter five, for the sponsor, they inserted an entire new section about quality management and risk management. I was a little disappointed when I saw it, like the risk management is straight out of a risk management textbook. There's no link to – it could be anything. It doesn't have to be clinical research or regulated research. It could be how do you build a widget, right? It's just that [inaudible]. It's risk – data process or data identification, risk identification, risk evaluation, or risk control. They need – that whole section needs to go back to E8 where they talk about the type of study it's going to be. That's where you – I know E8 is currently under revision, too, but even as it exists now, it talks about the different phases and the therapeutics phases and stuff. So even if they went back to that to say, "You know what? This will help you identify your risk level and your evaluation," you have to use these concepts in E8. I think also when it comes down to more risk control and risk mitigation, that's when they have to refer to other guidelines again. E9 is about study design and methodology. So very clear that scientific methodology and study design can absolutely help with that risk mitigation and risk control, how you've got to make sure the patient's safe. So again going back to those principles, what are the most important things to make sure that you meet your principles, but the way that this risk quality management or risk management is written right now, it's way too generic. It has to go back to, "we have really good guidelines in these other areas. You need to kind of use those guidelines to build your risk profile." [Follow-up: Then also as you said there needs to be much more cross-referencing of whatever is in E6. Go see this section in E8 or E9 or what have you so that you realize that E6 doesn't stand alone to all these other things that need to be considered.] I don't know all my E guidelines off my heart, but there's a couple that are about populations, the pediatric population and the geriatric population. I think E10 and E – I don't know which one is what. So those – because populations again talk about how to manage that from a safety perspective, which I think is still very important for the risk aspect as well. **[ID# 12]**
Define consequences of incorrect	B50	Well, the tough part here is we never want to be told exactly what to do. And we want acceptable guidance that we can work within, without being told that we interpreted things incorrectly. And so, for example, when it talks about Section 5 – A System to Manage Quality, Pfizer's had a fantastic system-managed quality for quite some years now, and we're comfortable with it. No one has complained about it, but do we actually

Aspiration	Reference #	Illustrative Quotations
implementation		know from the inspectorate what it means – a system to manage quality? There's a lot of work on quality management systems in pharma, in fact, I've been involved in some of those papers. So, it will be good that – hopefully no one will get a finding that says your system is inadequate, if we're left to interpret things on our own. …So, I think the thought is what are the kinds of things that we might get inspected on that pharma knew, and to what degree would those findings be? And another example because I'm going to think new – If you take the whole section on quality management, and it says that the sponsor should identify risks to critical data processes. Well, we don't know what happens if something comes up and the inspector says, "Did you identify that risk?" And we say, "No." Is that a finding? Are they going to say that we didn't do a good enough job? Is that going to mean that there's an impact to our data integrity? So, it's really tying together the what to expect. Are they going to tell us that we evaluated wrong, that our RBM wasn't quite what they had in mind when they talk about the section on taking a risk-based approach to monitoring? The tools, my personal opinion, the tools that are out there right now being used really aren't that great. Are we going to be told that "Well, that isn't quite what we had in mind." So, there's a whole bunch of things that we just don't know. Nobody's really had a full blown inspection where they can share their finding to say that we've implemented incorrectly. …We have so much experience on the basic building blocks of trials for 30 years of work inspected. So, we certainly know that if there were protocol deviations that weren't found, that's a bad thing. If there were adverse, serious adverse events that weren't reported, that's a bad thing. If there were errors in our programming, that's a bad thing. There's certain things that are obvious that are really bad. We know those because we've had years of getting caught with them. For the new things, we don't know how they sit on that weighing scale; if we do them in a way that may not have been in alignment with what was being considered. And I think that's where we're still kind of, I guess, a lack of understanding about – Like I said, weighing it to – if we were to have a risk assessment using, as the scribe, probability of current severity, and we do that, and we set a threshold that we think we don't have to mitigate for, is an inspector going to say, "Oh, you probably should've mitigated that." And what's the consequence, is it a minor finding? See, that's just where we just don't know. **[ID# 16]**
Clarify sponsor oversight study roles	B51	So, number two has to do with – you know as GCP evolved into R2 it reinforced the role of sponsors in the oversight of clinical research. And it was clear that the sponsors need to pay more attention when delegating to CROs. It was like when investigators delegate there is still a responsibility, still the sponsor. And they have to be looking at what CROs are doing. And there are different roles that have come up in the implementation of studies. There's one role called oversight – oversight staff or sponsor oversight. Oversight CRAs sometimes and it's a role where there are people hired directly by the sponsors and reporting to sponsors, overseeing how CROs and investigators are working in their studies. And making sure that everyone is in compliance and things are moving along. And if there's any risk, they should be identifying it. So that sponsor can manage the risk during the study. This has evolved. Before it was not like that. Before we used to have a lot of more monitoring. Monitoring when you monitor a study, you do quality control of the data. We have more of that. We had – we were monitoring deviations, some aspects that were critical to the study and there may be audits sent by the sponsor during the study. And now this is evolving. There is more attention to systems. Systems are configured in a way that collect that data – are configured in a way that sponsors should be telling the system what they consider out of the ordinary. And this oversight can be used to do special visits to see what's going on and ensure everyone is in compliance or not on behalf of the sponsor. So, this is new role. It's not an

Aspiration	Reference #	Illustrative Quotations
		auditor. It's not a co-monitor, it's oversight. In the same category there's a new role that also has appeared that is the sponsor liaison. The sponsor liaison is a person working for the sponsor again that usually – they can be hired through a CRO. But the sponsor liaison has a personal relationship with investigator in the sense that they communicate directly with investigator, and they engage them in the study. Whereas the CRAs have a lot of work, a lot of things to be thinking of, traveling, are busy. And sponsor liaisons is more direct to the investigator and works with equipment, compliance and makes sure the investigator is happy and everything is moving smoothly from their point of view. So, okay – okay, so these are roles that not everybody has, but they exist, and they are used more and more. And I don't know how universal they are. I am seeing them a lot in the region. But this is something GCP maybe also could look at explaining what in some cases these roles – what they are and what they do. Because the way that they are implemented may change, but what they are doing, and the role is the same. It's universal. So, it could be added. …When these definitions of roles are not clear, then maybe the relationship becomes strained because it's not very clear or transparent what you are there to do. So, that's why I think either now or in the future it would be good to add as results become more and more used and more and more universal. Maybe we end up calling oversight staff or site liaison – it's different from CRA, but still sponsor staff doing things. We could even introduce it into the guidelines sometime later. That needs to be a motivation to industry of course, but this is – I think it would be a good idea to start talking about this. **[ID# 03]**
Allow for flexibility in training requirements and documentation of training	B52	We say, "Hey, you want to do this study? Here's the protocol. What do you think? Can you do it?" They'll tell us yes and we see. We kind of go to places where you think they'd be able to conduct the study, but the true measure of whether you can do something or not is probably on the head of the person who says, "Yes, I want to do it," according to people's interpretations, ICH itself, extent of training records. I can't train cardiologists on how to do their job. They know how to do it. But the recognition that we are implementing protocols that are hopefully at least borderline pragmatic, meaning if you practice with a physician in Canada, U.S., anywhere, you should be able to implement this protocol, and you don't really need to read the 400-page investigator brochure. So, again, no flexibility. You have to have documentation that you've read the [investigator's] brochure. And what we try to do now, I was part of an initiative to streamline clinical trials in Canada, we actually wrote up our corollary to ICH E6 R2 saying, "Recognize somewhere in the documents, in the plan that these people don't need additional training." The only training they need is how to access the data system, for example. And we could have documentation of that, but the documentation is when they enter the system. And beyond that, if you need additional extensive training, it's our fault if they don't get it, not yours, nor does it need to be documented. **[ID# 13]**
Section 6: Clinical Trial Protocol and Protocol Amendment(s)		
N/A		N/A
Section 7: Investigator's Brochure		
N/A		N/A
Section 8: Essential Documents for the Conduct of a Clinical Trial		
N/A		N/A

Appendix C. Participant Examples Related to Aspirations for ICH E6 GCP

Aspiration	Reference #	Illustrative Example
General Aspirations for ICH E6 GCP		
Clarify whether/how ICH E6 GCP applies to non-drug studies	C1	I think it's more and more – especially in trials that are funded either through large philanthropic organizations or the government, we don't have a choice. We have to use, at least as me as an academic or university study, we don't have a choice. And we had to make a decision that we cannot, in a way we cannot support academics with the small trials that we used to do. Because at the end, even if we are not officially the sponsor, and actually it can be debated what is the definition of the sponsor per the European guidelines or even if we just give it one for academic research, then we have to make sure that the quality assurance and quality control is in place from our side. And suddenly, we basically had to pull out of a lot of interesting sites for local implementation study because even if the study itself only cost a couple of hundred thousand dollars, we don't just have the bandwidth and the muscle to be involved in the quality control and quality management of these studies and the sponsor oversight. So, we had to pull out from a lot of studies which, a few years ago, probably would have been conducted with single-center, small number of volunteers or subjects. …The academic burden for non-regulatory trials. So, they are regulated, but they are not intended very often to be used in an ICH regulatory submission. ***[ID# 08]***
Clarify expectations of reviewers	C2	I am coming from an academic organization…E6 gets applied to our clinical research whether it's for a drug application or drug approval or not. So, some of the type of work we do, for sure we may use some kind of therapeutic drug or device, but it's not necessarily for approval. It's to look to see whether one is better than the others and it's more of what we call "procedural."… So it's nothing to do with an approval of the drug…there's patients involved, so there had to be ethics, and we want to make sure they're safe and all of that stuff. So all GCP in general, the concept or the spirit definitely applies and we implement that. But sometimes the implementation or the expectations of the reviewers that are the key factors that come in that are still expected to dot some Is and cross Ts where it's not reasonable to do, just because it's the type of study we have. ***[ID# 12]***
Clarify whether/how ICH E6 GCP applies to non-drug studies	C3	When I started reading about the renovation of the GCP, which included the ICH E8, wasn't it, and then the E6, from my reading about – first of all, I understood that the appendices which they planned to put into the ICH E6, that they may be to do with – they talk about non-traditional trials and other types of trials. So, my initial understanding was that maybe they would cover non-drug trials, non-IMP trials. So, in the university setting, there are an awful lot of trials of say, it could be nutritional trial, it could be vitamin D, it could be physio or the occupational therapy – those kind of trials. For me, the lack of having a quality standard for those trials is a big lack. So, I had hoped that maybe we'd get some guidance on how to apply GCP or kind of a version of it shall we say to those type of trials. But since I've read more, I'm kind of thinking no, that's not what they're intending. It was my own initial misunderstanding of it, I think. But that would be something, I think, that would be terribly useful, is to have some kind of a quality standard. Because at the moment, there's GCP or nothing. And for some trials, it doesn't make sense to have GCP. For example, if you're not collecting serious, adverse events which you don't for other types of trials other than IMP or devices. [Follow-up question on type of non-traditional trials to include] …non-drug trials, non-IMP trials. …academic universities and so on, a lot of what people are looking at are, for example,

Aspiration	Reference #	Illustrative Example
		care pathways or standard of care. And they can be really, really important studies to do and to do properly. So, if they – there was a study which was done here recently where they were looking at comparing milking the cord versus clamping the cord at birth. And they discovered in very premature babies that milking the cord was actually – they had a higher instance of brain bleed. Now, that's really important research to know because both of these methods are commonly used in clinical practice throughout the world. But nobody has ever actually found out well is this better than another. So, I think those kind of trials really need to happen, and yet there's no quality standards shall we say for them. Just GCP and that's – it's not mandatory for them. …No, as I say, I think they've done a great job with revision 2, and most of it I'm very happy with. But I await the next one with interest, and I suppose my big kind of thing is having some kind of standards whether you call it GCP or GCP Light or whatever for the non-IMP trials. Because I think it's really important that they have some kind of standards that should be adhered to. ***[ID# 07]***
Require study team to develop a plan for use/non-use of ICH E6 GCP components	C4	We actually sat and thought a lot about this, and this initiative that we had up in Canada was great because it brought together people from oncology, and infectious disease, and a bunch of different areas. And the thing we said is we've got to get people to think about these things up front, even just to say, "That doesn't apply to me." So, where we create all these plans, especially for the big trials, you'll have a 45-page data management plan, when really it should've been, look, you're going to collect data and make sure that it matches. We don't need an entire plan for this. Well, maybe you do, and you want that, but you create something that's appropriate for the issue for your study, for each of those issues, and you put it together as your study plan. There's a protocol and a plan. Ideally, the plan could actually be embedded in the protocol. So, informed consent would be collected at an individual level and will be two pages in length and describe key issues and patient rights. And not going to the 84 pages of – what does indemnification mean to someone entering the trial? Nothing. Or insurance. I think that we've taken paragraphs to describe what we could do in sentences. So, I've gone beyond, but your point was what could we do? Ask each of these areas to be addressed by the investigators, and if they don't, well, that's a pretty good signal that they aren't actually ready to conduct the trial in my mind. ***[ID# 13]***
Require study team to develop a plan for use/non-use of ICH E6 GCP components	C5	I think if there was – 4.5 says compliance with protocol. Again, that does outline what is expected as per GCP, but if somebody was in a rush – quite honestly, if somebody was in a rush and they had taken the GCP training and their GCP is up to date, they're only going to use this document when they need it. And it would help them to be able to look at the table of contents and say – okay, Institutional Review Board, responsibilities, composition. That's pretty site specific. Section three is very site specific. So, having done my GCP training, I just have to be reminded that my IRB work is site specific. So, I have to make sure my IRB has all the requirements. So, then they could say – okay, I'll check the composition, section 3.2. Does my IRB meet composition as outlined in GCP? Yes or no? And then that's a quick check. And those are the kind of checks that GCP, I believe, is intended to have. It's not supposed to be this big lazy document that everybody knows they have to know but they don't really pay attention to it unless there's a problem. …So, it would be nice to have a site that you can say – okay, IRB. I need your list of IRB. And then I can get that list and look at the composition and say – hey, you know what? We're missing this. Can you explain the reason? Can we document it? Is it okay? Is everything good? And it's a documented story about why their IRB composition may or may not exactly meet all the GCP requirements, but it may be approved because of an exception based on another section of GCP or some kind of state or provincial or country requirement where it's met. But are you seeing where I'm building this one just about – …we want this to be proactive situation, not a reactive situation.

Aspiration	Reference #	Illustrative Example
		[Follow-up question on that GCP is only reviewed to if there's a problem] Very much, very much. …Well, proactive – I'm going to use the informed consent section again, 4.8, as my example. My company proactively uses GCP to help them build a checklist form that anybody in my company can access to look at the informed consents they're provided to make sure they meet GCP because my quality department has validated within their systems that the checklist they're providing meets GCP. I have confidence in my quality department that they're doing that. Because that's my proactive approach to it because the form is there to use. …Well, rather than having an auditor say – you know what? This component of GCP is missing from your informed consent form. How did this happen? And why did it happen? And that means then going back, possibly having to re-consent all your patients, possibly losing data, possibly impacting safety, which are the two key components of GCP. ***[ID# 14]***
Best practices for ensuring data quality and integrity for paperless trials	C6	Well, we always have questions concerning appropriately maintaining confidentiality among the patients. There's a lot of electronic correspondence that goes around, and within our own practice we have – it's kind of an internal e-mail system based on Outlook that helps us with that so that we're preserving that, but there's always concern, especially if you're communicating outside of our own organization – and of course we communicate with the physicians and others at Sarah Cannon on a daily basis because they're administering all of our trials. We're working very closely with them. So we just want to make sure that what we're doing is in accordance with all those guidelines. At this point, the level of complexity here is such that I just have to proceed on the faith that our IT team and the others who are tasked with watching these things have done it correctly because I think it exceeds the capacity of any physician to try to make sure of those things. As a general rule, we don't send texts because we know that those are not really protected in some way, but our understanding is our e-mail system is fine. Those kinds of things I think are kind of a constant worry, and it seems like there's not – you've got general guidelines that you shouldn't put a patient's information out into a forum where it could be leaked out, but you don't get much guidance on whether what you're actually doing meets that criteria or not, except for what our IT team tells us. …As somebody who really understands these systems, I think that would be very helpful to have some kind of statements from them that give examples for what kinds of things are acceptable and what kinds of things aren't acceptable. ***[ID# 18]***
Section 1: Glossary		
N/A		N/A
Section 2: The Principles of ICH GCP		
N/A		N/A
Section 3: Institutional Review Board/Independent Ethics Committee (IRB/IEC)		
N/A		N/A
Section 4: Investigator		
Clarify investigator oversight in multi-	C7	The other thing, I do believe that it wasn't, necessarily, the right approach to reinforce the responsibility put on the principal investigator as it was done through the recent

Aspiration	Reference #	Illustrative Example
site/multi-modality trials		amendment because the way it was done just does not necessarily correspond to the scope of what health systems in certain countries would naturally give to those doctors. For instance, again, multi-modality oncology, there is an interaction between the medical oncologist, the surgeon, and the various therapists. The way the health systems are organized in Europe, typically, those will sit in different departments and even sometimes, they'll not be in the same institutions. So sometimes, the various therapists' activities will be, like, different legal entities, which has, kind of, agreements with the main institution, but which, technically, is a different legal entity. So, if one of those doctors is named principal investigator, saying that he has to coordinate this team, seems to make sense, but actually, he doesn't have the direct authority because it's not in his department or it's not even in his institution. So, actually, the kind of responsibility to make it all working correctly is starting with the sponsor, and then it's put into place through agreements between the sponsor and concerned institutions. And, sometimes, per the agreements between institutions themselves and then, of course, you need someone to coordinate the communication, for instance. But, this is a completely different type of responsibility than what current GCP puts in place. So the GCP actually really thinks that this is all happening within the same department, then the PI will just coordinate sub-investigators and nurses, which somehow, are all in the same legal structure and dependent on him or her. And that's not how it's working. This is the first thing. The second thing, we do have more and more disease diagnostic trials. So, you see it, again, in oncology. So you would have a drug, which is targeting a biomarker. And so, the point would not be to register the drug on breast cancer, but on all those cancers which express this biomarker. And, actually, recently, there was a drug registered based on this. I think it was first in kind by FDA. And, so, it means that the patients that will be recruited in such a trial are, actually, with different types of cancer, they'll come from a completely different department. So, ICH somehow supposes that there is one PI and one institution. So, if again, you want the PI to somehow coordinate a team, you cannot expect a breast surgeon to coordinate someone sitting and operating on colorectal cancers. That will never happen. So, that's another point where the notion of PIs, kind of, drops. ***[ID# 19]***
Clarify whether/how ICH E6 GCP applies to different forms of consent	C8	Then, the other part is when consent actually can be waived at an individual level. So, for example, we're doing a registry. Well, it's an observational study on the effects of bleeding – or basically outcomes after bleeding. What happens is you come into the hospital, you're bleeding, and you often die before anyone can contact you regarding your consent. Or alternatively, you get discharged before, because you weren't that sick, anyone can contact you. That means this whole clinical trial that we're running, an observational trial, is marred by the fact that our own ethics process, it doesn't enable us to actually get those who are sickest and those who are healthiest. We can't develop effective interventions if we don't know the spectrum, and I'm pretty sure, at least in my experience, 90% of the people you approach want to actually address the questions that have affected them or their family members. So, it's almost like the whole approach to informed consent and the ethics of approaching people have forgotten the part where people have choice. We don't even give people choice. And in certain situations, for example, when our participants have died before we can contact, one has to assume that they're going to want to help research the thing that killed them. So, I recognize that people have rights, obviously. Declaration of Helsinki [audio cuts out]? Absolutely. And I know exactly where it came from. But now, we've actually gone the other way, and I think transposed as a [audio cuts out] that more trials are doing this fairly well, are trying to get people aware of the fact that current thoughts – not always legislation and definitely not laws – are actually impeding the

Aspiration	Reference #	Illustrative Example
		progress in terms of clinical research. ***[ID# 13]***
Misapplication of GCP safety criteria	C9	So, like getting trials, we did a study called IntraBleed. We have 2,000 people in the study right now, and we had to stop collecting drugs on antithrombotics specifically because we were told by our own government, according to ICH, that we would have to do complete safety reporting in an observational study, but it's just crazy. And there are some companies, like BMS came back – and BMS and the [inaudible] sponsoring them, it's BMS who raised the flag and said, "We've got to do something differently," and we argued that you'd actually lose important data because antithrombotics can cause antiplatelets and anticoagulants, and even within anticoagulants, obviously, there's a variety of different types and effectiveness and issues. Well, we now have to lump it all together. So, when the ICH guidelines limits what we can do to answer important questions, I really think people need to take a look. ***[ID# 13]***
Clarify requirements for source documentation	C10	And we are always practicing – all our regulatory practices are under ICH GCP. And we always have to make sites aware of their requirements under ICH GCP. And the addendums – I'm hoping they will define a little better some of the requirements for documentation and principal investigator oversight because those are the two areas that we struggle with in our day-to-day work – ensuring that documentation is completed correctly and as per the requirements so that it can be filed in the trial master file, as well as in the site files. That's a big part of the challenges of our work. It's not getting the study done, just making sure it's documented properly right from the source all the way through the documentation about training and about investigator oversight. For example, when you talk to a site about source documentation, this is a really clear, defined – there's a defined definition in ICH about what constitutes good source documentation, the ALCOA principles and such. So, something that I encourage with the sites I work with is to have a blank sheet in the front of the patient charts that we use for our auditing purposes and monitoring purposes. I encourage them to have one sheet so that every time the patient comes in they just have to write the date, go through the visit as they would for the study as outlined; but while they're doing that, they have a space to write any information that the patient might have imparted to them during the conversation. Because often I've gone to a site, and they're like – "Oh, the patient just told me this." That's great, but it's not documented. So, to encourage that documentation I say, "Just put a blank piece of paper in the front. Put the date on the visit. Write your notes. Initial and date it at the bottom." And that suddenly constitutes a perfect source note for me to use when you tell me the patient told you they were taking a new concomitant medication. Or the patient recently visited an outside clinic for other treatments that may be associated to our study though not necessarily an adverse event but something similar, just a concomitant condition that may impact our study result. So, that's an area where I hope the new GCP organization and the way it's laid out with the addendums – to really clearly define that for documentation. [Follow-up question on what hope GCP achieves] No. 1, audit success. Because auditors are looking for the complete story. When they check a part of the document, they're looking for the whole story. It will fill in gaps through documentation because, again, an auditor will say – oh, the monitor came visiting this date. This site log is signed. This is the discussion. Here's the followup letter and the confirmation letter, and the followup letter will have that we confirmed this information. So, show me this piece of information because – and then maybe it's just an email from the monitor that confirms that piece of information. But that's the kind of thing that I've noticed more recently auditors are looking to do. They're not just looking for – they're not just reading through everything. They're building the story of how this study is conducted and how this study is run. And that's the kind of thing that GCP – basically, we said we followed GCP, and GCP has to

Aspiration	Reference #	Illustrative Example
		make sure that sites and people working on studies are aware of that whole requirement for audit readiness. ***[ID# 14]***
Section 5: Sponsor		
"Spirit of risk management" – not a prescriptive checklist or a law	C11	I think something that is becoming apparent, and perhaps I should say that I've become involved a little bit along with other people in the committee who are much more involved, in this whole issue of clinical trial complexity, and it really has gotten to the point where it is limiting accrual because a lot of docs just say, "To heck with it. I'm just going to treat people in the standard fashion." We're seeing that, and I think most research organizations are. What seems to be part of the process is that the sponsors and the CROs are taking documents like E6 and they are engineering their own training programs to even exceed those requirements not just with E6 but also with the FDA and how the FDA views things in terms of what you have to do in the protocol for them. So you can just tell that there are lawyers involved here who are kind of engineering these whole documents. Protocols used to be 20 pages. Now it's unusual to see one that's less than 100, and I've seen a protocol of 400 pages. It looks like as you read through it that there's a whole lot of legalese with the actual protocol requirements of what a physician would do kind of scattered throughout. It's making these documents so it's so easy to miss things, and things get missed because they'll be on page two, but they won't be in the inclusion/exclusion criteria. We're even seeing this phenomenon where requirements are not even being put in the protocol where they have to be amended. They're being put in lab manuals and things like that where normally the clinicians don't read, and it has to do just with the fact that I think the CROs and the sponsors feel like they kind of have to over-engineer these documents to make sure that each letter of the law is accounted for, each letter of the E6 and what the FDA would say. ***[ID# 18]***
Focus less on regulatory readiness and more on creating the best protocol for a study	C12	There's kind of a bimodal thought to it, I think. They don't mind doing studies that are not so difficult to implement. So, the rehab part of the world, we can kind of get rehab studies started, but anything beyond that is that they can't deal with what's required. Concurrently, if we say – it's great when we go to the pharma sponsors and say, "We'd like to work in Somalia." "Are you nuts?" "No. They're actually the people who are now developing these diseases." It's not just the investigators. It's also the sponsors. [Follow-up question: So, the sponsors, explain that to me. When you say, "We want to do research in Somalia," and they said, "Are you nuts?" what does that mean?] So, we mean any part of it. Do they even have ethics board? Do they know how to collect data? Yeah, they really read well. And in some ways, are they GCP trained? And I feel like – do you know that the majority of the world can be GCP trained in 15 minutes because they go, "Yes, yes, no," and you've kind of answered what you think it should be. GCP shouldn't be something you have to be trained. It's something that's inherent in the process that you can't help but do it right, and that's what we try to empower people to say, "Stop worrying about whether you're going to be compliant with GCP." You put it through, make the best protocol, consider these important areas, and then it'll be implemented. But the sponsors are worried about drug handling, drug handling. They're worried about – I hate it – "reg ready". Are you reg ready in case the auditor walks in? And it means your site master file. Anyone who works in the study, do we have all of that documentation? What about medical licenses? What about insurance for medical issues? It isn't even a concept in Russia, so how are you gonna deal with that? This is how the negotiations we have to do. We've been able to make small forays into areas. For example, I just got Ecuador in a study. They're super excited and you should see how they performed. Perfectly? No. They're naïve to the whole process. But when they made a mistake, and we said, "Hey, can you do it this way?" they said, "Yes!"

Aspiration	Reference #	Illustrative Example
		And I don't know why – is it easy always? No, but it's quite fun, actually, I think going to the places that really could benefit the most from these types of activities, and I hope that ICH, the International Conference on Harmonization, could consider that. ***[ID# 13]***
Recognize challenges of handling investigational product in remote trials, under-resourced countries	C13	…have you had much experience with products and all of the stability testing and accelerated stability testing, etc.? When we do studies, we sometimes get the actual results and the degradation that occurs in different situations. The ideal is 25-30 degrees Celsius, but it isn't as if certain drugs aren't sold in, for example, Bangladesh, and I'm pretty sure, from what I've seen, nobody's keeping it between 25-30 [degrees Celsius], but the majority are. So, somewhere, someone has actually tested it and said – I hope, I hope – that under these conditions, we lose whatever percent potency, or I guess we're just worried about whether we grow things, but I don't know that they can control the specifics of the humidity issue. So, as long as we recognize that in these countries, we're not gonna drastically lose potency, which is the only thing I think happens – I might be wrong. I'm not really an expert in this area, but I might be wrong. If you lose potency, and we're okay with it as the trial, why do regulators care about it because GCP said you should monitor it? And I think we should be able to make that case. We had people come at us because – you're gonna love this one – the opposite of cold chain, regular room temperature chain drugs that went through Winnipeg, and when the drugs landed, somehow – I have no idea how this auditor knew this other than the fact they were from the area, and they must've been looking at this in all the trials, they knew that the drug was in minus 40 for a day in transport because we didn't temperature control it, and they managed to destroy the entire supply. And because it's the rules, right? And you say, "Well, that might be a bit more Division 5," but ICH has a chance to say, "Let's be reasonable," and I think that might be the other way to go. I mean, I talked a lot about how each section should have the key considerations and areas that investigators need to address but by recognizing – and I think that's what they tried to do with the monitoring section a little bit. I thought they were trying to say, "Hey, there's a spectrum here," and figure out where you are on it. ***[ID# 13]***
Specify that ICH E6 GCP requires reporting to local agencies	C14	It says, "Such expedited reports," – it's talking about two things, okay. And it says, "Such expedited reports should comply with the applicable regulatory requirements and with the ICH guidelines for clinical safety data management, definitions and standards for expedited reporting. That's the E2A. And my comment is – and I'm biased because I'm Latin America, remember. So, in Mexico and in Brazil the agencies do not comply with the requirements described in the E2A. So, I suggest to put at minimum – to add at the beginning of the phrase, "At minimum, such requirements – such expedited reports should comply. And the reason why I'm doing this is because in many studies we do, I am telling the people I work with in the U.S., "Look, I know you need this to be communicated, but the agency doesn't want it. They don't request it. Do you still want us to submit? How do we go about this gap?" And many times, they don't know what to say. And I think I see – to me, I see guidelines on top of regulations. I see guidelines and specific regulations outlined locally that you have to comply with. So, I think at minimum means if the agency has the same – is aligned, good. If it's not, you need to make it happen as well. You need to talk to the agency and explain why. …We need to comply with ICH. Sometimes the agency says I don't want you to report this to me. But I am looking at the E2A, and it says I need to report it to the company's authorities and their representative. And what do we do? And it would help to have it in the guideline because it would help us show – you see, we need to do it. If you are going to accept that we do these international trials in this country, you need to accept that we submit this information. [Follow-up question on submitting to the local agency when agency doesn't want

Aspiration	Reference #	Illustrative Example
		information] We still submit it. We find a way to submit it in some way. Sometimes with no one reviewing that because they don't – but we comply. Our goal is to comply with ICH. However, there is this gap. And having this in the guideline would help us communicate to the agencies, "Look, you know, you need to accept it. You need to find a way to review or do something with it because you need to be aligned. …In Argentina, the agencies are totally aligned. So, we're good. In Brazil, we submit to ethics committees. And we submit to [inaudible] once a year with the annual update to [inaudible]. Unless there are some specific safety events that are – but they need to be local, they need to be related. It's not SUSARS we are talking about. When we talk about SUSARS we talk about unexpected related and international investigational product related, coming from wherever. And these are not – there's no one in Brazil receiving this right now. …The same in Mexico – the same thing. I don't remember what my company is doing in particular. I would have to ask my regulatory expert in Mexico. But we usually either submitted on the goal or with a priority report. ***[ID# 03]***
Section 6: Clinical Trial Protocol and Protocol Amendment(s)		
N/A		N/A
Section 7: Investigator's Brochure		
N/A		N/A
Section 8: Essential Documents for the Conduct of a Clinical Trial		
Allow for situational variation in requirements	C15	I'm looking through Section 8 because this is the one that drives me the most crazy. Essential for what? What would happen if I don't have these? I'm pretty sure we can't even prove all the things we need to prove. I get the part where we have to handle medication appropriately, and in Canada, we call it the – I'm sure you've heard of Division 5. That is our law – our punishable law – when you're dealing with clinical trial material, but the part where you have to cold chain it right up to receipt or until we give it to the patient, and they can take it home and do whatever they want. It's not matching. We ask people to do things that are disconnected, and what happens is when we do our studies, we tend to do very large studies, and we don't pay pharma amounts because that's how we get the studies done and answer the question definitively. In doing that, you look back at how some processes have evolved and drug reconciliation, drug loss, and looking at investigational product material shipment, all that sort of thing – wow. You've got to make sure people know what they've gotten and how it happened, but the part where regulators now walk in and look at temperature logs to determine if there are excursions, it's a little bit contrived because you don't do that in the patient's home, and they take it home for a year. We're storing it for four months, they're storing it for 12. Maybe you should go to their houses if that's really the key thing. Or make sure the processes are in place. And again, the flexibility to write up the process according to the requirements for the study and the patient. ***[ID# 13]***

Appendix D. Additional Participant Quotations Related to Helpful Aspects of ICH E6 GCP

Helpful Aspects	Reference #	Illustrative Quotations
General Comments on ICH E6 GCP Helpfulness		
Overall helpfulness	D1	Everything is clear. I can tell you that my company distributes this pocketbook of ICH GCP guidelines. The one with the integrated addendum, it's in track changes or highlighting what has changed or been added, so I think it's crystal clear. [ID# 20]
Overall helpfulness	D2	I work in research compliance. And so, my focus is to make sure whatever research is happening at our institution is compliant with the regulations and the applicable guidelines and ICH and GCP being one of them. And so, a fair amount of what I do is distilling the information that is in the ICH GCP into educational programs. So, the pieces that I use is I just try to boil down to very simple points when I'm doing training on the documents. And I usually try to focus it based on the audience. [ID# 17]
ICH E6 GCP principles apply globally	D3	I would need to check, but in the law [in Switzerland], it says somehow that you have to conduct clinical trials with pharmaceutical products in accordance of GCP. If the regulation in the law is not more specific.. the regulation is developed based on GCP. [ID# 09]
ICH E6 GCP is a guideline for conducting trials	D4	We have always been very adherent to the guidelines. The way that I have used them is I take each and every line, put it into a spreadsheet, and I've made sure that we either have an SOP, a metric on quality gain, something that says yes, we've got this covered and therefore we're protecting our patients' rights, safety, welfare, and data integrity. Therefore, as a guideline it's doing what it's supposed to do. It's allowing us to align our work to ensure that we are covering all the bases. The sections that we routinely or originally deal with are just about all of them. [ID# 16]
Provides useful information on human subjects protections	D5	As we had mentioned in the ICH guidelines, three different parties working together on clinical trials or supervising themselves, doing some surveys like the investigator, who is separate from the sponsors, and both of those are guided or guarded by the ethical committees. [ID# 06]
Section 1: Glossary		
Useful for training and serves as a good starting point for beginners to be able to define terms	D6	Pretty helpful is especially the glossary because it lists all these nice terms. When you start working in clinical development, it's pretty helpful for beginners also to go through each chapter, and read all these wonderful names, and get an explanation of what this means. [ID# 06]
Section 2: The Principles of ICH E6 GCP		
N/A		N/A
Section 3: Institutional Review Board/Independent Ethics Committee (IRB/IEC)		
N/A		N/A
Section 4: Investigator		

Helpful Aspects	Reference #	Illustrative Quotations
Investigator responsibilities	D7	and then, I think that there was a good intention about investigators – and, let me just go to that chapter 4 –because there's a statement in that – "The investigator's responsibility for supervising any individual or party to whom that investigator delegates trial-related duties and functions of 4.2.5 and 4.2.6." …how the investigator's overseeing his labs, his radiology department, or even his archives …from a quality assurance perspectives, I consider these paragraphs very important. These parties generate possibly primary and secondary endpoints, and it's the overall responsibility from the investigator to ensure that the data which is finally entered in the [CRF] is accurate and sustainable. [ID# 05]
Section 5: Sponsor		
Clear guidelines for sponsor responsibilities; defines who sponsor is	D8	The other chapter that I do like, though some people may think it may be going too far, as well, but it's the Chapter 5 on the sponsors, "Sponsors Responsibility." And for me, this is one, also, which, though I do understand that it might not be the opinion of everyone, but I do believe it's something which shall actually apply to all types of clinical research because whether it's interventional or even not interventional, surgery, drugs, whatsoever, it's something which concerns human beings, so I think you need to have a clear responsible. And, even if you are speaking about plural sponsorship and it's several responsible, but you need the responsibility to be crystalized. And, that's why I do like this chapter on the sponsor. Though again, in different contexts, it's written differently depending on drug trial, non-drug trial. But this idea that you do define an organization or an individual or, eventually, a group of those as being clearly responsible for what is happening, I think that's good and that's responsible in the scope of human research. …And, about the sponsor responsibility, it's very useful in two ways because sometimes, again, outside the scope, it's sometimes not easy to understand who is responsible. And, it puts a certain mess in the project. And, then it's not always easy to understand, logically then, who shall have which right of, I don't know, ownership, IP, what's fair, access to data. And, then, one question that helps to get it all straight – which is starting to get it straight – is to ask, "Okay, but who would be that sponsor? If that would be a drug trial, who would be responsible? Who feels responsible? Which organization would feel responsible for that research which is being done?" And when you get this straight, then all other notions become easier to work out. So, this is a very useful working point. The word though is unfortunate because the word "sponsor" is ambiguous and introduces a lot of misunderstanding between regions. For instance, when you speak about "sponsor" to a U.S. partner, he will actually understand "funder." So, all the time, I need to say, "The sponsor in the sense of ICH Chapter 5." **[ID# 19]**
Sponsor responsibilities	D9	I guess if there's one chapter to answer your question very specifically, I'd say chapter five for the sponsor is where I take most of my – because the sponsor is the responsible person, ultimately responsible. [ID# 12]
Sponsor responsibilities	D10	I think [the CRO section] was quite helpful with the last revision that the addendum under 5.22, "The sponsors should ensure oversight of any trial-related duties and functions carried out on its behalf, including trial-related duties and functions that are subcontracted to another party by the sponsor's contracted CROs." This was really useful and it enhanced the understanding here. [ID# 21]
Quality management	D11	The other useful section was in the chapter on the monitoring, whereby the central monitoring is mentioned... Because we have been facing it once the clinical trial directive was implemented in Europe…and then many authorities and ethical committees were immediately understanding by "monitoring," they were

Helpful Aspects	Reference #	Illustrative Quotations
using a risk-based approach		understanding onsite monitoring. And, so there the ICH actually was very instrumental because it very clearly states that monitoring can be also central. And, I think this is very valuable and it can be further emphasized by stipulating that monitoring can have different methodology. It can be onsite, classical monitoring. It can be monitoring distant one, so still in the philosophy of onsite monitoring, but remote, now with more and more electronic ways of communication that becomes easier and easier. And, then you do have central monitoring and that can be a different nature, as well. [ID# 19]
Quality management using a risk-based approach	D12	What else have I found to be helpful? I would say again the risk-based quality systems for sponsor…But even to see from the point of view of sponsor, to be able to say well okay, where are the possible risks in this trial that like in the processes, etc. And to look at that at the start because I think for years, people kind of concentrated so much on getting the trial up and running. And there was only then maybe – a quarter way in, they realized well actually, a big risk is that there'll be no patients, for example. Because either they don't exist or we've made our criteria so stringent that no one can get into this trial. I think looking at those up front before you even start means that we take on trials that are more suitable for say where we are and our population, etc., rather than taking on things and then realizing no, we've wasted that time on something that not doable here…It forces you to look up front it before you get into it and then discover oh, that's a risk which you could have foreseen actually if you sat down with the right stakeholders – with the doctor, the nurse, the whoever – and look at this, the different – how are we gonna get the patients in and what's gonna happen to them, etc. Planning, yeah. It forces you to look at what are the possible risks and then to mitigate them before you start. [ID# 07]
Section 6: Clinical Trial Protocol and Protocol Amendment(s)		
Focusing data collection activities according to study objectives	D13	Now, to focus also on the main objectives, and to organize the collection of data according to the main objective of the study or even the secondary objective, if you want because then if you have to collect everything, which can be never used for the study, you waste time and money. … [Follow-up question that participant relies on the clinical trial protocol section and amendments] Yes. What – it's not badly done, but supposed to be a promoted thing saying that it will be used as a focus for collection of data. … Well, if you're either, concerned of your study's overall survival, you have to be sure that all the data for your overall survival be collected in a very nice way. …if your data because you are in a Phase 1, Phase 2 study now, you need to see the efficacy, but at the same time to see the toxicity. At that time you will focus, of course, on the efficacy, but you have to focus also on the toxicity. You have to make a distinction between what is known and not known. And if it's a Phase 1 study you have to collect everything, you have to find signal. If it's a Phase 2 study focused on safety, you pretty much know where you are going and maybe you are. You have to focus on the maybe 10 or 20, but not all of them. Before they were never modified and that type of thing. **[ID# 22]**
Section 7: Investigator's Brochure		
Guidance could be expanded to improve investigator familiarity with investigator's	D14	The RSI, the reference safety information, so this is something which also should be introduced in the GCP guideline, as we do have this Chapter 7 here and we really need it because it's our only guidance we have how to write an IB. And it's very helpful, but it also needs some updates. [ID# 23]

Helpful Aspects	Reference #	Illustrative Quotations
brochure content		
Section 8: Essential Documents for the Conduct of a Clinical Trial		
Examples would be helpful for avoiding incorrect interpretation of this section	D15	Going back to the essential documents has created some confusion of understanding that it is a list of core documents. Again, I think most companies are aware of this now and gather the appropriate documentation as part of the trials – but I think when the guideline was first produced, and companies were still pretty naive about all this, it was very helpful to have a list of at least the basic documents that needed to be obtained for the trial. [ID# 11]
Extent of necessary documentation unclear	D16	…if you then go into the details, for me at least, it's very difficult to say it's not needed, what is written there. That's the thing, documentation. Obviously, you have to have version control for the essential documents. Everybody thinks that you can show how the protocol developed with all the versions. Everybody expects now that you make transparent your statistical codes, that you share data, all these kind of things…most of the things make sense. It's a misunderstanding to think that what is dictated by GCP is just administrative burden. I mean, for example, the qualification on training documentation of people, you could say why should I have to document the training? But, does it mean that the trial can be done by anybody, you don't need to know, understand and know the protocol? …It makes sense to have training qualification of the people involved in the trial, they document this training and qualification. [ID# 09]

Appendix E. Participant Examples Related to Helpful Aspects of ICH E6 GCP

Helpful Aspect	Reference #	Illustrative Example
General Comments on ICH E6 GCP Helpfulness		
ICH E6 GCP serves as a common standard for research worldwide	E1	[Interviewer: Well, let me ask you this. When you're doing your research in, say, Sub-Saharan Africa, are there – have you found instances when you're conducting research there where there are differences in, say, how the Tanzanian whatever-it-is, board of health or whatever, essentially the country's IRB, feels that trials should be conducted versus what's codified in GCP? Because we talked about it being globally. It's guidance, but it's global.] Yeah, it's global. Not examples I know of. We were actually surprised when we did a trial in Zimbabwe about the quality of the feedback we received by the ethics committee. It was very – they gave us a very hard time, actually. Yeah, they were very good. They really assessed the protocol and looked at it. Whether that's related to GCP, I don't know, I have to admit, but indirectly, I would say they don't integrate it very differently, I have to say. But, it's indirect evidence, only based on the experiences we had. In Zimbabwe, for example, we saw that very good – they really scrutinized the protocol and really looked carefully into the protocol. *[ID# 09]*
ICH E6 GCP provides a framework in countries with less detailed or nonexistent legislation	E2	So, from that regard, it's useful because we can point to the fact that we're using ICH in the basis for the application in the event that nothing else was available. I remember, in one case, we were doing research in a Latin American country. I can't remember which one it was off the head, but the legislation around clinical trials was quite undeveloped. And so, what had happened was, the investigator at the site had negotiated with his local ethics committee equivalent and were trying to say what was necessary in order to support the clinical trial application for a biologic. And basically, it came back that they would want to see the documents that were discussed in ICH E6. So, for example, "Investigator's Brochure," the protocol, informed consent form; they wanted to make sure that any additional information that the sponsor felt was relevant should be included. So, that gave us the latitude to decide what additional documentation would be necessary. But the fact that they were able to point to ICH E6 as the basic documentation requirements meant that it was easier for the investigator to discuss how the clinical trial would be set up. It'd be better if I can give you the country example because the country would explain why the regulator didn't **[inaudible]** environment was so underdeveloped – *[Follow-up question: Am I understanding it right that – they said, "What do we have to do to meet ICH E6 or GCP?"]* No. So, what happened was the investigator went to the ethics committee to try and find out the documentation requirements. The problem we had was we couldn't identify any legislation that would outline what was required for a clinical trial. So, we didn't know what the timelines were, we weren't clear as to which documents should be submitted, who they should be submitted to. So, they had an investigator lined up who they wanted to be involved in this clinical study, and I believe we approached him at one of the major conferences to see if he was interested and he had suitable patients. And so, what we did was we had discussions with an investigator, and he went to his ethics committee and said, "Okay, how are we going to get this going?" And we used ICH E6 as the basic guidance as to what they would want to see if they couldn't identify legislation. And then, we built it out from there. ***[ID# 10]***
Section 1: Glossary		
N/A		N/A

Helpful Aspect	Reference #	Illustrative Example
Section 2: The Principles of ICH GCP		
	E3	So, I'm right in the seat of the clinical trial sponsor, the academic sponsor. Well, how we do apply it – basically, again, speaking, first of all, the principles, when we are in front of the research… we would go through the Chapter 2 to ensure that we still have something that would comply with several of those principles. And, then, for some of those principles, you would not necessarily follow everything that this full guidance would allocate to these principles, let's say, but that you would, at least, have something that reassures you that you have measures in place that enable you to comply with it. And, I find it nice, kind of, checklist, if I may say so. [ID# 19]
Principles useful for ethical determinations during trial design	E4	I told you I had an example and I'm sure this is as good a time as any for it. Very recently, I had a discussion with a – it's more of a biotech testing company – where the idea is a certain group of patients that the proposal is that we would identify in our own practice patients who've had a particular response to a drug. Then those patients would go for a separate biopsy to obtain tissue to try to understand why the patient responded favorably to the drug. There's a lot of very interesting biology that goes with it, and on a first glance, you go, "This is great. Scientifically, this would help a lot," and there's possible benefit to the patient and that the patient would also get whole-exome sequencing as part of this. But then you come up to the point where you're saying, "But this biopsy that you're asking the patient to go through is potentially dangerous. The tumor type is such that the areas biopsied are not typically easy to get to, and there may be complications." It's something that at least clinically at the point in time that they would be doing the biopsy is not something that would normally be done. So at that point, you rely on the principles of GCP to say, "Is this something that we should get involved with or not? Scientifically, it's appealing, but are we really going to try to, in essence, talk our patients into it?" This is one of those situations where if your physician says, "You can do this. You don't have to do it," well, some people are going to do it because the doctor suggested it. So we are having some internal discussions now about that. I think GCP is helpful in that regard just to try to give you some guidance about what types of things are reasonable and what aren't. Any research trials now require biopsies as part of the treatment, and of course, that's in the consent form when the patient does it. In my view, this situation is a little bit different than that. So I think that we're looking to GCP and other things plus our own common sense to try to decide whether this is something that we should get involved with or not. **…**I'm trying to think if we – we're kind of rubbing up against this a lot, this whole biopsy question. I know that there were recently some ASCO guidelines that were issued on this, and those I think are helpful to a point, but they kind of force you as a physician to decide what kind of biopsies are minimal risk and which ones are moderate risk. That's kind of a hard thing to parse, but many more trials are requiring biopsies as part of it, and in general, we do those kind of trials. But these are trials where the patient's on a treatment that we think at least is potentially beneficial to them. But I think these are real quandaries for a lot of physicians who are wondering about for their individual patient getting them involved in a research trial. I don't know if – I think because this biopsy question has come up and ASCO's spoken to it, I don't think there's anything in GCP that specifically would address that. I think it's addressed much more generally. [*Follow-up question: So do they need to address that do you think?]* I think it would – well, I think it would be helpful. I don't know how they're going to address it effectively, though. Frankly, I'm not sure if there's something in here that already speaks to this idea of weighing the potential patient benefit versus the risk of the procedure. I believe there is, but this is a more specific thing where these biopsies that

Helpful Aspect	Reference #	Illustrative Example
		are done – for example, we're doing another trial now. We're actively enrolling to this where the patient either has a recent biopsy, which many of them do, or they go for a biopsy and screening. Then they start their treatment and they get another biopsy two weeks later. This is a situation where it's part of the trial for the experimental drug to help figure out how that works, and let's see, in this trial, as I recall, I think **[audio cuts out]** patients who enroll have to agree to biopsies, and then after that it's optional, which interestingly occasionally patients will do that, even optionally. But in **[audio cuts out]** That's just on one side of the line, and I'm concerned that the other situation I talked about where the patient is just getting a biopsy and just that the biopsy is the trial, that may be on the other side of that ethical line. I don't know if it's within the purview of ICH to comment on that either, but I think that everybody's looking for some kind of guidance or maybe some safe harbor on this type of thing of how do you do it. That was the purpose of these ASCO guidelines that got published earlier this year. So it's something that I think is of concern to people not just for biopsies – that's probably the main thing – but other procedures as well that are done more in service of this study than on it's something that the patient medically needs at that point. **…**If you were confident in your diagnosis and you're going on to another standard treatment, most of the time you wouldn't get a biopsy, whereas these studies, depending on when the patient's last biopsy was and what the adequacy of that tissue is, the patient may need to get two biopsies in short order to participate in the study. *[Follow-up question: I see what you're saying. When you were talking about – you cut out a little bit there. I just want to ask your indulgence to back up. You were talking about ethical line, so I missed that part because your voice cut out. Could you recreate that for me?]* Well, what I was saying is that in the research trial that we're enrolling patients to where the patients are on a treatment that at least has scientific backing and other data to suggest that the patients may benefit from doing it, I think that that's on one side of an ethical line where you can say, "So we'll get these biopsies that are required. In particular, the biopsy two weeks after the patient starts on treatment," whereas the other example where the patient's responded to treatment, they're doing fine, and the whole study is just doing a biopsy to obtain tissue to analyze perhaps why that patient may have responded well to the drug. But the patient didn't have to get the biopsy to get the drug. The drug is not experimental. The only way that the patient would benefit from that is that within the trial they're going to do whole exome sequencing and that data is supposed to be released to the patient. So it's conceivable that something of value to the patient may turn up on that, but it's certainly not guaranteed. In my mind, that may be on the other side of that ethical line. It's pretty close. I'm still debating this myself. We actually have our annual meeting where I'm going to talk with some other docs about that particular issue because it's just one of those things that you just – as I think about it myself, I'm going, "Is this really something we should do or not?" Ethically, should we do this is what I mean. Not just participate in the trial, but is this something that we can sleep well with? **…**It's a situation where patients when they're doing well …when patients are doing well, they come in, "Oh, you're doing great," they think they're walking on water. It's just the opposite when they're doing badly. They think – they're not going to do anything. It's a problem there where I think that that situation lends itself not to coercion so much, but just to that sense that, "My doctor suggested this. He wouldn't do that if it wasn't good for me, and look how great I'm doing with the other suggestions the doctors made. So I'm going to go ahead and do it." I'm concerned about that dynamic in the relationship. ***[ID# 18]***
Section 3: Institutional Review Board/Independent Ethics Committee (IRB/IEC)		

Helpful Aspect	Reference #	Illustrative Example
IRB/IEC guidance strengthens research in countries where IECs not established or required by law	E5	I have to say I think that I would not say that there is any chapter which is not important. It depends in which environment or country you are working in. For example, I'll give you an example. So, if you are working in Germany for a – or you have a good law for clinical trials and everything or a lot is governed by the law, then you might find Chapter 3 on ethics committees and IRBs not necessary. But I am also working in countries like in West Africa and doing audits, or other countries where there is no law, and then you can have this as a fallback strategy; or ICH really, if you're not of security here, because you can obviously refer to here, and then you would need Chapter 3. So, I'm not saying there is a chapter which is not necessary because I'm working on a very international basis with the audits, and I have had situations where I was in a country, there is no drug law or nothing. Then everything becomes even more important, of course, because then the standard really is sort of a ring of security – I don't know how you say it. You have a frame in which you are working in, and this is an international frame, so you can do good research there as well, although there is no law. **…**It's even more necessary. It really becomes – and my example would be the Chapter 3 because countries with a law or regulations, they have a very clear outline of how you have to work with the ethics committees, how to submit, and how to submit with regulatory authorities and stuff. So, you have it all in there and even to more detail than in this guideline, but when you are in a country where there is nothing, then you are very happy to have ICH GCP, also Chapter 3. ***[ID# 23]***
Section 4: Investigator		
Informed Consent	E6	Section 4.8, informed consent – we incorporate that information as part of our checklist to make sure that we meet all the requirements. Those are the ones that I find most useful…when we get an informed consent form, we have a checklist at my company. We have an informed consent checklist that we go through with every informed consent form we receive. And that informed consent form actually refers to sections of this part of ICH GCP. So, for example, 4.8.6, the language used in oral and written information – nontechnical, practical, understandable, legal representative, impartial witness. Those are the items that we confirm are included in our ICF in the manner that GCP expects. Signed and dated, making sure that the information is correctly documented, and signed off. And 4.8.10 – all those points (a) through (p) – no through (t), we double-check to make sure that information is included in the ICF. [ID# 14]
Source Documentation	E7	…I don't think that we ever request oversight documentation, how the investigator's overseeing his labs, his radiology department, or even his archives. This is because I think we don't want to bother investigators, especially key opinion leaders, with that, but from a quality assurance perspectives, I consider these paragraphs very important… [Interviewer: And so, am I understanding, then, that it's not something that you document that they're actually doing that? Is that correct?] I don't think we do it in a constant way. I think we outsource it. They do selection of site feasibility, but I am expecting – and, I got some feedback about this – that the investigators are not too much bothered in really showing evidence about this. [ID# 05]
Section 5: Sponsor		
Sponsor responsibilities	E8	…but there was a need to really think through how our clinical trial oversight needs to look like in the spirit of ICH E6 R2. So, we had a lot of discussion and eventually really ended up with proceduralizing study oversight as something, which includes really a very robust oversight plan template which speaks to each different area which we consider key to perhaps some level of oversight. And this is not a rigorous template, so it really needs to be discussed and agreed upon and customized on a study by study case based on the risks the teams really consider appropriate for study. But again, I think ICH E6 R2 really triggered this conversation and helped us with implementing this oversight

Helpful Aspect	Reference #	Illustrative Example
		process. [ID# 15]
Quality assurance and quality control	E9	A lot of resources are spent on monitoring and auditing, and there's still this very large debate and a resource spend on their source doc verification, their review and all that, out of the general concern that those sites are not compliant, even though the data says by doing this, but if you're not gonna find a lot of things anyhow. But I think that's an ultraconservative kind of fear factor regarding inspections. When it comes to our partners, like a CRO or otherwise, we want to see what their quality management system is, and we review to see if it's affable and aligns with what we would require if we were doing the work ourselves. **…**because the guidelines say that the sponsor is ultimately responsible for everything. So, we have to treat it as if it is our own. [ID# 16]
Encouraging a move toward electronic records may ultimately lead to wider acceptance of electronic documentation and e-signatures	E10	Because we work in regulatory affairs, we are often in a scenario where we have to maintain paper records. For example, we may have to maintain document copies, original copies; we may have to maintain signature pages, etcetera. So, from our perspective, as regulatory professionals performing applications – knowing that we're gradually moving towards electronic records in ICH will gradually, hopefully push countries outside of ICH towards accepting electronic documents rather than the paper ones; and that reduces the burden, for example, for filing. It allows us to use and to take advantage more of things like ETMS systems rather than paper TMS. Moving towards electronic documentation really helps. The other thing is moving towards electronic signatures. It allows us, again, to reduce the amount of burden from production of applications, that allows us to file applications in a more straightforward manner. And so, yes, seeing that ICH is gradually discussing what is expected for electronic records. I believe it discusses the ALCOA principles. So, the fact that this is now being recommended, I think, will hopefully help to push in that direction, which is to be welcomed. [ID# 10]
Section 6: Clinical Trial Protocol and Protocol Amendment(s)		
N/A		N/A
Section 7: Investigator's Brochure		
N/A		N/A
Section 8: Essential Documents for the Conduct of a Clinical Trial		
N/A		N/A

Appendix F. Participant Quotations Related to Unhelpful Aspects of ICH E6 GCP

Unhelpful Aspect	Reference #	Illustrative Quotation
General Comments on ICH E6 (R2) Unhelpfulness		
Need flexibility to accommodate different types of research/address applicability for non-clinical trials	F1	…I think we've got to bring clinical trialists together. You've got a broader interest, particularly those leading investigative networks. We've got to bring those together with the regulators and the sponsors. And we've got to sit down and figure out what's critical that we must keep and what can we change in a way that facilitates research…we need to say do we really need this? Do we need this for all trials? [ID# 02
Modernize ICH GCP guidelines to reflect changes in drug development, types of data sources, and study types	F2	I mean, we want to have one common standard, and I have to say that it has really worked very well over the last decade, but I also welcome very much to modernize this a little bit because drug development is changing. So, we need to really – yeah, go with this new approaches of data sources and types of studies, which now might be very important also for submissions to regulatory authority, so to get market approval or labor extensions or whatever, but the use of the real-world data I think is very important. . . And I would really welcome it very much that the GCP would also cover these types of studies and data and data sources, which I think it's not easy to be very honest. I think it's not easy, and I have to say that with the draft of the E8, Revision 1, I was actually disappointed I have to say, if I may say so, but I still think the whole GCP renovation initiative is a good one, and it's very necessary. [Follow-up question about how his concerns could be addressed by ICH] Well, I think there is already quite a plan on how to do this. I mean, as I understood the GCP renovation document, there is an instruction paper and I think they wanted to solve it or address this by different annexes, and I think this is what – I like this idea. I mean, that we have a different set of quality factors for the RCTs, so randomized control trials, and then get sort of a list of what we should be watching out for when we have still a comparative trial, but the comparative arm comes from a registry for example. Yeah, so we have a mixture of – we go to other data sources to sort of modulate our comparative rule, out of data which already exists, so they are already documented in some database or in medical records, which is also a database. So, we can use that. I think this is not easy. I think really it's not easy to come up with a list of bullet points. . . but I think that would be very, very helpful. Still, understanding that this is a guidance, that this might not work all the time, but it gives us, the ones who work or are involved in such trials and studies – that we know if this registry now something we can use to extract data, which we use as a comparator arm, or it's just not possible? Because have, like, the data set we define for the study what we are doing, and we have more than 50% missing data, then we should say we can't do it, or something. Yeah, and just now trying to give a simple example. There might be very different data sources, which come in, or the guidance would say only a registry which is established by a renowned study group or whatever. I mean, but the question will be, what data sources can I use? What types of data sources? And so, it's not easy, but generally I find the renovation initiative, so the GCP renovation, this reflection paper, I find the idea quite interesting how they want to go about it. And I think in general it's a good approach to govern this through different annexes. Yeah, so I think that would be a good approach. I mean, Annex 1 is the usual RCT, randomized control trial. Annex 2 is sort of a mixture. It's still an interventional study, but you have different data sources, not so traditional ones, like registry. And the Annex 3 is a pure observational, non-interventional design. [ID# 23]

Unhelpful Aspect	Reference #	Illustrative Quotation
(Mis)interpretation by sponsors in the U.S. that ICH GCP requires repeated GCP training for every sponsored trial	F3	…the problem is, again, the interpretation, GCP itself doesn't have a need to repeat a GCP training for every trial you do. At least I'm not aware that GCP says anything about it. Interpretation in Switzerland, we have kind of a standard that is set by the ethics committee about it. …in this sense, it's obvious that it's not GCP itself, but in this case, it's the ethics committees that set a standard, a certain standard here in Switzerland. In the U.S, it seems to be the sponsors. We know that, also, from industry trials here that if you are an industry sponsored trial, you need to complete GCP training and if you're bad luck, then yes, you need to repeat it again for every single trial again and again, which, useless, I agree, but it's, again, interpretation. [ID #04]
Section 1: Glossary		
ICH GCP definition of clinical trial is not consistent with WHO definition	F4	And it says, "Any investigation using subjects intended to discover or verify the clinical pharmacological element of an investigation or product. Or to identify any adverse reaction of the investigational approach." We've already got a problem before we even get out of the start. That's what a definition of a clinical trial is and that is not the WHO definition of a clinical trial.…It's all about investigation of drugs. But what if you want to repurpose a drug? Is that investigational? You could say it still is. But what if you want to do open surgery versus robotic surgery, where does that come into that definition?…the definition is wrong so they've got a problem. [ID# 02]
Additional information needed regarding definition of "validation of computerized system"	F5	When we talk about computerized system, I think there is computerized system validation. The document… I'm wondering if that would not require more definition around it or more information around it with regard to what is proper computer system validation. How should system environments look like that are used in clinical research to generate data for market authorization application? . . . 1.65, "Validation of computerized system. Approaches of establishing and documenting that a specified climate of a computerized system can be consistently [reading the section] from design until decommissioning of the system or transition to a new system. The approach to validation should be based on the risk assessment that takes into consideration the intended use of the system and the potential of the system to affect humans after protection and reliability of trial research." I think the FDA gives further guidance on how a computerized system would look like, and by that, FDA overrules or emphasizes the expectation towards that, but yeah. This maybe something that ICH itself would like to – and also to give more guidance on. [ID# 21]
Section 2: The Principles of ICH GCP		
Concern about the GCP principles being very high level and being used as a checklist for inspections, which is not how they are meant to be used	F6	I don't think that anything is completely not helpful. I think it's sometimes much easier to understand how to implement certain things than if you lead expectations when you implement it because there are so many different readings about the guidelines. I like the principles of ICH GCP, but these principles are so high-level because it's our principle that whenever you want to find a reference for an inspection finding or an audit finding, you could go back to the principles, and I don't think that's why they are in there, and I don't think that's how they should be used. [Follow-up question about whether the principles are used as a checklist in audits or monitoring visits] It's more from the inspection side than auditing side. If you go somewhere, you can only write up an observation if you have a criteria you use to reference against. That's like "All clinical trial information should be recorded, handled, and stored in a way that allows accurate reporting, interpretation, and verification for something you can use always." It's so high-level. Or, if we go to 2.30, "Systems with procedures that assure the quality of every aspect of the trial should be implemented." It's very good to use –for any audit or inspection observation because it's so high-level. [ID# 05]

Unhelpful Aspect	Reference #	Illustrative Quotation
Section 3: Institutional Review Board/Independent Ethics Committee (IRB/IEC)		
Update--recognize variation in ethic committee requirements by country—specify necessity for following local ethics committee rules	F7	The IRB ethics committee procedure because it appears that for the one in Europe, if you work from default ethics committee, it's different from U.S., you have IRBs. I know that you have central and local IRBs. I know also that it's the investigator who is submitting to the IRBs, and in lots of country in Europe, it's the CRO who's submitting, not the investigator, and we can have a unit of ethics committee in some countries such as France …. But the other country you have the central committee, local ethics committee. And in each country, the ethics committee has different requirements. Some will ask you I just want a yearly summary of all protocol regulation happening on the study. Some will tell you we just want to receive it at the end of the study. Some would say I don't want it, some will say on a six-month basis. So, I found they are all deciding to follow rules with some specificity but not a general to be like the procedure. The procedure should be all the time for all ethics committees. [Follow-up question about the type of guidance that they would like to see added to this section] Each time you have something happening, you need to check with them what they want to have. [ID# 20]
Update section to recognize variation in ethic committee requirements by country--add information on responsibilities of IRB vs. responsibilities of health authority, technology that affects trial conduct, and data privacy in regard to long-term sample storage	F8	Then, as I said, institutional review board, independent ethics committee – I think that really needs to be revised because it's not up to date anymore. [Follow-up question about how they would revise this section] I think you need to consider what is really the obligation and responsibility of an ethics committee or independent review board, what is the responsibility of a health authority, what is your expectation that they should check, especially in the modern times, where you use **[inaudible] [00:30:51]**, you use YouTube, you use all the social media. Also, in clinical trials, where you use different technologies. So, is the list of document or the list of information still up to date? Should it be changed? What about data privacy, which is in the guideline overall only very shortly mentioned? What about future research? Does it go into areas like oncology or immunology, where you collect samples from patients where you possibly want to do testing years later on? When do you need to ask if it's community later on for a reoccurrence? So, I think that's something that just needs to be read very carefully and see what is still up to date, what's not up to date. [Follow-up question about how the conduct of clinical trials would be improved if updates were made to the IRB/IEC section] It depends on what you're going to put in there. If you would make the scope of their work possibly more precise, it could possibly speed up the start of the clinical trial because they don't have to review each and everything. Depending on what you're going to put in there with regard to information, they meet in between. You could possibly also increase patient safety because they would review certain information in between. But, this is really to harmonize and discuss the different role of IRBs and independent ethics committees around the world because their setup is so different. And then, as I mentioned before, we do not even have a chapter about health authorities here, and there's also the question of whether health authorities have to be mentioned in the future in the document or not because they also play a role with regard to data integrity and patient safety. [ID# 05]
Problems with multiple ethics reviews—	F9	I'm talking about sense of purpose, I'm not suggesting we should do things that are unethical. I'm not suggesting that we shouldn't have oversight, but what I'm suggesting is that it needs to be fit for purpose. And it needs to be designed in a way that

Unhelpful Aspect	Reference #	Illustrative Quotation
reviews need to be fit for purpose		encourages research at the same time as protecting the rights of individuals. And what we have now is a system that discourages research and maybe protects the rights of individuals but it does so in a way that is so – You know what happens, right? You get one protocol, you know is a 10 IRBs. How often does it get through all 10 without a change? Because they all think they know better. They all think they know better than anybody else, and they don't. And so, IRB is fine but why do we need 20 of them? Who do we need 100 of them? We've done them all over the country, you've got them too. You've got centralized IRB in the U.S. now, which is most helpful, but it goes to an IRB – One place goes to a different IRB, they change it. So, does that mean the first one was unethical? It doesn't mean that at all does it, right? It means that they've got a different view about this but in the end, we'll all try to do the same thing. So, we are definitely going to do research. We are definitely gonna do research that protects the rights of participants and those doing the research. But at the same time, it needs to be fit for purpose. It needs to integrate with clinical medicine, in which consent is normally required. And why is it unethical for me to do a trial of, say a repurposed drug, in clinical medicine with a one page consent, which is all there is. And why do I need a 20-page consent to do the same thing as a clinical trial? It doesn't make any sense, does it? It doesn't make any sense. [ID# 02]
Section 4: Investigator		
Allocation of responsibilities--need to clarify meaning of investigator/institution responsibilities	F10	Yeah, I don't think it's a major thing, but that the heading of that whole section of responsibilities of the investigator. But then, as you start reading through the section, it switches from talking about the investigator to the investigator/institution. Again, this is all a reflection of the way clinical trials have developed. I think, when the guidance was first produced, most contracts were directly with the investigator but now, of course, the institutions are much more heavily involved. So, I think, again, perhaps, for the future, more clarity around how those respective responsibilities should be address would be helpful. [Follow-up question about whether investigators/institution should be split apart into separate sections] Not necessarily because I think there will still be some countries where the contracts will be directly with the investigator, at least at the present time. And again, I think it depends, very much, on local conditions which responsibilities will go to the institution rather than to the individual investigator. So, I don't think it's necessarily something that can be split out in the guideline. Some think. But in order to understand where the responsibilities lie in the trial it probably needs to – those respective responsibilities need to be documented somewhere. [ID# 11]
Allocation of responsibilities—Allow flexibility in who submits reports	F11	[Question on participant reporting that these topics should be modified "Should submit written summaries of the trial status to the IRB/IEC annually, or more frequently if requested," and "Promptly provide written reports to sponsor"] Yup, because this obligation is also within section 5 regarding the sponsor because we both have these obligations, but I think it's sufficient if just one of these obligations – either the sponsor reports to all IRBs or IECs for our sponsor, plus all the investigators should do this by themselves. I think it's absolutely up to the state or whatsoever, but there could be some reference in chapter 4 or chapter 5 for the same obligation and vice versa, to indicate that this is some sort of common obligation for all of us, and we should have to do it, and it might be agreed upon locally or by the sponsor, whomever is really doing it, and for all or just for the investigator.

Unhelpful Aspect	Reference #	Illustrative Quotation
		[Follow-up question on the need for clarity that this is a shared responsibility, but that only one party – whether it's the investigator or the sponsor – needs to actually be doing the reporting, not both] That's if it's allowed by local law, I would prefer this. And of course, if a sponsor provides this information, for example, to health authorities or IRB, there must also be a copy to the investigator to assure the investigator that the sponsor did it. [ID# 06]
Allocation of responsibility—need to recognize variation in reporting requirements and submitters	F12	"Final reports by investigators," I think the issue I had was that I was aware that, in not all cases, the investigator was responsible for the submission of the reports. … So, for example,… a scenario with the Central Ethics Committee, it may actually be the developer that provides the clinical study report to the site rather than the investigator report. And, again, though, if you read the particular text, it says that, "Upon completion of the trial, the investigator should inform the institution." It does say, "where applicable," but I think most people would view that as "where applicable" would be the clinical trial has been conducted, therefore you have to provide the report rather than – perhaps providing that clarity of language…Upon completion of the trial, the investigator should inform the institution that the study has been completed and the outcomes unless the responsibility lies elsewhere, such as with the developer. I don't know. But – yeah – I'm thinking that would have been my thought at the time given the fact I was doing so much work around investigator-initiated studies. [ID# 10]
Allocation of responsibilities—recognize investigator's responsibility for medical care in remote trials	F13	[Question about their views on source data and CRFs in remote trials] I think they're pretty helpful because it decreases the burden for a patient – for example, not to go every week to a hospital, but just once a month or once a quarter, so it's quite valuable. But, if you use things like this, there must be clear rules that the data go – for example, first, I still think the investigator or physician is medically responsible for this person, so the investigator must see this data and interfere, for example, immediately with a patient if he sees something that bothers that physician. [ID# 06]
Allocation of responsibilities—reallocate responsibility for assessing subcontractor qualification from investigator to sponsor	F14	The other section that's challenging is looking at the investigator. So, the poor investigator, as we know, is responsible for almost everything. And the latest – where it says if they are – okay, fine. If they're supervising anybody, they have to be – it has to be cleared. But the other bit is if the investigator retains the services of any individual or party that they have to basically ensure this individual is qualified. So, does that mean – and again, there have been various kind of discussions about interpretation – so, if an investigator is using say an outside body to carry out a test, like I don't know – an x-ray, an MRI, a lab, whatever – it almost implies that the investigator has to go audit that lab. And yet, they really don't have that skill or knowledge to be able to do that. So, I think that that's quite a big ask that if the investigator – well, it says investigator or institution – retains the services of any individual – to me, that's more like the sponsor. The sponsor is setting up the study, so why is it the investigator's responsibility? I think that that's – can be looked at. [Follow-up question about whether they think the ICH should address this allocation of responsibility in the revision of EC (R2)] Why not the sponsor? Because generally, the sponsor has bigger resources and staff who can do that kind of thing. So, if the sponsor is wanting to do a study and it needs say a particular test that can't be carried out within the investigator site, then shouldn't they go and audit and make sure that the testers, the people who are carrying out the test, that they are doing what they should be and that they're fit for purpose, etc. It seems odd to me that it's an investigator responsibility rather than a sponsor. Just

Unhelpful Aspect	Reference #	Illustrative Quotation
		putting that in there. [ID# 07]
Update to accommodate new technology/processes--Recognize environmental impact of archiving paper copies and provide guidance on what can be archived digitally vs. on paper	F15	Another thing where, maybe, I'm wrong, because here I don't remember anymore what the addendums say, so I can be wrong in the next comment. But, we have in 2020 and there is a lot of concern for the climate change and for environmental issues, and everybody is striving to, among other things, save paper. Then anytime auditors or quality assurance officers or inspectors take the GCP literally, we have to print everything. We really have to print everything, and this was correct in '95 – sorry, in '96 – because in '96 you could not update or have digital archive. But, these days, the amount of paper that we are printing just for the purpose of being archived and not being used, well, it's really huge. So, I completely agree that what exists in an original, signed paper version that should be kept in paper. Right? So that it exists. But to what extent can GCP try to be a little bit environmentally friendly and say we are in 2020, almost. Let's be clear on what can be legitimately archived on paper, because otherwise, you will always have people making an ICH-plus interpretation of the ICH. [Follow-up question about the meaning of ICH-plus] I think more than what ICH are asking. [Follow-up question about being 100%+] Yeah, exactly. Just because for being afraid of doing wrong, it's not really clear if ICH allows us to archive essential correspondence in email or print. So, just to be on the precautionary side, just print everything, and it's really a lot of paper that nobody used that could have been kept digitally. And, the harm to the environment is something which, also, ICH, perhaps, could start considering. [ID #04]
Update to accommodate new technology/processes--Need for human oversight of data collected by AI	F16	[Follow-up question about programming red flags in electronic data collection or mobile data collection] It's a little bit like a labyrinth, because also, we've outlined all those flags, and a physician has to look at it – is it a problem, or is not problematic? And, an error regarding the sampling due to age or whatsoever – but, I think it has to be checked by a person, not just by a machine, because artificial intelligence is not yet as intelligent, as we all sometimes assume. [Follow-up question about artificial intelligence and the need for oversight] There must still be oversight, and the other thing is the more of these machines you program or the more apps you're doing, you're pretty easily crossing a line because all these things are, at a certain moment, becoming a medical device. It's a medical device, and if you start a clinical trial with a drug and add on a couple of apps which are not yet certified – you're just still fiddling around – you're running a clinical trial also of medical devices at the same time. [Follow-up question about whether the use of AI to collect data in clinical trials needs to be addressed as part of the GCP guidelines] I think it should be addressed because on the other hand, it's also a clear and good opportunity to transfer the burden or decrease the burden for the patient. If you have a patient in homecare and have the data transferred to the investigational side and checked there, but then, of course, you have to address the additional data protection guidelines, you have to address the guidelines regarding proper programming and validation of these things. Because you're transferring patient data, it must be secure, it must not be affected by hacking, manipulating, or whatsoever. It must come 1-to-1 out the patient to the site. It must not be corrupted. And, it must be mentioned that it was started here in the last revision regarding validation of software and computer systems, but there should be additional things

Unhelpful Aspect	Reference #	Illustrative Quotation
		regarding also apps, data transfer, and remote data collection, and make it clear that we also talk about these things, and I give my students always a nice example of actual file. They put in height and weight to calculate the body mass index because they would like to apply insulin. It's pretty nice – hardly anybody knows – really, it's height in meters – no, its weight in kilograms divided by height in meters to –multiplied by the same height – how is it called? I forgot the English word. And, everybody –gets confused, but then they start dividing the other thing by the other end, so they just program a little tool, but then, it's really software you've programmed, and hardly anyone thinks about it. If you go to U.S., you add it in pounds, feet, and inches, and then you must always check what are the measurements of all these things. I think it'll verify to add a little bit more gratification on this validation of the things. [ID# 06]
Address consequences to trial of investigators having inadequate resources to recruit a sufficient number of participants	F17	So, the section on the investigator should be able to demonstrate a potential for recruiting the number of patients that they said they're going to do. Well, that clearly doesn't happen all the time. So, it's like, "Do you understand that GCP says that you have to do this," and the reason why is – for GCP, it doesn't matter if there's slow enrollment. For GCP it matters if we can't finish enrolling because then you end up, perhaps the trials you can't complete, and then all those who are in the trial did so for no good reason. And they took investigational drugs and they had blood drawn and all that, and that's for no good reason, which is the opposite of GCP. [Follow-up question on how can GCP then address that] I don't know. Yeah, I'm sure other people have thought about that. But do investigators understand why that is a GCP issue, as opposed to "Oh, well it's just slow." Slow to enroll doesn't bother me; not being able to complete is a problem. [Follow-up question about how the ICH GCP could explain the importance and reasoning behind an investigator needing to have the potential to recruit the required number of patients for their clinical trial] Yeah, I don't know if it has to be put into the guidelines, as opposed to some kind of nice white paper that big investors understand that it's not all about them not being able to approve, it's the thousand plus other patients who now will be in a study that cannot be used for any data purposes. [ID# 16]
Clarify language	F18	… [Section] 4.9.2 regarding source data, data entered directly on the CRF, because then you have all the source data. To make it a little bit clearer, it's a good opportunity, but then it must be really reflected up front as which data can be recorded on a CRF. What "source data" means is actually now pretty clear in the document, but for some kinds, CRF is really the source data because, for example, if you measure blood pressure by these –I don't know the English word, some sort of belt around your arm and print it off, you can also record it on the hospital chart, normally once a month or once a quarter, but for a trial, you might need it on a daily basis, and pretty often, you don't record it on the hospital chart, but record it directly on the CRF. It should be a little bit more specific here. [Follow-up question: So, they're not necessarily – for the purposes of a trial, for example, blood pressure might be recorded more often than in standard practice. If you have standard practice, it will go into the hospital file, which would be the electronic medical record source data.] You just mentioned it perfectly – because the standard practice must also be in the source data, but if you exceed the standard practice for a clinical trial, having additional data, I think it could go directly to the CRF. [ID #06]
Section 5: Sponsor		

Unhelpful Aspect	Reference #	Illustrative Quotation
Quality management using a risk-based approach— problems with understanding quality tolerance limit, consider using "set thresholds for action instead"	F19	Well, they're all helpful; there's not any section I don't think is helpful. I would just say that Section 5, particularly when you get to area in quality tolerance limits, I am giving a workshop at a conference this week for three hours to help people still figure out what quality tolerance limits are. So, three years after (R2) was released, people still do not get what's being asked of them. So, the concept – what they were trying to do was helpful; the lack of understanding – I guess not knowing the customers has been problematic, because the concept of quality tolerance limits is a very manufacturing thing which you can control, and with people saying that it's a little more challenging. So, it's an important thing around risk management three years out – still talking about it. [Follow-up question on what can be done to improve the guidance on this] I think they probably shouldn't have used "quality tolerance limits." …Probably not, should not have used that word because – so in manufacturing, let's say you're making nails. You may have an upper and lower limit where the metal is too hard or it's too soft. So if you cross the upper limit, it's too hard; when you hit it with a hammer the nail will break. And if it's too soft, you hit it with the hammer and the nail will bend. So, upper and lower limits. We don't have anything in pharma where we do our trials with upper and lower limits. We're not going to say that we had too few serious adverse events. We're not going to say that we had too few patients that were inappropriately randomized into the trial. I wrote you a list; it can go on and on. So therefore, the terminology became very confusing and if they would have just said "set thresholds for action," that would have been fine. But they used "quality tolerance limits" and so us in pharma leading the way have had to push back and say you probably mean "thresholds" and not "quality tolerance limits." …if had good quality in a clinical trial, you would likely see no deviations. That's what we're shooting for. So, why would you set a lower limit? [Follow-up question on focusing on the upper level of what's unacceptable] Yes. …Well, when you think about quality, quality is the absence of errors that matter. You can have errors as long as they don't really matter. [Follow-up question on using the term "thresholds for action" instead.] Yes. [ID# 16]
Shipping, manufacturing and labeling investigational product(s)	F20	Also, the part on investigational drugs, it's not really good. If research is going to be or international research in lower/middle-income countries, we know that there are big problems with ensuring quality there. So, the fact that the GCP guideline, now, will only ask you check compliance with the GMP. Okay, but GMP from a country which doesn't have a stringent regulatory authority, there is no assurance about the quality of that medicine. So, again, why they keep on ignoring this because this is really a serious problem and it seems completely ignored …a number of things are going unnoticed …The reality today is that, according to the WHO data, only 26% of WHO member states has a stringent regulatory authority. So, only 26% of WHO member states have the full capacity to check the quality of medicines in their territory. So, there may be a number of problems which just go undetected. [ID #04]
Shipping, manufacturing and labeling	F21	Other things…it's very often it's probably the interaction between GCP ICH, GCP other local regulations, and if we look at the manufacturing, the packaging and mailing, holding the investigational product, in the ICH it needs to be make absolute sense. I

Unhelpful Aspect	Reference #	Illustrative Quotation
investigational product(s)		think very often, especially if you look at the European clinical trial set up and the whole process of having a qualified person and things like that and for labeling issues. It's making things very complicated, especially with compounds that are not necessarily first in use, but used in other indications, used in other presentations almost as a standard of care, but the labeling adds a lot of work and a release from the GMP even if it's not – if GMP manufactured, the GMP stored and still a 25,000 franc bill to get it to release. But that's probably not an ICH issue but probably a European issue. [ID# 08]
Sponsor responsibilities—define sponsor responsibility for an investigator-sponsored study	F22	I think I probably have touched on a lot of them. Yeah, and as I said, at the moment it might be the sponsor responsibilities for regulatory trials. Yes, it's important. It doesn't cover at all what would be the – how would you define sponsor responsibility if it's an investigator-sponsored study? In a way, it almost – and again, I think from an ICH perspective, that makes complete sense because that's what they want to see what the sponsor has done to ensure data quality and integrity is done, and it was conducted for a study which is not coming to a regulatory review and is not having a formal sponsor like an outside sponsor from our industry. [ID #08]
Sponsor responsibilities—distinguish between non-commercial and commercial sponsor	F23	Then, there is absolutely no distinction between a non-commercial and commercial sponsor. And a good thing that this is also something like a detail, but in fact, commercial sponsors are also always the funder of the research, uses its own money and, doesn't need that to get external money. Yet, non-commercial researcher, which are doing a lot for orphan drugs, for pediatric oncology, for lots of tropical diseases, blah, blah, blah. They depend on external funders. So are all the sponsor's responsibility on the sponsor, or should they be shared to some extent with the one who decides on budget allocation? I'm not sure. I don't have an answer, but this is a question which is ignored in the ICH guidelines. [ID #04]
Guidelines need to be updated to accommodate new technology/processes—update guidance on sample sharing	F24	Then, the next things are not in our papers, yet, there is a huge debate these days about the data sharing and the sample sharing, especially in international collaborative research, this is a very important thing. I found it surprising that this was not appearing in the addendum, because – but now, in 2019 or 2020, this is hotter and hotter in the international debate, international research. So one would expect that the ICH GCP to provide, at least, some guidance about which are the minimal criteria for governance for samples and data collected in research. To some extent, they are still very old… I don't want to be--I know it's easy to criticize people who are doing the job when you are not doing the job, so I do not want to be – I give this disclaimer. It's allowed. It's really a guideline which feels it's left to the research world of the '90s, and yet, our group has implemented valuable improvements, especially based on new technologies available for some aspect of quality control or quality assurance, but that it's still a little bit the research environment of the '90s, with the commercial sponsor playing the major role, the high-income country playing the major role, and yeah. But, I think it's a little bit normal. I mean, there should be much more involvement of other stakeholders. [ID #04]
Obtaining IRB/IEC approval—add information about obtaining multiple ethics reviews for multi-center, externally sponsored, and	F25	I mean, there are some which are really less helpful or less clear when they talk about the need of ethics review, for instance, they are not helpful at all in deciding what to do in multi-center clinical trials, or in externally sponsored clinical trials. There is a 20-year-old debate about should you have ethics approval only in the country of the sponsor or only the country of the study or both of them? The ICH completely ignores this question. So, that's one example. [Later in the interview when asked a follow-up question requesting an example.]

Unhelpful Aspect	Reference #	Illustrative Quotation
multi-country clinical trials, particularly those conducted by the global north in the global south		But, just to make a short summary, what is not there. First, this issue of double or multiple ethical review, in case of studies, especially, which are done by research in the global north, in the global south, etc. [ID #04]
Creation of the revision— consider adding a separate document listing resources for interpreting ICH E6	F26	[Question on whether ICH GCP should be more directive] I could list. I think maybe it should not be part of the direct document, but there are – when you look at the grey book of the MHRA, for example, this is kind of an interpretation of ICH where they write – it's kind of also – it's a compendium of findings of the MHRA, but also in the approach that the MHRA takes with regard to proper clinical trial conduct. And this is quite helpful because it interprets, to some extent, ICH E6. Then, there are other sources where you can find help for this. For example, the Avoca Quality Consortium or there are other consortia like the Metrics Champions Consortium where you can get more insight into key performance indicators, also quality indicators, and where you can discuss these quality tolerance limits that are or have to be implemented with R2. However, we are defining this on our end; by ourselves currently and it's a difficult question. I think it would be difficult if you would come – if ICH would come up with a quality tolerance limit that we would not accept. Then we would be in a better place than we are right now, even though we would run the issue of the risk of not adhering to it. Maybe an addendum or I don't mean an addendum like the R2, so maybe an additional document, some loose guidance would be under staffing or supporting the ICH E6 with better to get some proposals, maybe not to that extent, legally binding or binding like the main core document. ….Give opportunity. …So, that you do not get – so, that is not like the black and white that the core text is, but more gives you freedom to interpret. [ID# 21]
Other concerns	F27	[Question about their experiences implementing GCP in different countries.] For the most part, it was very good. The ICH GCP guidelines certainly gave a very good harmonized approach that we were able to take forward and regulate it, and most countries would work with that. Where I think there are issues – it wasn't so much with the guideline itself as with the way it was, sometimes, interpreted in countries. [Follow-up question on providing an example Well, one example that caused us a lot of problems – again, this goes back to the electronic data capture that's been putting it in [crosstalk and inaudible] [00:11:49] now. Like most companies, I suspect, certainly large global ones, a lot of the systems were first developed and used in trials in the USA where we were able to do those and successfully got through inspections by the FDA without any great difficulty. But then, when we started to bring those systems and processes over to the EU, we were running into problems in inspections because of the – again, this goes back to systems being provided by the sponsor to the investigator if the investigator did not have sufficient control over the data that they were generating in the trial, and there was always the potential for the sponsor to interfere with that data. And that caused a lot of problems in Europe, whereas it's something that had never been raised on FDA inspections.

Unhelpful Aspect	Reference #	Illustrative Quotation
		[Follow-up question on how to address] Well, at the moment, it is handled through, in Europe, usually, having the data controlled by – well, access through data control through third parties…And again, that's not – so, the systems are only applied for Europe to get around the European approach. So, again, it's not something that is always done on a completely global scale. [ID # 11]
Section 6: Clinical Trial Protocol and Protocol Amendment(s)		
Section is not very helpful for protocol development	F28	…it's just giving the minimum content and is not really up to date anymore – just the headers, but protocols contain a lot more information, or they're going to leave it in the way, but make clear that they think protocol needs to be simpler, more feasible, and operational, and then they really should provide some more guidance on what should be possibly not in the protocol. [ID# 05]
Section is not very helpful for protocol development	F29	for protocols, I wish there was more depth to what you can do for quality control and quality assurance for the trial execution. And there's really not that much there. I wish there was more. …Well, it says, ethics – description of ethical considerations – a few things. I would like to see what are for quality control and you should have regular checks of the data. There are ways to do those. I just wish there was more in here…quality control is different from quality assurance, so they could be saying okay, quality control. Quality control is regular checks of the data, versus quality assurance is a snapshot of the overall performance of the trial. Regular quality control checks should be done throughout the duration of the study. Just having some recommendations on what that is. [ID# 17]
Section 7: Investigator's Brochure		
Need to expand upon the content and purpose of the investigator's brochure	F30	It's chapter 7, regarding the investigator brochure because on the one hand, it's just a really brief section, on the other hand, it's actually a wide variety behind the content of the investigator brochure. It just gives you some very brief remarks regarding investigator brochure, but not so detailed – as I mentioned, for the protocol section, chapter 6, it really clearly describes which information you must have, for example, in your study protocol, or also, in chapter 4, regarding all these issues in informed consent. [Follow-up question about their statement that the investigator's brochure section is both very brief and very broad] Actually, the information in the investigator's brochure is pretty broad, and very comprehensive information on that trial drug and the researcher, so it's not completely reflected in this chapter 7 because it's just very brief and rudimentary information, I think. On the other hand, it might be sufficient in the document E6. For example, later on, additional document regarding –all this information regarding investigator's brochure, so it's brought up in an additional guideline. I think it might be a better way. [Follow-up question on the kind of detail to include if the investigator's brochure was a standalone guidance document] It should go more in the direction – for example, in our chapter 6 in the current guideline regarding the study protocol, it gives more information on the contents, and the purpose of these contents, and things like this [ID #06].
Emphasize importance of version tracking investigator's brochure and	F31	And for the investigator brochure, that's also version tracking. And planning impact of versions in other study documents. Many times, brochure change, or updates does not impact, but many times it does impact; particularly informed consent. Sometimes the protocol.

Unhelpful Aspect	Reference #	Illustrative Quotation
the need (as appropriate) to update other study documents when changes in the brochure occur		[Follow-up question about whether changes in the investigator's brochure need to be reflected in the updated informed consent] Well, not always. That's a trick. I think as to your comment about assessing, yeah, because if you have, for example. If the investigator brochure reviews a new event – new adverse event that is becoming more frequent or the intensity is changing, and we need to alert the patients that they may go through that. And they need to consent again because it's a new potential adverse effect of the IP. Then it's important to – that brochure will have an impact. Maybe it's information about new owned stability study with the same drug and the same – everything is the same. It's just new information, a chunk of new information you are putting into the brochure that you need to have it there. And maybe it doesn't need to be communicated to the patients. Or it doesn't impact the protocol. But I think it's a good practice. And I think everyone would agree to – as you develop a new version, to assess how it impacts other documents of related studies. So, that you can plan ahead and make sure you are not missing communicating or changing anything. And we do it as good practice every time a document changes, but I think this is something everybody is doing; could be written in the guidelines. Would help to keep it in mind. For the management of studies, it's key for us to know. What are the changes? How are they impacting? What are the things that we need to do next regulatory wise if we need to obtain new approvals or implement immediately because it's on the benefit of the patient's safety? [ID #03]
Section 8: Essential Documents for the Conduct of a Clinical Trial		
Clarify purpose of insurance statement and consider providing country-specific examples	F32	Well, section 8.2.5, the insurance statement – it is very vague. It makes it hard for someone who is not aware of how insurances work to make sure that the site has the correct insurance statement for their files. Maybe there needs to be an appendix about country specific examples or things like that or really, a better explanation of what the insurance statement – the purpose is clear. But what the expectation of the document is, maybe? That's what I'm looking for, the expectation. The purpose is here but what the expectation at the site should be. They will have this document that covers personal, and there should be a phrase in their insurance statement that states this for the study or something like that. Maybe a little clarification there would be good. [ID# 14]

Appendix G. Participant Examples Related to Unhelpful Aspects of ICH E6 GCP

Unhelpful Aspects	Reference #	Illustrative Example
General Comments on ICH E6 GCP Unhelpfulness		
Applicability of ICH GCP to different types of clinical trials and need for flexibility	G1	Basically, we have one set of SOPs that apply for what we call our epidemiology/observational studies versus our clinical studies or interventional studies. So our interventional studies are those studies that have some kind of intervention, and the interventions can be procedural. So when we randomize a surgeon to on-pump versus off-pump, that's still interventional because we're – so for those studies then again we have different approaches depending on – it starts with the study design and what the safety profile of the intervention is for the patients and how – I'm going to say how we randomize that's back to study design. So we absolutely follow GCP, but we do look at – as an academic organization, our biggest focus really is quality data and quality conduct. So not that it shouldn't be, but records, it has to be a by-product of the quality conduct that happens. So we're going to make sure we focus on the things that are important and things that matter. So when an investigator site has a patient in, they get a blood pressure, they're going to make sure that we have a qualified person taking that blood pressure whether they're trained or experienced or have a professional designation, but that it's someone that can take a blood pressure and knows how to use that piece of equipment and is interfacing with the patient to get this right quality data into the system. Peripheral to that is kind of where I got into that calibration. So regulators might come in and say, "You don't know that piece of equipment is measuring properly." We're basing it on the environment they're in. They're in a clinical environment already. It's being used for other clinical purposes outside of research, and therefore, we've made some assumptions because to have to go down that road really kind of blurs the whole picture in terms of what our real objective is, it's the quality data for the primary endpoints and trying to really kind of filter out what's important versus what's not important. It's not to say that we don't feel – so it's really the detail that's not even in the GCP. It's sometimes evident that the peripheral stuff that we feel isn't as – it's definitely not as important, but it actually can be detrimental because you lose focus on the stuff that is important. [ID #12]
Applicability of ICH GCP to different types of clinical trials and need for flexibility	G2	It's really the scope of the ICH GCP because there is a lot of confusion out there. Should it only be for clinical trials with new medicines? Should it be with clinical trials with medicine and vaccine? Yeah, everybody agrees. But when it comes to the diagnostic research, I heard people saying, "Oh, no. The GCP are not applicable because it's not the medicine." Yeah, but you are testing the new test. So, it's important. The other side, I have seen ethics committee referring to the GCP for social behavioral studies, which is not really the case. But, the principle can be applicable there because principle of informed consent or ethics review are checking the quality of data as easily applicable there. So now, it's a little bit vague. It is easy for clinical trials, but it can also be used for another kind of research. Perhaps, there should be – there could be – some more clarity on when it is really mandatory and when it is considered as an inspiration, of sorts. … So, for what kind of research GCP full compliance is mandatory, and this will be clinical trials with medicines and vaccines, but maybe other ones. Maybe, also diagnostic research. I would say "yes." Some would say "no." I mean, other kinds of research, like, epidemiological research, what about cluster randomized trials? [ID# 04]
Need for flexibility in guidelines	G3	… we were responsible for the data management in Ebola vaccine trial in New Guinea during an outbreak a few years ago. That was a kind of public health emergency and under emergency conditions, you need to adapt to what is possible in the situation. The

Unhelpful Aspects	Reference #	Illustrative Example
clinical trials conducted during global health emergencies		thing is, the situation should never be a kind of excuse in the sense of I don't need to think carefully or I – what I want to say, if you have – you should start from the ambition, from high ambition, and then realize, okay, we need to compromise, but then it's an explicit compromise, and you say, okay, that would be the target. We are not able because the situation doesn't allow, for example, let's say full documentation of the expertise of the data entry personnel. I don't know exactly whether that's true, I have to say, but I could imagine that, as a data management center that we set up there in New Guinea, maybe not for all data entry staff, we had full training documentation and FEBE ready because it was, really, everything was in a very – hurry. But, you start – okay, actually, in reality, I would like to have a good documentation that these people were qualified to do their job. That's what we would expect and that's actually what we're aiming at, but we will not invest all resources because at that moment in time, there are other priorities. We want to get the data in and we wanted to collect the data, so we put other security measures into place to mitigate any of those problems, and then some documentation was probably imperfect. The thing is, the important thing is, you shouldn't start with, oh, it's all very difficult so we do it like this, this, this. You know you should start from – okay, in theory, that's what we want and then you make the explicit decision, risk is low so we don't do it like this, we do it like that, or situation doesn't allow it but there are higher – how do you say? The public health situation mandates that we do something and there is global request for something, so we need to compromise because we need that data for this vaccine because of this emergency. Then we need to compromise. [ID #09]
Section 1: Glossary		
Clarify definition of certified copy	G4	I could tell you that there was a lot of confusion around the certified copy. I got so many questions about this and it took me a long time to get my head around this. Do you know the whole thing of having a certified copy? I think even the wording of that could be possibly clarified because it basically says that it has to be verified. So, say if you're printing out lab results from a computer. You have to then sign and date to say yes, what's on the page is exactly what was on the computer database. That's our understanding of it, but it's taken a while to get here. The same with if you photocopy a document, make sure it exactly matches the original. There's no pages missing and all that. There's no data cut out of it. So, in a way, it's quite simple. But it did seem to cause a lot of confusion initially...Because it talks about paper media, which I suppose is the easier one, but also it talks about any media – any other type of media. [ID #07]
Section 2: The Principles of ICH GCP		
Update Principle 2.9 to reflect different types of consent	G5	… if you look at it in terms of even informed consent, again from our perspective, informed consent has different relation than if it's verbal or if written or it's digital – and if it's e-consent. And it actually says prior. And the work that we do, involves delayed consent. So, that – 2.9, in 40-50% of the trials that we do it doesn't relate, if that makes sense, because you don't – it wants the regular consent and might be verbal consent. And most of the time it is delayed before the participant is involved – and then after they're involved with the study, they will have opt out options or they have different discussions after they are part of the study. It just depends on the nature of the study. And most of the emergencies, the trials or the clinical trials that we do, this doesn't relate to them. With the type of trials that we do, we don't do this type of consent. Maybe the terminology could be revised – if we could – I'm not quite sure, but in different regions if delayed consent [inaudible] globally, how common it is–so, not sure if the board could be there … – so, yeah. Some of the wording, if you could revise or it doesn't really relate. But then, if you go into a bit more detail into different sections, there is information in there. [Follow-up question about whether an example of delayed consent is if you're in the ER

Unhelpful Aspects	Reference #	Illustrative Example
		and something is going on and a procedure is done, and then you consent to it after it's been done?] Yeah, yeah, absolutely. So, it could be either delayed consent because that procedure is part of the standard of care that you're comparing. It could be emergency trial that the patient does need the treatment. It could be that the patient is unconscious…– and their relatives are not there. And this is for – it's actually better for the patient to do this [may have said "experimental"] thing. And it's a couple of different times that – you could have delayed consent. And then, obviously, if it's a cluster trial, you can have opt-out consent because within the unit of the hospital you're changing practice. And the whole unit is following that procedure, but then the information is available – but we're using this process, if you don't want to be part of this, let us know and then we won't use your data. Really, it's a product…. But the information is there but you're not – not everybody that comes to the unit, you don't sit down with them and say, "By the way, we're changing our standard practice and this is what we're doing." We don't do that on an individual basis at the same time. It's not – I don't think it's common just leading up to the – it's a common design that, especially for the past six or seven years. It's a different form of collecting data, looking at a broader patient and a bigger group. And sometimes it's not feasible of the unit of study design …. [ID# 01]
Clarify in Principle 2.9 that informed consent needs to be fit for purpose	G6	Well, I think it's a matter of, again it's about fit for purpose. If it's an experimental drug, it's never been given to a human being, then there is one type of revision. There is a certain amount of consent, a certain amount of detail, I should say. Because if you're comparing open surgery to robotic surgery it's a different level of consent. What I'm trying to say, is that there is – consent is a critical part of the practice of medicine and somehow or another we've created, I don't know about neurology, but in oncology, they've consent forms, like pages and pages and pages. And how that makes – Most people don't read them, most people don't understand them, most people don't want to read them if they're in life threatening situations. …my experience in consent forms is only oncology, which is a life threatening disease generally. Maybe when you're dealing with arthritis or, maybe with some sort of chronic arthritis, maybe people will read a 20 page consent form. But I can tell you that in oncology they tend not to read them, they tend not to understand them and they're not helpful. And remember, not all oncology is about new drugs... [It's about] any number of things. Even if it involves drugs it's multiple things, but it may have nothing to do with drugs. What if you wanted to do something about emotional support, what if you want to do something about information, a trial about information permission? There are all sorts of trials that go on and we've only got one guideline. [ID# 02]
Principle 2.10: All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification	G7	I think that's probably part of challenges the company I'm working for right now experiences, so again it goes back to the level of experience in let's say smaller sized companies – what retention actually means. Meaning obviously we meanwhile really deal with all different types of records, being electronic, being really simply just data, or being really written documents with writing signatures. And it's sometimes really not well understood how really record retentions depending on type of format needs to look like. Because at the end, we know that it needs to be not only retained in appropriate manner, but also accessible and reproducible, etc., independently how long it is stored and giving more guidance in terms of what this really means medium and long-term could be really helpful. [ID# 15]

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Principle 2.2: Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks	G8	I feel like with this one…I'm not sure that this is actually being done…if there was a way to quantify [might be helpful to add] [ID# 17]
Provide additional guidance in a stand-alone document about how the data privacy principle (2.11) can be met in the context of global guidance; provide guidance on how to reconsent patients for follow-up research	G9	I think the only reason I selected this one is really since it really creates – well, obviously, I'm not kind of – I'm totally aligned with this expectation. It's more like it's very difficult to really realize this in a global setting where we know let's say each region or even each country has different privacy rules. And from a sponsor perspective, it's extremely difficult sometimes to navigate that space. And then in addition to that, sometimes yes, you conduct your clinical trial, but after a couple of years, you realize You actually want to do some additional research with those data, and you don't really have direct access to those patients anymore. So, how do you actually really re-consent patients without having certain data points so that you can actually reach out? So, sometimes privacy rules limit the amount of research you can do from a sponsor perspective, which is on the one hand really a good thing because of all the past and historic reasons why we have those rules in place. On the other hand, it simply limits research to some extent as well. So, it's more a question on how can we achieve the best possible outcomes in terms of research and development without really jeopardizing actually privacy laws? [Follow-up question about the difficulties sponsors encounter in re-contacting former trial participants for follow-up research, given the variation in privacy rules across countries] And I mean, really even in my current company, good examples where actually the FDA requested after a couple of years to have some specific questions to data which we only could answer by doing additional evaluation on data we had. So, we had to find a way to really go back to patients and really ask them whether they consent with additional research on their, in our case, bone scans. So, we simply had to find a mechanism, and it was very hard. And obviously, you have then to go through investigative and get there and to really reach out, so it's very difficult. [Follow-up question about how to address these issues] I think it's difficult because ICH obviously as a global guideline where let's say to deal with the GDPR and then other countries, safe harbor [inaudible] ask me about our regulations. I think – I'm not sure whether the ICH itself can at least come up with some recommendations on how on a global trial about data. [Follow-up question about whether they would like to see the clarification as part of ICH GCP guidelines or as a stand-alone document] . . . I think not necessarily in the guideline itself because I think the guideline itself should

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		be a really more framework as it is. But again, kind of accompanying document which then really gives additional feedback, Q&A, etc., I think would be helpful. Or even, I'm not sure within the ICH whether there are certain topics specific or in groups which could really bring out additional guidelines taught in certain sections in the ICH GCP guidelines. I think there are several ways how additional content or additional guidance could be really provided through the actual guideline without touching the document. [ID# 15]
Section 3: Institutional Review Board/Independent Ethics Committee (IRB/IEC)		
Challenge of composing IRBs in countries with low study density and suggestions for ways to address this issue	G10	It's about this structure. One is not so helpful. I think it could be improved. It think the GCP is fantastic. I'm in love with the GCP. So, you have to understand. So, I think 3.2.1 where it says the IRB/IEC should consist of a reasonable number of members who collectively have the qualifications and experience to review and evaluate the science and medical aspects and ethics of the proposed trial. I think – I made a comment that finding these capabilities and resources to maintain IRB remains a challenge in worldwide locations with low study density. And there's dichotomy I think in many developing countries depending on how ethics committees are structured. But there may be local hospital levels if they don't have a lot of volume. They may be deficient in the number of members or the experience that they bring versus commercial IRBs that have a lot of volume. Sometimes the countries are working on regulations to decentralize and move – and recognize local ethics committees so they can have more volume. But sometimes these ethics committees are not prepared. And the way the training, qualification, and experience to review and evaluate the science doesn't really explain how much – how thorough this training should be. So, when it says how to improve it, I have been thinking we may agree on the way the members are described, but the guideline may be more specific about the type of training and the type of training records to make sure we can have a robust training plan for the people who are doing the reviews and also or mention the opportunity of IRB to collaborate cooperatively on have remote members. To make it more possible bringing experienced qualifications and ethics and medical science knowledge to IRBs that maybe don't have the volume of protocols coming through their institutions. So, I don't know – it's just an idea. From what I see in the countries where I work. [Follow-up question about the suggestion for ways to address the issue of maintaining an IRBs in countries with low study density] Yeah, so maybe you have one public hospital, it's very big. And then you have one physician that has experience in research, and he says, "I can be part of the ethics committee, but here we don't usually – many times no resources to support it." And they are on their own. They are a volunteer. And it's difficult to have people experienced in, for example, biostatistics, ethics. It's difficult to meet this requirement. Not so easy. And I think it would be easier if the idea of flexibility, but good records of who and how and what the training background is. In many Latin American countries, there are no inspections of how ethics committees are composed or what. Some jurisdictions the most important. In Brazil it's regulated at the national level. In Argentina it depends on the jurisdiction. Some jurisdictions are really thorough, and they do a lot of audits. And they credit their own ethics committees. Others just certify them. Others register them. It's very diverse. In Mexico too. So, I think – I don't know. And this is something – it would be interesting to work on. It's very difficult to harmonize I think because of the different ways this is being implemented in different countries. But many times, this is challenging and perhaps introducing idea of like we are doing remote – it's doesn't say face-to-face meetings. It doesn't say then you have face-to-face meetings. But maybe to introduce the idea that meetings could be via teleconference. At long last

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		there is meeting minutes – I don't know, I'm thinking. But how to make it flexible but preserve the quality of the review. . . . Or the concept of collaborative review like in three or four ethics committees working together as one in different institutions. [ID# 03]
Need for clarification regarding IRB vs. sponsor responsibility for monitoring site compliance	G11	So I think I'm going to go through this from the perspective of where we are as an academic organization. So you know what I – but it's mainly – again because it's not as applicable for us is chapter three with the IRBs, firstly, because we don't necessarily have – especially the central. We don't have as much interface with them especially – we do as an – when we're the sponsor obviously we have our own academic IRB. We actually call them our ethic boards here in Canada. So we do from that perspective. I think there are some really good things in here about composition and the function and the operations. What I don't like, I find it's actually a little bit – they talk about how there is a requirement for them to monitor some of the investigator sites in terms of some of their compliance, and I think that actually confuses a little bit with sponsors. So I think it needs to be way clearer in terms of what the IRBs should be responsible for. Typically, I think a lot of people think IRBs out front to give that initial ethics approval and then obviously do some annual reviews to make sure they'll align with what they initially approved, but whether or not it's there in the right position – so two things. It's kind of conflicting of that kind of diffusion of responsibility if somebody else is responsible maybe I'm not even though it says here in chapter – I should be. But it's also – so not only is it confusing, but I'm not so sure that they're in the right position to actually be able to have any effect in terms of whether they can make the right assessments and whether they can actually supervise or monitor the sites as well as a sponsor could in terms of that. [ID# 12]
Need for guidance about oversight of ethics committees to ensure that they are following GCP	G12	I'm just wondering now about the ethics section. Let me see. Because again, ethics committees are very varied, certainly in my country, in Ireland. And you wonder if they had a kind of a standard set of SOPs or something. It does actually show their responsibilities, doesn't it? Yeah, I think it does outline the responsibilities, and maybe it would be overkill to tell them how to do their job. It does say the composition, the functions, yeah. It does actually give quite a lot. Should establish in writing the following procedures. Yeah. I would say implementation of that with that explanation again is, who's checking that? Is there anyone checking that? If they are following GCP, people check that the sponsors and the investigators – are we following GCP? But from what I know in my country, people aren't checking – that the ethics committee is following GCP. But sometimes, the ethics committee will actually tell you to do something that is directly contradicting GCP. [Follow-up question about what happens in the above situation] What happens then? Well, then you have to decide do you want to get your study approved, or do you want to be right? Maybe that's a particular local issue. And I think that's all I have to say on that one. But yeah. I don't know. Probably in other countries, they have someone who kind of oversees and inspects the ethics committees and ensures that they are following GCP and that they have the procedures. That system isn't in place in Ireland. And GCP has been around for many years. [Follow-up question about oversight of ethics committees] Yeah. And making sure they're following GCP, and that they're aware of what GCP says so that they're not contradicting it when they ask you to do something. Like for example – I'll give you an example. Reporting serious adverse events for an observational study. You don't collect serious adverse events for an observational study. So, if someone comes up and tells you about one, absolutely. I'm sure you'll report it, but it obviously isn't

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		linked to anything you're doing. [ID #07]
Concern about independence of commercial IRBs in the U.S.	G13	What I am a bit struggling with is the consistent approach when you look at the institutional review board that we have in the US and also the commercial aspect to some of these IRBs. And that's a question that, from a European perspective where these bodies are non-commercial always, it is raises some questions with regard to the trust that the society brings towards IRBs. If you have really professional suppliers or an industry-like approach to institutional review boards—are they independent and the profit orientation might question or might undermine the acceptance of their decision. It's more a philosophical or more a basic question. I know that this is maybe driven by the US and the IRB setup based in the US. Yeah, and I don't know if that always can be ensured that they – [In response to a follow-up question about whether Europe has commercial IRBs]: No. . . .We have – the independent ethics committees and most likely bodies of the – in Germany they belong to the Independent Board of Physicians and these are steered regionally, so we have regional independent ethic committees and they are paid only partly out of the fees that we have to pay to them. But then more official parties like – they're not for profit. So, when you think of organizations like Advarra or these organizations who provide experts in the US to – IRB review bodies. Yeah, so, but this is the problem. [ID# 21]
Section 4: Investigator		
Update to accommodate new technologies/processes	G14	Source data in an era of eCRFs. Let's go back to the era of not-eCRFs. When I started doing these clinical trials long ago, a group told me – this is my favorite – we're writing down the blood pressure on this worksheet so we can write it down on the case report form, and I said, "Just write it on the case report form. You don't need a worksheet to prove the case report form." We've kind of moved beyond that, but not really. It's just amazing to me how that still doesn't kind of ring true to people, write it down once and that you have to have some sort of source documentation. What has helped us is to define in a risk-based way where we might find source, if there is source. [ID #13]
Streamline safety reporting process to decrease investigator burden	G15	I think that the one thing that I find problematic – and this is not just the GCP, but this is – I'm looking at section 4.11 now, the safety reporting, and this is pretty brief here. But the way that safety reporting is done these days, I think that you end up – as the physician involved, you end up getting overwhelmed with these documents. Sometimes the same adverse event is – usually the SAEs may be reported in five or six different documents, and they're reported piecemeal rather than aggregating them in some way that's more understandable. So as a result, I think what happens is most of us are looking at these things and signing them off one after the other, but each report is kind of a one-off event. So I don't know exactly how the GCP requirements could address this, but I think it would be much more helpful and informative if SAEs were – you've got a more concise and understandable report that really talked about the episode itself. You get these reports and they're five pages long, and because the first one has to be done in 24 hours, usually the first one on a particular episode doesn't have the resolution or doesn't have the relevant facts then because when we have SAEs, usually it's a hospitalization. Our coordinators are just trying to figure out why the patient was admitted and what the first round of information is, but a lot of times that doesn't really explain what's going on very well. So you get all of these subsequent reports. I really think it would be much better if the SAEs, you got it more as a list of, "Here's the things that have been reported and in some way aggregated" rather than – there's so much emphasis on immediately reporting that you end up just getting overwhelmed with paper for each one, but you don't get a sense of, "Three percent of the patients on this

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		drug have had side effect X" because you see them all as one-offs as you go through, and you'll start to notice things. The other thing about AE reporting is that there's no differentiation made between known side effects of the drug. Lots of trials and using drugs especially immunotherapy drugs now where the side effects are known and well-documented, but you still get a report every time somebody somewhere gets pneumonitis or colitis or one of the well-known, well-documented side effects that can happen occasionally with these drugs. To me, that's not very informative to keep getting informed about a side effect that everybody's already well aware of. So I think that some kind of statement that known adverse side effects of drugs that have FDA approval can be reported in an abbreviated fashion. Something like that. [Follow-up question: I'm looking at the section 4.1.1. So the FDA is – as I understand it, they are the ones who require reporting within that particular timeframe. So should the ICH be addressing that or should the FDA be addressing that?] You're right. It probably is more of the FDA. …For safety reporting, and a little of this is kind of in this statement already in 4.11, but I think that this is another section where it would be nice to see ICH sort of give permission for a more effective reporting scheme. [Follow-up question about reporting requirements in Europe by country or by the EU.] Yeah. What's happening now, all of these things are getting reported, but everybody who's on the receiving end of these things is just drowning in all of this. It's just mostly electronic not, but it's just there's no way that you can review all of that. So you can't get the big picture because you're constantly looking at this adverse or this adverse or this adverse effect, and they may have happened – they may not have anything to do with each other. Many of them that are reported have nothing to do with the drug. So there needs to be some serration of that I think. [ID# 18]
Requirement for PI to have adequate resources is often not respected	G16	So in terms of at the investigator level, the ICH GCP mentioned to have adequate resources, and this is not respected. [Follow-up question about the meaning of "not respected"] We face, in a lot of sites, the people, for example, the data manager entering data for the CRF being overloaded by the number of studies they have to manage. So, we see delays in data entry, which have an impact on a lot of things because I can't see you on a timely manner, the information. It can be also that the principle investigator I would say because he's European leader or a very well-known investigator, he's selected for the participation of a trial, but you found out that you would never have contact with him because he's never available, and you have to manage with a sub -investigator. So, maybe one way, because we decided that we have a principle investigator and one signing, for example, CRF that all the data entered are the correct data, why not ensure that in the ICH GCP, there is information that if it's not the principle investigator who is following the patients that another investigator who is classified as the sub investigator he has the possibility to sign CRFs because he's the one knowing what is in the CRF as he follows the patient. [Follow-up question on having a clear statement on whoever is actually following the patient] It can be the PI. Most of the time, yes, it's the principle investigator. And to be sure that the PI understands that he has to be available on a regular basis, and I can tell you that's very difficult with some PIs. And that's a general statement in all countries. [ID# 20]
Need for clearer guidance on	G17	Let me look at my bit about source documents. I know that there's a – certainly, from listening to our study nurses point of view – it seems that the amount of writing in the

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adequate and accurate source documentation		source documents that has to be done has gone up and up and up in the last number of years. Records and Reports 4.9. Adequate and accurate source documents and trial records that include all pertinent observations – yeah, and again inspector's interpretation of all pertinent observations – there is a lot. So, say for example if you're seeing how somebody regained their capacity. Somebody comes in unconscious and they're in a study, like for example, the CRASH-3 trial, and the inspectors want to make sure that if and when they regain their capacity to consent that you consent them. How often do you have to do that? Do you have to check every hour? Do you have to check every day? So, it's kind of open to interpretation when the guideline says adequate and accurate source documents. So, there seems to be a huge amount now more of writing in source documents. I've been a monitor say 15 years ago, and there was a lot less of that. So, doctor's time, as we know, is very precious, and for them to have to write so much in the source documents is quite onerous. [Follow-up question about how to address various interpretations in the guideline]] That is a very good question. We could be here for a long time. Because when you use words like "adequate," adequate for me might be one sentence. Adequate for you might be one page. And I think really it's not something that can really be specified in that detail in the guideline. Otherwise, it becomes a kind of a tick box – fill in what you want. But I guess things like the – I know in Europe, the Inspectors Working Group – they do a lot of kind of trying to harmonize what they look at and how they look at it, and what kind of findings they're coming up with. So, I think they do help from what I… You know, it's human nature, I suppose, that different people would concentrate on different things. But I don't really think the guidelines will sort that out for us to be honest. [Follow-up question about whether examples would be helpful] Yes. I think examples – or even where it says as you mentioned "adequate" source documents. And it could say well, a minimum would be… [ID# 07]
Clarify language	G18	And, we have the issues of informed consent…in countries where there is illiteracy or there is no written local language, informed consent could benefit from the use of audio/visual and video tools, etc. This, may be, a minor thing, but I find it so amazing that in the addendum, they speak so much about technical tools of quality assurance, but not for informed consent, where it could help the procedure. That's strange. [ID# 04]
Informed consent—Need to recognize how decision to participate in clinical trials is shaped by a lack of access to health care among socially vulnerable/excluded populations	G19	What I have seen, for instance, in my research and we also published about that is that when you do clinical research in a socially vulnerable population, and in particular, in population with no free access to healthcare, the freedom to decide whether to participate in the research or not is very biased and there is nothing we can do about that because if I am, let's say, in a sub-Saharan African country, where payments are out-of-pocket, and if I refuse to participate in the malaria trial, I will have to pay for my medicine test. If I accept to be in a malaria trial, I will be treated for free during the duration of the study. I will receive other medical treatment for free. They will reimburse my travel expenses, which is fine, but which also means that I will have the opportunity to travel to capital, and maybe to sell my things in the market. [ID# 04]
Sponsor's concern about investigator's section because least amount of control over it	G20	For the Section 4 on investigator, that part for me is probably the one I use least likely and am most concerned about, because I have no control over it. As I say, except for when we do our contracting, it's all "Do you understand GCP" and things like that. … I mean, none of us is in there holding the hands of what goes on. Yeah, we have – companies the size of Pfizer, we have our own Phase 1 clinics, for example. And with our own Phase 1 clinics, which is a site, we can say here's the SOP; here's how we do

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		things. We're in there. And when we go around the world for the other investigational sites, we're not. We pop in according to a monitoring plan, and hopefully we've put all the tools in place to make sure that everyone understands their job, they understand quality, and they do what's right. So, in some ways it's a nerve-wracking world out there. [Follow-up question about GCP training for investigators] So, all investigators must undergo GCP training. And so that's always tracked in systems that they did the work. And then at an investigator meeting there will be discussions about the protocols. But you sit and you go "Well, if we do such a good job, then we would never find deviations." So, I don't know what the answer is; you know, there's training and then there's effective training. But we certainly – it's extraordinarily important that everybody is trained. Let's figure it out; see how you can train somebody to drive a car, and they have an accident. [Follow-up question about participant's previous comment about the "fear factor" and if researchers follow these guidelines, it should reduce the risk of having deviations, but there is an assumption that sites are not complying appropriately] Because we are – we will find protocol deviations. And it's normal to find them. And that only says that the protocol is not being followed exactly. There are important protocol deviations, and there are just deviations. So, I wouldn't call them not important, but let's say you have a trial where every four weeks you need to come back to do something. If you're back in four weeks and a day, it's a protocol deviation, but it's probably not going to impact the data. So, that in itself is a deviation but not terribly important. If a patient starts, you find out, taking instead of a pill every day is taking two every other day; that's a serious event that is also a deviation. So, there's important ones, and if they're taking like a concomitant medication they weren't supposed to take, that would be an important deviation. We also get quite a number of things we call quality events that come in from the sites that we have to mitigate during the course of a trial. There's always audit findings. And so, clearly for all we do to ensure that people are trained, people do the darndest things. And just from a kind of statistical perspective, I don't know if that's in your background, but when you look at correlations between things, a perfect correlation, having an R-square of 1.0, so this happens and that happens. And in manufacturing when you try to predict things, you usually have correlation coefficients of some .9 plus. When it comes to people, you generally say that there is a good correlation if that R-square is .4 because people are inherently just unpredictable. And when training that we always see and whatnot – and we aren't bad at it because we get drugs approved – but it's always bumpy. And we all have the best intentions; we have a great protocol, we have a great team. You think we're picking the best investigator, the best monitors, but there's always issues. [Follow-up question about the meaning of "fear factor"] I think the biggest fear factor is that there's something that is missed. [Follow-up question about what types of things would be missed]: Yeah, serious adverse events. Let's say a site didn't report it, and it wasn't picked up maybe by a monitor, but then when you put together the – their, whatever we're looking at, you go "Oh my God, where did all these come from?" And that can dramatically change what you're thinking about for the efficacy of your drug. And if people don't report things then we won't know things. [ID# 16]
Section 5: Sponsor		
Monitoring—Allow flexible	G21	You may have a lot of smaller research, which is done by noncommercial entities. We just do not have the financial resources to hire an external monitor, and to pay the

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approaches to monitoring for low-risk studies conducted by non-commercial sponsors		travel expenses of the monitor. So, perhaps, there should be some flexibility there. And I don't say that – of course, I see the added value of the external monitors. They're an external look at the research. But, in absence of an external monitor, when there is a low-risk research, these, we just don't have anything. So, either we have the full machine with expensive CROs, or we don't have anything. And, perhaps, it would be a good idea to give some guidance about some internal monitoring that you could have some factor internal monitoring carried out by a trained colleague who is not part of that specific research. So, give some of the advantages of the monitoring. Because, today, it's either full machine or basically nothing, and this is really not good. Again, this monitoring can be very expensive and it can also be very environmentally harmful because of all the flight, travels, and – I don't know, but in some researchers, you have one monitor for the research and one other monitor for just the blinding of the medication. I wonder if we are really going too far in terms of adopting [inaudible]. I know that not everything can be done remotely. When somebody told me, "These days, we can do it always remotely," no. We cannot do it always remotely because the real source data verification, there is local data. You can only do it there. Without that, you can skip huge mistakes. But, some more flexibility. Also, having in mind the need to reduce a little bit international travel and the need to reduce cost when it is feasible, so wouldn't be bad. [ID# 04]
Monitoring—guidance needed on how to implement monitoring in home-based decentralized trials to address privacy and confidentiality issues	G22	. . . Section 5.18 around monitoring, and the addendum allows for on-site monitoring, centralized monitoring, remote monitoring. And my concern in this section is, what does it mean if you need to monitor someone who is at their home, because suddenly patients' privacy is now broken. And so, we can't send a monitor, I think, to someone's home. That would be invasive. We could send a caregiver; I'm sure if we need to do a blood draw or something like that, that might happen. But again is that now a privacy, a de-identifying thing? If someone's got a car that says Quest on the side and they drive up to a house, is every neighbor going to know something? So, that's just like I don't know how that's going to work. [Follow-up question about how this should be dealt with and the type of guidance needed, if any] Yeah, I mean, is it a breach of GCP if somebody goes to someone's house to do something? And therefore, would the answer then be, none of those things can be done at somebody's house? What I don't know is for all the – if we do something at someone's house and they go in through their internet, is their IP address blocked? So that you don't know where the data's coming from? I just don't know; maybe someone's already thought about that, but I don't know. [ID# 16]
Monitoring—challenge of implementing a quality by design approach to risk-based monitoring requires a mind shift from a retrospective to a proactive approach	G23	You get the first ideas on risk-based monitoring, which I think overall can work quite well if you don't make it too complicated, and that's more coming from the CRO side…because the overall concept is easy and everybody can implement it. With quality risk management – the overall concept of quality risk management is not so complicated; it always depends on what you're going to make out of it. If you have to – a lot of people don't understand that risk is not equal to issue. An issue can be either an undetected risk, an unmitigated risk, or something you have expected because you were willing to accept this risk, but a lot of people document issues instead of risks. [Follow-up question: And so, are those two things not well defined – that distinction between risk and issue?] I think they are well defined, but I don't think that people have the mindset. We are back to – this is the mind shift. It's moving from retrospective controlling, like monitoring was or auditing is, to a proactive quality-by-design approach ensuring that you don't have these issues. That means that you have to think about things which could happen, but

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		have not happened. And, it's the same with monitoring. In the past, you always went back to the investigator side; you were checking data which has been recorded some days or even some weeks before. Now, you can really do that onsite, even remotely, because the data comes in at weird times, and depending on how the future goes, even with the electronic health records, you can access the source data more or less in real time. But, risks or problems – can you detect it immediately from the sponsor side instead of like it was in the past? So, that new approach is coming with electronic data flows collecting more electronic data, getting the data directly from the laboratories, or from radiology, or from any other party who is generating data into one single system. That was actually what I talked to in the beginning. My expectation of ICH E6 is whatever they're going to write – and, I don't know how many documents they're going to talk about – it's really taking the way into consideration how clinical trials are conducted today, but also, how they will look like in the future. [ID# 05]
Monitoring roles and responsibilities have changed and need to be updated in the guidelines	G24	Inspectors and auditors. The monitors are not the problem. The problem with the monitor itself is that that's possibly something which also needs to be updated because when the document was written originally, the monitors became a huge amount of responsibility. They are actually the only role which is clearly described under the sponsor section, and this role is not existing in this way anymore. None of the roles and responsibilities which are on the monitoring are done by other people or other functions, and that probably also needs to be clarified. Also, the introduction of roles besides the clinical monitor is useful. [ID# 05]
Monitoring—clarification about different types of monitoring is needed, particularly how they relate to remote clinical trials	G25	[Follow-up question on how the conduct of clinical trials could be approved if the guidance was revised to address differences between risk-based monitoring and centralized monitoring and data-driven monitoring] Yup, I would – currently we have – when I look at the market environment and see the providers of these different solutions, they also all try to sell you a solution. Some of the providers, for example, promise you that by risk-based and centralized monitoring, you could cut down your monitoring costs. I'm not so sure if that really comes to an improvement of the monitoring. I'm also not sure if 100% false data verification as a lot of companies did in the past, is really improving the quality of the data. Apparently it's not because otherwise we would not be in a discussion where we could opt for risk-based monitoring. But I think the clarification of these terms is really needed in order that people talk about the same thing and that we get awareness of the different meanings behind it because you can't have risk-based monitoring without having a centralized or data-driven monitoring approach. You cannot also have – but you can have data-driven monitoring, then it's already part of the risk-based monitoring approach to some extent, and you can have central monitoring. Then you have someone sitting somewhere remotely looking at the data and the question is to which extent is that able to verify or falsify source data? And the question for me would be, to which extent would ICH buy into these approaches and not take on top remote clinical trials?, where the source would be the patient or a cellphone of the patient in which the initial data gets captured. How are we going to verify these source data and how are we going to monitor in the – compared to our former monitoring approaches, these data, ensure reliability and acceptance of the data from regulators? [ID# 21]
Monitoring—concerns about the adequacy of the centralized	G26	I think the addendum introduced the concept of centralized monitoring and monitoring, but I get the impression that that's still not being picked up very widely across the industry, and I think there is a concern that it can at least feel it's not actually checking everything based on the risk on inspection. I think something that makes it a bit clearer that, if there's

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monitoring approach and its implications for inspections		been an adequate risk assessment and monitoring is conducted according to the plan produced from that risk assessment, then the monitoring will be considered appropriate. [Follow-up question about whether the same applies to audits] Yeah, yeah, that's right. Yeah, again, if you employ a risk-based approach to monitoring, then some sponsor auditors may not be entirely happy with that. So, I suppose a lot of it comes down to internal communication, actually, between the CRO and the sponsor. The approach needs to be agreed and clarified, upfront, so that everything's clear. [Follow-up question to confirm that approaches aren't created in the moment; but rather, the plan is to reduce risk at all levels that we are going to proceed with, and it means A, B, C, and D.] Yes, that's right, yeah. [ID# 11]
Monitoring—risk-based monitoring can be taken to the extreme and allowances need to be made for variations in the standard of care, particularly in low resource settings, to avoid minor deviations being classified as major deviations	G27	[Question: So, what are your views, for example, on coming up with a quality risk management plan?] Well, how do I say this without – I hope I'm not an egotistical person, but I kind of wonder what people thought they were doing in protocols before them because when I look at quality control, and I say, "Yeah, sure, let's do it with what we have." That's the whole emphasis on the protocol. We try to keep it simple, and we are a bit of a different beat, straight I'm not Phase 2 trials, and that is a different end of things, by the way. I should've maybe explained my bias initially in that the studies we do, there is known safety profiles. When there isn't, man, then you gotta do it a lot different, and I agree completely. But when you do have a known safety profile, and you want a quality risk management plan – I'll give you a great example. This is one that drives me craziest – actually, there's so many I can give now. They're all…inclusion in a study. We write out the inclusion criteria. Most of our studies are looking at cardiovascular events, and so all we're doing is basically adjusting the risk levels. Are we doing primary prevention? Well, then you're going do risk factors. Are you doing secondary prevention? Then, you have to have a clinical event. And as I said before, I don't believe that many people who said they've had an MI have not had something fairly similar to an MI. It might be enduring them, it might not be. It's that cardiovascular risk. They're in that category. I'd say the criteria for entry is MI, and we find out, oh, you didn't meet the entry criteria. In our world, because of studies at large, we say, "Oh, that's a hit." We take the hit, put it in the trial unless there's a contraindication to you taking the drug, which we've already checked through the exclusion criteria. You continue on, and this is what ITT [intent to treat] is all about. We better make sure that we work with the site to recognize this. This becomes known as a major protocol deviation, again, somehow emanating from ICH E6. Well, no, guess what? Life isn't like that. Sometimes the information you're reading may have said there was an MI, and there might be some contradictory information. It happens a lot in stroke – stroke of unknown origin, lacunar stroke. I'm trying to take the few scans to really get to know what happened, and I don't think that this study could actually monitor these components, and we do through our demographic page. You know it's happening. We can correct it at the site. No further activity needed. That, to me, is a risk-based approach. I'm risking basically our event rate because you're not getting high enough risk, but I can do that because we've got 27,000 people in the study, and I don't think this is going to happen for every one of them. And let's say, then, what we do then is monitor to overall event rate as the study's going on because we're blinded. We then say, all right, it's coming in right about where we think it is. We must be getting the right people, or it's a little bit low, then what we'll do is actually introduce criteria to increase the risk of the patients entering the study. So, that, to me, is a process that is inherent in every protocol we implement. Now that we're going this

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		risk-based approach, we have to have a risk analysis, and I think people take it now to the extreme where – two components to that – everything has to be assessed for risk. Come on, life isn't like that when you're running very large studies. Risk was subsumed by the sample size. That's why we did it. And then, the second part is – I want to make sure – oh, what was my second one? I was thinking something is in my head. It was pharma. It was one of our sponsors requested this information. I'm going to forget it now, but idea on the risk plan is that the protocol should say both things that are absolutely, absolutely required. That's another good one. People then talk about these major protocol deviations because they think of deviation from your risk plan being exposed through these major protocol deviations that you have to report. There was – not on a study I was working on, it was a monitor who walked in and said to somebody, "Revisits are five days out of the window." Again, a Phase 2 study, then there's some specific things happening or any study where you have to have specific time frames, that might be a major risk. Otherwise, that's life. I wouldn't call that a major protocol deviation. There's sites that they're obviously seeing the patients, but they're enrolling in trials, and we've had issues with regulators watching and just say, "Hey, these lab tests are ordered as part of the study, not part of the usual practice," and the physicians involved were actually given a 483 for what I felt was exceptional usual care. We do this all the time. What are you talking about? And it wasn't in the U.S. This was a clinic outside the U.S... And so, that recognition that this risk approach has to allow for the flexibility of usual care looking differently in different parts of the world, and I'm constantly reminded of how we put a North American – because I do think our practices are similar between Canada and the U.S. – a North American view of how things should be. [Follow-up question on an example outside of North America, the U.S. and Canada, in a low-resource settings] So, in that risk plan, one of the things that always comes up is how we're going make sure we collect all the events. Simultaneously, we create the definitions for events. I go back to the, it's either MI or stroke. You can use either. MI, you always need enzymes. A stroke, imaging. You need imaging to confirm that something happened. In many low-resource settings, those that are the most severe event will never get worked up. They don't have the money. Families can't afford it, and we know that the situation is dire, and the likelihood of interventions to affect that in any sort of way is very, very low. Physicians work very well with what they have. So, in your study, in your risk-based study, does anyone ever look at whether the definitions actually match? And yet, if we took this study to the FDA and said, "We have to have enzymes," and recognize that, you know what – and again, because they don't have enzymes – we would be under some of orders brought to task. So, I think that the risk plan could be tooled to say there's going be some leeway in these areas, but then it doesn't have to be yet another plan that you have to memorize and then have someone go through with a fine-toothed comb, as you now see people do with protocols and say, "Oh, you didn't do that exactly as you said you were going do that." I don't think it's nefarious practices, especially in a blinded RCT. I'm being nefarious to both groups equally because I don't know their allocations, so how can you claim this to be an issue? [ID# 13]
Quality management using a risk-based approach--Lack of clarity about meaning of quality risk management	G28	[Question: Could you give us some examples from your experiences of where the document as it currently is written has not worked for you or is not working for you?] I think we – a lot of the updates and changes were made with the best intentions. Nevertheless, because they want you to introduce a mind shift and remind all different parties involved in developing drafts and running clinical trials to focus on the important issues, and not on little stuff, and that's why they introduce quality risk management and quality tolerance limits. But, there's a certain uncertainty of what's really meant with that, and I have to say – and, I'm not alone with that – we are still struggling with quality

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and quality tolerance limits impacts their implementation		tolerance limits. People were not understanding that this should introduce risk-based thinking or quality by design. They were using it as building up another very formal, very complex system of documentation, making trials even more complex than making it easier. As I said, I think the intention the working group who revised and edited ICH 2015-16 was a different one. They wanted to make it easier, but we are sometimes so afraid of the CRO and industry perspective that we do too much. [Follow-up question about what other sections of the document that they find to be unhelpful] I personally don't have any problems beside the quality tolerance limits. . . . [Follow-up question on providing specific examples of when participant applied GCP and it didn't work so well] I can give you an example of quality tolerance limits because even the new guideline is out since 2016 and valid in Europe, there are still projects ongoing, like TransCelerate, which were just discussing quality tolerance limits and how to interpret them. I'm not speaking about myself only. There is a still a huge uncertainty within the industry what is meant with that. Therefore, it's difficult otherwise to see what's working and what's not working because not many trials have been inspected according to the new guidelines, so you don't get any real feedback already on what's working well, what's not working well. [ID# 05]
Quality management using a risk-based approach--Lack of clarity about meaning of quality risk management and quality tolerance limits impacts their implementation	G29	As I said, quality control/quality assurance is a heavy burden and sometimes I almost feel like it's a self-fulfilling prophecy…it's a vicious circle, you generate more and more documentation, more and more procedures because it starts with a small avalanche. And in similar order, we say that handling **…** probably it's not spelled out in ICH E6, but very often then what follows afterwards, people starting to think very hard what could be the necessary safeguards and everything, and move very quickly from fit for purpose to the – we have to implement Xstate of the art across the board for everything. [Follow-up question about previous comment that this can shut out smaller studies] That could shut out smaller studies, smaller studies, smaller initiatives, because it's just suddenly no longer feasible to conduct this research. [Follow-up question: So, the standard, if I'm understanding correctly, is if you adhere strictly to ICH GCP regarding, for example, QA/QC, data handling, all of that, that the standard is so high that… that small, investigator-driven studies are just not going be able to keep up with it?] Yeah. Not necessarily investigator-driven studies as well as studies that are…, even standards from non-pharma funded studies. And even pharma industry might walk away where they might have been a small grant to investigator for a post-approval drug study to test the hypothesis whether drug A also works in related disease to the one where the label before they engage in another protocol [Question on what sections of GCP have been found to be least helpful or useful. . . . It's a bit difficult to see how that should be implemented – what is necessary for this whole list of section 5. I think quality management is a big issue and has created a lot of I think unnecessary… Quality management is important. I think the risk-based quality management makes a lot of sense. However, I have the impression and that's a lot of the sponsors, including us, don't see that as an opportunity to actually conduct better research and fit for purpose. It's actually used to increase activity and paperwork. So, it's not really a risk-based, it's just some more quality control and quality management. That's probably not in the ICH fault, it's the fault for the people involved in it and implement it on the sponsor side. [Follow-up question on sponsor interpretation]

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		Yeah. [Follow-up question on clarity on quality and risk management to reduce various sponsors interpretation]: Well, I think from an ICH perspective, it makes absolute sense. Again, let's look at what is ICH GCP? And mark it with an asterisk and say this is really what we want to see for a submission and this is what you need to implement for any clinical trial. I think that, for example, 5.0,4, risk control should decide which risks to reduce which could mean that some activities you don't have to do that, because if the sponsor says there is no risk or very low risk that this might happen, then we don't have to put procedures in place to follow up on these risks. And I'm not sure whether that's understood everywhere that on the risk-based approach using predicted events that are highly likely to occur and have a major impact, this is where I focus my resources, and a low likelihood to occur and a low impact, I don't have to do anything. At the moment, I have been left with the impression let's have the low likelihood and low impact is 100% resourced, and the high impact or high likelihood is then 250% resourced. So, it doesn't help you in planning these activities because suddenly you need three times as many people to do it because it's not a risk-based approach. It's actually just going up a notch or two or three. …it's a prospective thing. But I'm not sure whether we are, as a community, using the risk-based approach as an opportunity to improve what we are doing instead of just doing more without thinking. If you apply the risk-based approach properly, you have to do a lot of thinking before and you have to make some decisions where do I focus. Yeah, you could argue it's increasing your oversight, increasing your monitoring activities on everything plus it's a focus because you allocate even more resources to something which might happen whereas I think with a properly adjusted risk-based approach, you would focus on what needs to be either highly likely or highly probable and having a major impact. And in a business environment, this is what would happen. You would say okay, that from the top down, turn of the economy and we are being an exposed industry. This is something we have to monitor. Well, the winter gets cold and snowy. It's something we can't do anything, so we don't do much. But I think in the business setting, a risk-based approach is actually used to say okay, you look at risks A, B, and D, but I have impression in the clinical trial management that very often the sponsors don't do that. They do the risk assessment, and then they still use a shotgun approach to look at everything at the same time. . . Probably, they're using two shotguns instead of one. [Follow-up question about being overkill] Overkill, yeah. And I'm not clever, not clever. Not using the opportunities that a risk-based approach actually is offering. [Follow-up question about how this can be addressed in the guidelines.] In 5.0.4, the first sentence – the sponsor should decide which risks to use and which risks to accept. I think that's probably – it's probably written there. [Follow-up question: Okay. How could it be reinforced, then?] I have no idea. [ID# 08]
Quality management using a risk-based approach—	G30	[Question: What can the ICH do to address the ways that it's interpreted and translated?] I don't know, actually, because I don't know exactly the role of ICH in this game, in this sense, you know? I'm not sure whether it's a problem of ICH or whether it's the problem of the community. I mean, a lot of things people mainly debate about, monitoring

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Lack of clarity about meaning of quality risk management and quality tolerance limits impacts their implementation		procedures, and so the on-site monitoring aspects that they think come out of GCP, but I don't – I never integrated – I never thought that what is done by industry in terms of on-site monitoring is a direct result of GCP. It's basically their interpretation and their risk management approach to the problem. For me, it was always the risk-based approach that is now explicit or in more detail explained, too. It was always – myself always integrated that like this. I think it's not – in my humble opinion, it's not GCP that is the problem, but industry set some standards and then everybody thinks it's GCP, but it's actually only the industry's interpretation of GCP, or what the risk management people tell the trials or the study teams within the company have to do, but it's not something that GCP mandates. [Follow-up question on examples of interpretation and translation.] Then we would need to talk about it more specifically, but I think the whole aspect regarding the quality management and monitoring, and ensuring whatever you want to ensure via monitoring is – examples. [ID# 09]
Quality management using a risk-based approach--Lack of clarity about meaning of quality risk management and quality tolerance limits impacts their implementation	G31	For the current state – I do feel that we are told in the industry to take risk-based approaches, be innovative, and all that. But we're kind of hampered by what's written in the guidelines. And nobody wants to take any kind of chance that turns out to be the wrong choice. These are $50 million, $100 million mistakes. So, what a lot of companies do right now is, for example, when it comes to these decentralized trials they're doing things that are really, really simple. …Well, let's just say trials where the endpoint is more cosmetic and something that can be visualized, as opposed to something that requires some kind of a sensor or a blood draw or anything like that; kind of putting a toe in the water that way. [Follow-up question on the use of keeping it simple] Yeah, I think there may be some visualization tools but not necessarily sensors. But the things are moving that way. [Follow-up question on visualization tools] If you think about, let's say psoriasis, atopic dermatitis, where you could take a picture of something. [ID# 16].
Quality management using a risk-based approach--Lack of clarity about meaning of quality risk management and quality tolerance limits impacts their implementation	G32	Yeah, I think if I go directly to what I do and what is most important to me is of course, the quality management section where we had for the first time now with R2– the definition of quality management systems and how that should be implemented. The definition of critical processes, risk identification, risk evaluation, and also risk control; however, if tangible guidance missing, how that should look like? So, on the one hand this is good because you can decide as a pharmaceutical company on how that should look like. On the other hand – so, it has pros and cons. Now, on the other hand, you might be stuck or come to a situation where you have to argue around what – if your measures have been appropriate with what you have been setting up and whatnot. [Follow-up question on providing an example] For example, how should a risk management plan look like? What are essential elements of a risk management plan? How does a risk assessment should look like? There are examples given, so the sponsor should identify risks to critical trial processes and data. What is the definition of a critical trial process? Of course, we have an interpretation to that. We would say, okay, probably the informed consent procedure is a critical trial process because the consent of the patient has a high value and without a proper consent you would do harm potentially to a patient that has not consented to the trial-specific procedures. So, this could be – this is already interpretational of my end. I don't know if the regulator would see too the same.

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		Then, risk should be considered at both the system levels or for standard operating procedures, computerized system personnel, and clinical trial level. Example given, trial – define data collection, informed consent process. Okay, there they've got it already, the informed consent process. [ID# 21]
Quality management using a risk-based approach—inspections are still largely based on R1	G33	So, we've been doing a lot of these things long in advance of (R2), but I can't say that anyone has – any inspector has specifically said "Hey, your risk-based approach is wrong" or "You didn't identify something." We've got none of that feedback. So, we're moving along and everything's fine, but we really haven't had any feedback. [Follow-up question about what they attribute the lack of feedback to] I think that the inspectors are still inspecting the way they used to inspect…. [Follow-up question about not inspecting in a way that reflects (R2) or anything else moving forward] Right, and there's so much in here about saying the risk-based approach is that – let's say we take a risk-based approach and something happens. And we say to the inspector, "Well, we took a thoughtful risk-based approach" and in this particular example, something happens. Well, hopefully they'll say "Well, too bad," you know? [Follow-up question about needing a paradigm shift in terms of are inspectors catching up to the risk-based approach] There are some in pharma I was talking to that do say that they have started to get some questions here and there – so, I think the answer is going to be yes. But then if we're going to move the bar again, and then what? Yeah, so I don't know. [ID# 16]
Quality management using a risk-based approach—inspections are still largely based on R1	G34	So, in 4.0.2, risk identification. So, what we have seen – so, this is new as of November 2016 in the R2, so it's an addended reflection. I have not seen an industry-wide standardized approach to this because every sponsor decided on their own how to phrase that out. This is also what we did and I don't know if our process would meet the expectations of the people who have written ICH. Either has written the R2, if that was the true intention behind it, and I also would not know if our current process would be – because we are missing now the thorough inspection on the new process if that would meet the expectations of the inspectorate See where we are? That's the danger that I fear for the next revision. Something is implemented in best intent, but the uptake, really the proper setup of – to meet the expectations that are issued, this is something that I'm a bit struggling around. And there's also not too much on the ICH homepage. I think there was some helpful information given on top with some presentation on the ICH homepage when E6 R2 came out and I used that a lot, but it stays on a high level, which I can understand because apparently ICH wants to give freedom to operate. …I would not say that we are considering ourselves to be uncompliant. We give it a decision as the guidance states. So, when you go a little bit further down, so it's 5.0.4 where you have risk control. "The sponsor should decide which risks to reduce and which risks to accept." So, we do analyze our processes, we take that decision; however, an inspectorate might come to a different decision when they look at the risks. So, we are entitled, according to ICH, to decide is the risk high? Is it low? Does it need to be mitigated or not? If we consider the risk is low, then we would accordingly not decide to mitigate, but if an inspectorate would come retrospectively to the conclusion, "Oh, you should have seen that this risk is high and should have taken the proper countermeasures," and we would be in a potential incompliance. …Inspections are quite rare, so I have – so, we are monitoring ourselves against it and we are taking measures in order to identify these potential risks. So now, if a mock inspection that you conduct on your end where you look at this. So, but I think we asked

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		you in a situation where we tried to get more comfortable and when you think of how long the R1 was in place, it was a long time to get comfortable to what the regulators would look at. Now this. After this is only in place for two and a half years, it can affect us, I think. With 2017, even if it was published a bit earlier, we are trying to – we are still trying to understand the true expectations. We also understand that there's always a change in the environment. Even if you have it now, inspectors, regulatory bodies might take a different stance after some point in time based on experience they have made and all findings that they had with other sponsors. So, they also – regulatory bodies are learning and are shifting the scope of their work or where they look at based on their experience or something they recognize. [ID# 21]
Trial management, data handling and record keeping—Lack of clarity on data handling and record keeping	G35	[Question on the sections of GCP that have been least helpful and why] Okay. And maybe it's not that it's least helpful, but the computer system validation is a big difficulty, I think, for many people. For the investigators on the one side because it doesn't make much sense to them, and for sponsors on the other side, and particularly for the implementation of electronic health records. So, in Ireland, we're just starting to implement electronic health records, and I know of a regulator inspection where they basically said to the site "well, show me the validation for the electronic health records for the hospital." We don't have that kind of control over our hospitals, unfortunately, so they just weren't able to do it. And yet, they seem to be being held accountable by the regulator for this. So, that's a difficulty. That is a tough one. [Follow-up question: Okay. And how could that be addressed?] I think it has to be addressed at the national level where our Department of Health would talk to the service provider, the people who are putting in these systems and maybe – I mean, we're a very small country – so, ideally putting one system across the board and make it fit for research. And I think in other countries they found they've put in systems and they're not fit for research. So, for example, if I as a monitor and auditor, I want to look at patients X-Y-Z in the hospital system, it's very difficult to block – to not allow me to see every patient in the hospital. And I think that's one of the big things, especially with data protection. So, that's something that – I know in the UK, the regulators are sitting down with the people who are designing these systems, but it's a bit late now because they're kind of halfway through of implementing in the hospitals. So, that's a big one. So, the computer system validation for patient health records, I think, is a major difficulty. And it's bigger than the investigator and it's bigger than the sponsor, and it needs to be tackled on, I suppose, a national health department kind of level. [Follow-up question on how to improve that question] I suppose maybe it's more the implementation of how inspectors are monitoring to the guideline maybe – that there has to be some acknowledgment that okay, GCP says X-Y-Z, but you can't actually do it because it's not under your control. Maybe it could specify that the site and sponsor are responsible for validating systems that are under their controls. [Follow-up question about being up to the national level and variation by country] Oh, I'm sure there are already. Because a lot of people provide this kind of service of putting your hospital records on the electronic, in an electronic system, and they don't tend to talk to researchers when they're doing it. They tend to talk to the hospitals who don't really always remember the poor researchers. [Follow-up question on the use of electronic health records and consulting with researchers] Yeah. Or even, maybe even maybe to be compliant with GCP. I don't know. Because

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		most of them aren't even aware of it, but they should be. [ID# 07]
Trial management, data handling and record keeping—Lack of clarity on data handling and record keeping	G36	So, I think that's probably part of challenges the company I'm working for right now experiences, so again it goes back to the level of experience in let's say smaller sized companies – what retention actually means. Meaning obviously we meanwhile really deal with all different types of records, being electronic, being really simply just data, or being really written documents with writing signatures. And it's sometimes really not well understood how really record retentions depending on type of format needs to look like. Because at the end, we know that it needs to be not only retained in appropriate manner, but also accessible and reproducible, etc., independently how long it is stored and giving more guidance in terms of what this really means medium and long-term could be really helpful. [ID# 15]
Trial management, data handling and record keeping—Lack of clarity on data handling and record keeping	G37	But right now, because the ICH GCP is applicable in the European region, I want that specific information about the general data protection regulation should be mentioned, but I know so that it's mentioned, applicable regulatory requirements. [In response to a request for clarification] If we could be maybe more specific to speak about general data protection regulation, GDPR. That is now enforced in Europe and has triggered a lot of documentation and with sponsor and sites so now we ask people to sign that data protection agreement. Every company has a data protection officer in the hospital as well. Now, we have modified ICF in accordance to that and some specific requirements. So, I wondered if it would not be needed to consider what's happening and the effects on the documentation. [Follow-up: I see what you're saying. So, perhaps give concrete examples of – I'm just making this up – but in order to protect confidentiality. You may need to, depending on the requirements of wherever you are, your region or your country, you may need to have a data protection agreement or a data protection officer, etc., etc.] And really to follow the general data protection regulation. [ID# 20]
Need for greater clarity in sponsor section and throughout guideline—clarify language related to "may" vs. "should"	G38	And then, I think – I don't know. I know that seems like 5.5.2 – the sponsor may consider establishing independent data monitoring, and that's fully more [like a requirement]. If you talk to someone in the UK, a sentence like the sponsor may consider is almost as close as the sponsor has to consider establishing independent data monitoring. So, sometimes it's between British English, American English, and what we in Europe or elsewhere understand. It's very often very difficult to tell the difference. [Follow-up question on the various interpretations and implementations of this word "may"] If I go with 5.5.2 to someone from the UK, and say "we don't really need an independent data monitoring committee because it just says may consider," then someone would turn around and say "no, no. You have no choice" the way that's written. And that's probably across the board the sponsor should designate how legally binding should be that "may". I think that's something the wording just needs to be more – this is something nice or this is where you have flexibility. And this is where the wording in my brief interpretation that there is flexibility, but if you really are point blank, this is no flexibility, you have to implement it. I think that's across the whole document and I think it's probably not only ICH, but it could be much clearer between what it [inaudible] but at the end of the day, there is no politeness. It's you need to implement. And probably to why that we need it, like a military order, and to indicate this is something where there is some interpretation and wiggle room based on the nature of the research you are

Unhelpful Aspects	Reference #	Illustrative Example
		proposing. …We require you to do. You have to. You are required. And that's probably because it's an international documentation and not everyone has the same sensitivity to this kind of small differences. They look small in writing, but in understanding it's probably very clear for an American and less clear for someone who English is not the first or second language, it's something completely different. And I think that's very difficult in this guidance document for someone then who reads it and says "well, just the sponsor should inform the investigator in writing." Should – it's not has to inform the investigator in writing, so I don't do that. But I think in this case, it's pretty clear that this is just a nicer way to say he has to inform the investigator in writing. …It means you are required. [ID# 08]
Safety reporting	G39	So, the safety reporting is also something that, I believe, can be adapted to the level of knowledge already available, and it's not working like this. So, in terms of the timelines of reporting, or in terms of the frequency of reporting, and of course, anything which is serious and unexpected, yes. But, then, in terms of the more comprehensive report, with all different types of cases, this is something that can also be adapted to the risk much farther than it's currently foreseen. [Follow-up question on the sponsor holding primary responsibility and having the flexibility to adapt, rather than to use the ICH as a checklist for every single line] Completely. So, another thing, also, to relate, which builds into different – so, I was speaking about the types of research, but we have more and more types of research where a different modalities and different elements come into the one research. So, we would have a drug. You have different treatment modalities. But, you may also have a new device. You may also have a new in vitro diagnostic tool. And, so also speaking specifically about the safety reporting, so if you went to the safety reporting, it's too much drug-oriented. So, it's already not taking enough mixtures, which is a big piece in oncology, so that definitely needs to be worked out, that sometimes the relationship cannot be allocated strictly to the one drug when you use a mixture in the cocktail. And, the whole thing is really developed into the mode of single-drug development and single-drug use. And, then it becomes the same to the multi-modality. For instance, we would expect to report the secondary effects of drugs, but what if at the same time, you have something serious happening on the side of radiotherapy or the device used? So, it's, like, sometimes, you would in some countries in your reporting line, in some instances, you would even report to different bodies. And, it does make sense because I think you lose the global picture and, maybe, the global effect on the patient and the risk population. So, now, there are more and more calls for core development, for instance, of drug and devices or in vitro devices. So, one can think anymore that it's all to put a single drug on the market. That's not true anymore. So, it needs to think about multi-modality and what's the most appropriate as reporting and as management to ensure the patient safety. And the more isolated view on events is not in the sake of patients. …The more isolated, like, the fragmented view. They are not looking at siloes. Because, it's like the entire combination. This is what will affect your patient. [Follow-up question about clinical trial no longer limited to a single drug, and almost exclusively about drugs, rather than about devices and other methods of treatment] Yeah, because again, it calls to the initial stakeholders and those are drug registration agencies. But, that's not how it's going anymore. [Follow-up question on how to revise]

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		Yeah, so it's again about the stakeholders. So, it's about inviting the stakeholders from those domains, from devices, from in vitro devices, etc., on the one hand. And, actually, making understanding that it's not about products, it's about patients. So, there is a research project which patient will go into and it will help. So, it can, potentially, put patients under risk, not only from the perspective of the drug, but from different perspectives and from different elements of it. And, these different elements are not entirely independent. They can interact. So, it has been described that some drugs interact with radiotherapy. So, secondary effects of radiotherapy get potentialized by a drug. I mean, this is just one example that comes into my mind. But, potentially, all of them can interact. And, though I do appreciate that people specialized in the drug evaluation are not the same experts that those specialized in the device or in vitro evaluation, but they need to speak to each other, and they cannot just continue not speaking to each other and asking to sponsors – just presenting their advices or exigencies in an independent way because sometimes it may not match. So, I think, really, regulators of all kinds need to realize that though their interest is to ensure the security of putting a product on the market, drug or something else, but the actual first interest of everyone is to protect the patient. So, we are all speaking a lot about being patient-centered, but the whole system is product-centered. And, so I think that ICH, by the fact that, true, it's starting from drug regulators, but it's not like, you know, in a country, you have a drug agency. You have this agency and you have a ministry, and they're all built in a different way. I think by the fact that ICH is an assembly, in a way, so it's already a multi-stakeholder group, which decided to gather together. It's probably easier for them to just decide to bring onboard other stakeholders and experts and to position itself which is really, truly patient-centered, and it's about, right, when we are doing an interventional clinical research involving patients, how we shall set it up in a way which is safe for this patient. …it's assumed that the only reason to do clinical research is to put a drug on the market, and that's not correct. It's – no. It can be drug on the market. It can be another type of product on the market, like device, like IVD. It can be not to put the product on the market, just to improve the quality of the healthcare. [ID# 19]
Safety reporting	G40	What can be a problem is – for the investigator is to have maybe more statistic on the event of the study. Regular business, it should be done once a year, but sometimes can be easier to do it every six months or all the investigator understand what he's doing there. What I did several, very large data monitoring committee involving my study and all the work and to be in China with 1,000 patients and yeah, yeah. We had every six months or every three months some paper with statistic where we could follow the situation and we ask not to make a clear separation between what we got and the other answer so we will be not mixed everything. So, you are somewhere of looking very precisely on your data, not with the end of the study or at least with the company at the end. So, together the ICH provide recommendation on the user statistic and adverse event reporting within a study. [ID# 22]
Guidelines need to be updated to accommodate new technology/processes—update data privacy and	G41	So, the recordkeeping, we haven't [used] as much because I think that information has been outdated and quite different to what we do. But we use it as a minimum information that's provided. And they probably don't use that as a reference point because there's a lot of more detail that we need to provide to… [Follow-up question on regulatory recordkeeping practice] It's more rigid – than what's mentioned in ICH. . . . And I think the main section of GCP that there is not enough information, I would say, from the data and the privacy – that needs to be updated. And the recordkeeping.

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record keeping guidelines		I'm not sure – if you looked – I think our preference would be a little bit more information on consent. But I think there's enough information that – in comparison, the different regional – there's enough information that we could fall back because it needs the specific different regions. But, besides that, what I could see that we don't really use, or we don't reference back, is the data portion of it. [Follow-up question on the need for updating] Yeah, it's a bit outdated. So, if you look at it, you go, "Oh, we can't – it's more that we want to see." But looking at it now, it's quite different to what is mentioned in there. [ID #01]
Guidelines need to be updated to accommodate new technology/processes—add guidance on data sharing and compliance, including examples of implementation	G42	[Question on providing examples] Yeah, so perhaps maybe a section on data sharing and the compliance. Those are quite lean and what would happen …. But that is regulation that's in place. Before there was a – you had the data, how you're going share it if you're doing a publication. What are the recommendations – what are the privacy – how, if you change the data, what is the responsibility of the other bodies of the institute of protecting the privacy and what they could do with the data. So, that's all those portions of it – that's going on out there in those regulations, and it's a good – there's really not much information here to see that it's been going on for years. That there's a section added in there, I think would be beneficial. And it's a common – it started being to see who's going to start and practice it? And I think what's happening officially with GCP and those in Europe – from this year onward, from 2020, to see the change that actually implemented. And it's actually a good time to be able to make a recommendation. And even 12 months – ago, it was sort of new and we talked about it, but no one could actually do anything. If that makes sense… --state that the trials that – we said, "Oh, I was going to see this. I was going to share the data with [inaudible] to say, "Okay, well now you have to share your data and it's acceptable." We want to see how could that be presented? What guideline's in place? Is there a place in GCP to talk about that? I'm not sure. [Follow-up question on experience in implementing clinical trials in various countries of the world, whether it was in East Asia and the Pacific, or in Latin America and the Caribbean and trying to implement and follow GCP] So, documenting in Europe, US, and also in Asia. And I think the biggest variation – the two top variations – are content and data and appear to be different in different region. And to go through the process – regulatory approval process – of data collection and data sharing is completely different. And even though you have the GCP to fall back on, they're ultimately considered the minimum standard …in Australia about data collection and fall back on GCP. But then, you go to different region, obviously, depending on data, let's say from a consent – the data consent from some of the studies is common. But in China, you have to have consent. It does not matter what type of study you have, you know that it's going to be problematic collecting consent. So, you're actually changing the entire design of the study and that's – even though you have GCP, you have information, it still goes back to the – there is a big variation between different regions and to be using consent because the information's in there and you could go back – you could always go back and argue the point that it falls back on GCP, falls back on the information and you could get through. But we've had issues in Europe with data and privacy. There was quite a complaint where we had to share – it took many, many months to find agreement. So, there's quite a variation. But the top two that I can think of that have been problematic at the region – in most of our studies…in either consent or data portion of it, on how it's [data] shared and what kind of data becomes a private deidentified data and all that you're allowed to take from present data that's collected.

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		It's different in different regions [ID# 01]
Laboratory quality management— expectation of using accredited labs not always possible in lower/middle income countries	G43	I find the laboratory quality management, the laboratory parts very poor. It's just poor. It just takes it for granted that every research will be using an accredited laboratory, which may be true in Japan, U.S., and Western Europe. But, with more and more globalized research, you may have laboratories which are not at that level. And, again, there is a very good clinical laboratory practice guideline, which was initially issued by Barka and then implemented by the WHO TDR. Again, why this is not the at least referred to GCP yet. That's something that we also had a paper about that one, and we also send that one. When it comes to the labs, well, we have seen in a lot of our research that when you go to do research, for instance, for neglected tropical diseases, you have to invest a lot in the upgrade of the labs. And we have referred to the legal guideline for the good clinical laboratory practices, but it would be nice to find a reference to that in the GCP. Because once I was discussing with somebody who told me that there is no need to update the GCP guidelines because what is not in GCP guidelines, it is in other guidelines. But, we are asking a substantial effort to researcher to scan around for the different guidelines. And on top of that, at the end of the day, it will be often the GCP guidelines which will be legally binding and not the other ones. [ID # 04]
Investigator qualification	G44	…so like I just described right now, let's say we –the issue about qualified physician needing oversight, perhaps we could enroll more patients or faster patients if we could use a nurse practitioner or something. So, my primary care "physician" is a nurse practitioner. So, we might have access to more potential subjects if we were free to look at physician assistants or other medical professionals. But right now, no one's going to take that chance. [ID# 16]
Investigator selection	G45	I'm going through Section 5.6, the Investigator Selection. What I would like to see as far as well, 5.6.1, each investigator should be qualified by training or experience and should have adequate resources to properly conduct the trial. So, I feel like what I see is investigators who think they can answer that question, but they don't know how to say that they're qualified by training or experience. So, I wish there was some sort of checklist or something to say – so, as an example, I have a physician right now. She did research when she was doing her residency. And now she wants to be the PI of an FDA regulatory study. And she felt that she was qualified by training and experience to be able to do that. And so, my assessment is that no, when you do research as a resident, you might be doing say a retrospective data study — or a quality improvement project. When you're going to FDA regulatory studies involving investigational products that have to follow ICH GCP guidelines, there is another level of oversight that you need to have and understand what your responsibilities are. There is a difference there. And so, I feel like by just saying I should be qualified by training and experience isn't enough. I would like to see that expanded upon. I would like that to say okay, you have to have training in GCP. This document is GCP. It needs to be more specific to say how are we going to say that this investigator is qualified by training and experience? It's more of like the how. [Follow-up question on what is used to determine that somebody is qualified by training and experience] Yeah, because my assessment right now is no, I would say not. But maybe somebody else would say yeah, they are because they had – that physician I mentioned, yeah, they did some research prior. Well, I feel like it's too vague. And then, the adequate resources. Well, what if they are a physician who is a really busy clinic and they – so oftentimes, they don't have enough time to oversee a clinical trial. Well, I wish there was a way to – what I would really ideally like to see is like a checklist to say okay, do you have this? Yes. Do you have this? Yes. And then, you would be able

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		to say yes, you are qualified by training and experience to be able to do this study. [Follow-up question on incorporated this into this revision] Maybe it's more – I would like more standardized tools to be able to assess investigators. I would like to have more tools, more tactical tools to be able to implement. …I think of like physicians – if they want me to get board certified in a certain area, there are certain criteria that they have to do to be able to – there's testing. There's different proctoring. There is a And what I feel like – I think the industry as a whole is trying to take steps towards proving competency in clinical research with the Joint Task Force on the clinical trial competencies for clinical research professionals. And then, the ACRP is working on that as well. I think we're trying to move towards that, but we don't have that right now in clinical research. I think that's what I'm really looking for is I want to be able to have some sort of like way for say investigators to say okay, you've got – you're competent in GCP. And here's what you had to do to get to that level. [Follow-up question about his being outside of the guidelines] Yes. [Follow-up question on by whom] That's where I'm not sure. So, historically, how it has been is ICH has come up with these guidelines? And they're somewhat general. And so, it's up to the institutions. It's up to organizations to figure out how they're going to implement it. So, probably – I don't know who has that. I'm just looking at my day-to-day and how I wish that there were more ways to be able to prove these things that are in this document. …And investigator selection – how will we make sure that they're qualified by training and experience? I wish there was more meat to this document to show that. How do you prove that, that person is qualified and competent to conduct the study? I don't feel it's specific enough. [ID# 17]
Guidelines need to be updated to accommodate new technologies/processes	G46	I think I would like to come to the CRO section again. I think it was quite helpful with the last revision that the addendum under 5.22, "The sponsors should ensure oversight of any trial-related duties and functions carried out on its behalf, including trial-related duties and functions that are subcontracted to another party by the sponsor's contracted CROs." This was really useful and it enhanced the understanding here. What I would like to see here more, this is what I issued before, was which tasks do you consider as trial-related duties and which tasks are not considered trial-related duties and would not fall under ICH GCP? That's the clarification I would need because it would facilitate our life, also with the need of qualification and then monitoring and auditing compliance at CROs and put the focus on the right stuff. [ID# 21]
Section 6: Clinical Trial Protocol and Protocol Amendment(s)		
Provide an interactive tool about protocol development as part of the ICH guidelines	G47	Section six is the protocol. I'm not an expert in writing protocols. I need to say this. However, I have worked with people writing protocols international GCP compliant for registration protocols next to me. And I think the information is okay. But the approach that the CTTI has with the common protocol. You know about this project where they developed a protocol that everyone can complete with information. I think it's more hands on if – I don't know if they are dynamic – I don't know if ICH – I don't know. I know it's a guideline, but sometimes when these people were writing the protocols and we were looking at the ICH GCP, it didn't help much in the development of the protocol. I mean it helped to pick out to make sure that you are not missing any elements.

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		So, it would be elements of clinical protocol. But it didn't help in practice developing it. So, maybe having an addendum, an annex, an online tool. I know that ICH doesn't do this kind of thing.. . . But I think it would help to have some kind of more interactive tools as part of the guidance. I don't know if it's possible. [ID# 03]
Section is not very helpful for protocol development	G48	I have not ever spent a lot of time on chapter six on protocol because I think that some of the other ICH guidelines do a little bit better job in that. There are definitely some basics here in terms of what's expected, but I don't think chapter six is very helpful really at all. So again the one for nine for protocol design and methodology [probably referencing E9] is pretty – that that's going to be a way better guideline for the protocol. This protocol section looks like it's a little bit of checklist again. It's like you should have these things. [ID #12]
Protocol section is too vague and open to interpretation. Different interpretations and implementation of protocol guidelines in multi-site trials can result in poor quality data. Consider developing a GCP-compliant template and add guidance about the importance of conducting a QC check on protocols	G49	One area as we were talking, Section 6 on the protocol, it does state – I guess the area that I really would like – I still see so many poorly written protocols. They don't have – it's not clear. It's too vague. And so, then what happens is people at each site interpret things differently. So, Section 6.3 on the trial objectives and purpose, detailed description of the objectives and purpose of the trial. Well, I just – if there could be more information to expand upon that. I guess what I feel like – and then it goes into 6.4, the Trial Design, specific, and about the primary endpoints. Yes, you do have to have these things, but I wish they were – I guess where I'm making the disconnect is I see so many poorly written protocols. And if they would just technically, yes, they do have these things in there, but they leave areas so that it's too vague so that it leaves room for interpretation. And so, that's one, if you have a multi-site study, one site interprets it this way versus another site interprets it that way. And then, you end up doing this whole trial, and you don't show the outcome that you were expecting, because the trial wasn't implemented the same way – there was such variance in the way it was implemented. So, if I could somehow, like with that Section 6, as far as being problematic, I wish there was a way to make – and I don't know if you're gonna be able to change the document, but I wish there was a way to make protocols more clear, crystal – so that people – because it's your blueprint for quality. And if you don't have a well written protocol, it's gonna cause problems quality-wise. So, I'm just not sure how to change that section. [Follow-up question on how making more of a blueprint or more specific] A specific statement of the primary endpoints, to be honest, I just don't know. The things that I see, I wish you could say things like being as specific as possible or like I'm just looking at Section 6.5, The Withdrawal Criteria. Honestly, I've been kind of reading through this, and everything in this is – and all of this is – sometimes they don't necessarily have these things in there. So, it's written in the documents. Hopefully the investigators are gonna follow this and there's nothing really you can do. I just don't know if we could change this document. [Follow-up question: Right. If a PI doesn't want to look at this, would something like some sort of graphic, presenting it differently – I'm just wondering, based on some of your previous comments, whether that would make a difference because you said some PIs aren't really following. For example, in 6.5, including a statement of exactly when and how to withdraw subjects, the timing and type of data, whether or how subjects are to be replaced. And these are four things that have to be included in saying, if people withdraw, what are the withdrawal criteria? Is there a way that this could be presented differently so that it would capture, engage, I don't know?] The only way really, is if we had – or one way, I would say, not the only way, is to have protocol templates that have all of – like if you could have a GCP compliant template. So, as something's ready to go – well, there are – I know Trancelerate has a standard protocol template. There's different websites you can go to where they have standard

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		protocols that if you say okay, we looked at the ICF GCP documents and this protocol template has all the things that this document requires. That could be one thing. And then, what about putting in, I don't know actually, if there is a statement to say you should do a QC check to make sure as far as the quality – well there is that section Quality Control. [Follow-up question on needing a QC check] Yeah, right, because there would be a statement to say, there should be an objective person who would review the protocol to make sure it has all the elements that are specified. [ID #17]
Section is not very helpful for protocol development	G50	Identifying tracking versions is important and also the impact of these versions. Whenever we are looking back to our site audit or site inspection, we map all the versions of the documents, all the impact of these versions and when they took life onsite. Maybe it was approved but maybe it was implemented some days later. We look back at that, and we understand the movie. I always say it's like a movie. And we understand. And it's always important when you are writing an amendment or a protocol or when it's improved, or it's being developed to understand the impact. And when it's tracked for implementation. Maybe it would be a good idea. [ID# 03]
Section 7: Investigator's Brochure		
Need for guidance about the impact of local regulations on the content of the investigator's brochure	G51	…what I was thinking of there really comes down to local regulation rather than the guidelines. For instance, one of the problems a number of companies have had relates to the safety and efficacy section of the investigator brochure, in Europe, because the regulators here insist that there must be a specific section within that titled reference safety information, which is, essentially, the information that is used to determine whether an adverse event is considered already known or is new and, therefore, reportable to the agency. That's a very specific EU issue, but it's one that's caused an enormous amount of problems for companies because it's not clear, from the guidance on the investigator brochure, that such a section is required. That wouldn't be in their territory. So, I'm not quite sure how you get around that within the ICH guidance. But again, at least some reference or clarity to the fact that there may be particular requirements in these sections in local regulations. [ID# 11]
Need for sponsors to better educate investigators about the investigational product	G52	Yes, number three is to strengthen the role of the medical monitor and the decoding of the investigator brochure to clinical investigators. I think – I like this section of the investigator brochure. But I still think many investigators are not totally familiar with investigator brochures. I think there's an opportunity there to improve that; improve that from implementation which is what I do every day when I work. But also, how can the guideline help. So, I wrote many investigators working for sponsors need to be better educated about both investigator brochure information and potential foreseeable risks in products and research. Many are not coming from scientific background. We see the industry needs the patients; they need the investigators. Many are physicians that became investigators. And they – there's a lot of hard scientific information in the brochure that maybe is not always easy for them to read and digest. And I think sponsors could support them better in this education activity of explaining more and working with them in the understanding of the investigator brochure. There is a role called clinical science liaison which I think has to do with taking the science investigator on behalf of the sponsor. There is a role of medical monitor in 5.3. And it says the sponsor should have a medical support information available for investigators at all times. They should advise them and work with them in understanding the product and potential safety profile they need to be familiar with. But I think maybe the wording can be stronger. And maybe a little emphasis can be put on the sponsor should educate the

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		investigators in the safety profile and the information of the safety brochure. We see it in some studies that are like very special that maybe this telephone call where the new alerts come up and sponsors talk with investigators about the ongoing safety profile of the drug. And I think – I would like to see more investigators that have something happens to a patient, and they are not sure – I would like to see them more communicating and giving an opinion. And I think the brochures are great. But sometimes they need to be communicated better in addition to giving them the documents. Particularly people that English is not – is their second language. Maybe they know English. And in addition to that, no scientific background. Maybe clinical or clinical epidemiology, clinical research. But no hard science. The brochures are very – sometimes there's a lot of hard data…. [that is] difficult to be decoded. And sponsors have a key role in helping [to better educate investigators]. [ID# 03]
Section 8: Essential Documents for the Conduct of a Clinical Trial		
Sponsors' interpretations of GCP impact the frequency of having to update 1572 forms	G53	So, we are facing – maybe it's also depending on the sponsor, but I will give you an example. I know that FDA 1572**,** if you have a US sponsor, and you are working with a sponsor on this side, I know that the guidance given by the FDA is that if you have a change – so you have a first 1572 signed, I would say when you initiate the sites. So, with all of the staff and investigators that will be involved in the trial. But then, the FDA guidance--I hope you don't change because it has been some time since I looked into it-- in the case that if you have a change of an investigator because you know some of the investigator aren't staying in the same place and are moving to another hospital it's not mandatory to update the FDA 1572 but to inform the sponsor and to have the final available one at the closure. And I think the sponsor requiring to have these documents any time you have a change to be done again and to be signed again, and I can tell you that investigator found this exercise quite exhausting. [Follow-up question about whether it was the investigator who found updating the forms to be exhausting] No. I would say the CRA is in charge of preparing the form and giving it to the sponsor for signature, and sometimes we've seen that if you have – so let's put an example in front. Every six months, the hospital physician can change services. So, it's six months, you can have a change of the staff participating to the trial, and then it means that you are not always informed immediately of the names of the people joining the study, so you can [inaudible] elaborate once and then you go on a site visit and [inaudible] that you have another person that you didn't reteach, so you have to recreate a new form and resign the investigator and usually investigator is quite annoyed because I understand that for him, it's administrative, and it's not helping to make the trial working well to have the patient being treated. [ID# 20]
Provide guidance about whether electronic site investigation files are consistent with GCP	G54	I would say that I know that more and more sites require if they can have electronic investigator site file let's say on a portal to avoid paper because of the space it takes and you know that hospitals are sometimes fighting with space…and the huge number of patients that you can take and the duration of your study. At some point, it's a full wall of documentation just for one study. I wonder if the committee can work on having this more reflecting the, I would say, the century and that now we are using also a lot of portals to get documentation. [ID# 20]
Advantages of further defining "accountability" and providing relevant	G55	…because it said shipping conditions and accountability, but again, they could put example – condition of boxes, temperature monitoring. It's those little things like that that people – we go back here, and we're like – ugh, it doesn't tell me enough. I have to

Unhelpful Aspects	Reference #	Illustrative Example
examples in the shipping IP(s) and trial-related materials sub-section		go to Google now. I have to do this. I have to look for another source to supplement what GCP is providing me. Follow-up question about how the guidance would be phrased] There's a phrase that I've learned to use in the business that says – includes but is not limited to. And that would be a great phrase to incorporate into some of these definitions on purpose to give people just that touch more guidance so this would be their only reference. Because that's the other thing. When they can't find it here, they go on the internet and will look it up and say – how long should this be kept? Or what's the definition of a CV? And then you'll see a multitude of hits because a multitude of institutions have defined – okay, this is what GCP says. This is how we're interpreting GCP. [ID# 14]