

Exploring Good Clinical Practice guidance in clinical trials – meeting summary

Summary

The ICH Good Clinical Practice (GCP) guidelines are currently being revised, providing an opportunity to review the application of ICH GCP and how useful they are in different settings. The Wellcome Trust, Academy of Medical Sciences and Bill & Melinda Gates Foundation held a joint workshop to bring together a range of perspectives to discuss the current guidelines, how the guidelines might be improved in the future, review potential revisions, and discuss possible alternative approaches.

Key discussion points and conclusions included:

- ICH GCP guidelines were originally intended to provide advice on the technical requirements for drug registration trials that are acceptable to regulatory agencies of ICH. However, in the absence of a widely accepted alternative, these guidelines are now applied to very broad research beyond what was intended.
- ICH GCP has increased the cost and bureaucracy of trials without necessarily adding value for all trials, thus impeding research. This can potentially harm patients either by encouraging researchers to follow one-size-fits-all procedures rather than considering which measures or processes are important for a particular trial design, and by delaying access to innovative treatments.
- To reduce the burden of inappropriate application of GCP without compromising safety and accuracy it is necessary to consider what individual studies and trials are aiming to achieve and how good clinical practice can be appropriately incorporated into their design. This may entail redefining what is meant by 'high-quality' trials.
- There is a need for broader culture change so that current and future guidance is interpreted and implemented appropriately
- Revisions are needed to ICH GCP to reflect the core scientific principles of clinical trials.
- The ICH working group, in accordance with its remit, mainly comprises regulators and industry. The development of new guidelines and revisions to the existing guidelines on clinical trials should involve a wide range of stakeholders including academics, funders, policy-makers and patients.
- All good clinical practice guidance should, as far as possible be 'future proofed' so that it remains relevant as new technologies and trial designs are developed.
- There was consensus to avoid introducing different standards for different research settings, but there was broad support for a flexible approach such as a 'decision tree' that allows high-level principles to be *adapted* to different research settings.
- There were calls for an ICH GCP guideline review to focus on the specific set of trials they were intended for and for alternative guidance for clinical research and non-drug registration trials to prevent inappropriate application of ICH GCP.

Opinions expressed in this meeting note do not necessarily represent the views of all participants at the event, the Academy of Medical Sciences or its Fellows, The Bill and Melinda Gates Foundation or the Wellcome Trust.

Introduction

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) was formed in 1990 to develop guidance on the design and conduct of clinical trials for the registration of new drugs. Its aim was to provide a single set of international guidelines to ensure that the rights, safety and wellbeing of subjects in such trials are protected, and that clinical trial data are credible. The resulting ICH Good Clinical Practice (GCP) guidelines include section E6 on trial protocols, which requires tight standards on aspects of trials such as documentation, recordkeeping, training and facilities. These standards are enforced through quality assurance and inspections.

However, concerns have been raised that ICH GCP guidelines have increased administration costs without adding value. These guidelines are also increasingly applied to different types of studies, far beyond the drug registration trials for which they were originally intended.

An interim revision to the ICH GCP E6 guideline, intended to address some of these criticisms, was published by the ICH in June 2016. However, there were concerns that the ICH working group, according to its remit, included mainly representatives of regulators and industry who focused specifically on drug licensing trials and lacked patient and academic expertise. Therefore this joint workshop looked to widen this discussion by exploring more generally how ICH GCP guidelines might be improved or whether alternatives are needed.

There were two key aims of the workshop. The first was to expand the range of views – to hear different experiences and perspectives relating to how ICH GCP guidelines are influencing practice now and how they may do so in the future, in settings that spanned trials on interventions for emerging infections in developing countries to adaptive trials and precision medicine. The second aim was to explore potential future solutions for improving good clinical practice. How can we build on the strengths of ICH GCP to make a system (whether part of ICH GCP or not) that is fit-for-purpose in the 21st century?

Scientific underpinnings and first principles

ICH GCP was originally created for use in registration trials. Section E6, which covers trial protocols, was intended to ensure data integrity; to protect the public from drugs that could be harmful or ineffective. Other parts of the guidelines were intended to provide a strong scientific rationale for trials and to cover the basic principles of randomisation and blinding. Participants noted that the guidelines had indeed provided a valuable framework and fulfilled an important need for building confidence in trials data.

Concerns were raised, however, that although the aims and high-level principles of ICH GCP are good, the details of the guidelines themselves – particularly E6 on which clinical trials are audited – do not always reflect basic scientific principles. For example, some delegates argued that the recording of safety data mandated by E6 is excessive and does not increase the scientific quality of trials nor necessarily avert serious dangers. Participants argued that this over-recording contributes to high costs and poor practices even in the registration trials where the guidelines should be applied. It can also pose a safety risk for study participants if key adverse events or signals become lost in the noise.

A broader issue beyond the content of the guidelines is that they are now being applied much more widely than originally intended. This is partly propagated by funders such as the Bill & Melinda Gates Foundation and National Institutes of Health often mandating ICH GCP guidelines for all trials rather than only those for which it was intended to apply. It was argued that in these cases, GCP should be built from scientific principles relevant to these different types of trials (using a bottom-up approach) rather than necessarily according to ICH GCP.

It was pointed out that in the UK, following the specific details of ICH GCP guidelines is not a legal requirement; researchers are simply expected to follow the high-level principles of ICH GCP. In contrast, most delegates felt that they are obligated by sponsors and inspectors to follow the guidelines in detail, and that this is hampering research due to 'ticking boxes' regardless of the actual risk to patients. Several delegates argued that more people may be harmed because this burden results in research being delayed or not carried out, than are harmed because trialists do not follow ICH GCP. There was support for a shift in focus to ensuring the reliability of an overall result rather than the correctness of individual data points, so that resources are used most efficiently.

Impact of ICH GCP guidelines in different settings

Infectious-disease outbreaks

Participants described their experiences of following ICH GCP in challenging situations such as infectious disease outbreaks, including Ebola, Zika, monkeypox and plague. In such situations, it is often necessary to set up a trial very quickly in a setting with limited resources. These settings provide an important lens for thinking about what data are important and how to conduct trials in a way that allows them to progress quickly, while also providing quality evidence and ensuring patient safety.

Participants conducting trials in locations such as Vietnam and Rwanda said that they are required by sponsors and funders to implement ICH GCP guidelines. They expressed concern that the guidelines do not take into account the specific challenges of these contexts, such as obtaining informed consent from patients who may be unconscious (given the severity of some outbreaks) or unable to

understand or interpret study information, or a lack of qualified staff, electricity supply or even Internet. Guidance needs to consider, and allow for, these real-life settings.

Delegates also felt that when carrying out inspections, ICH GCP inspectors often strictly adhere to the guidelines without paying attention to factors that matter to individual studies. This is more broadly applicable than just infectious disease settings. Examples included checking for the existence of ICH GCP training certificates but not asking whether staff are qualified for the lab procedures they are carrying out or checking for consent signatures without considering whether the consent is valid or genuine. The current guidelines also do not cover critical issues such as whether samples are handled appropriately (for example, whether biological samples in hot climates are kept refrigerated).

One speaker described the challenges of meeting ICH GCP guidelines in the setting of an Ebola outbreak. For, example, all materials had to be sterilised before leaving the treatment tent and so researchers had to photograph consent forms on a tablet in a protective case that could later be dropped into bleach. She and others expressed concern that such stringent requirements are hampering research, particularly in low and middle-income countries. In a survey of over 5,000 researchers in these countries, respondents overwhelmingly said that they would be unable to conduct a vaccine trial because of the difficulty and cost.

Community-based trials

Another delegate described experiences with community-based trials, which investigate interventions such as behaviour change in large populations. One example was a cluster-randomised trial in Pakistan looking at whether educating Government health workers could reduce perinatal and neonatal mortality. In such trials, obtaining informed consent from every individual as required by ICH GCP is not possible. It may be more appropriate to obtain group assent from community leaders, as well as individual consent from a sub-group of direct contactees. The current ICH GCP guidelines do not address such issues.

Innovative trial designs

Innovative trial designs also present challenges in the context of ICH GCP. Adaptive trials use early outcomes to change the trial design going forwards – for example to improve statistical efficiency or better estimate treatment effects. The ICH GCP guidelines do not anticipate or acknowledge this type of approach. One speaker suggested modifying the language to be more compatible with such innovative trial designs. He also pointed out that the guidelines assume the use of frequentist statistical analysis; rather than prescribing a particular school of statistics, he suggested simply requiring that a protocol specifies criteria for success and so allows for use of different trial designs.

Learning from others

Delegates described their experiences with the US Clinical Trials Transformation Initiative (CTTI), a public-private partnership between Duke University and the US Food and Drug Administration (FDA). The aim was to develop practices to increase the quality and efficiency of clinical trials, while involving a range of stakeholders including industry, academia, regulators and patients.

The speakers described how, when considering issues such as monitoring and investigator training, they concluded that following ICH GCP does not necessarily lead to high-quality trials. Instead, they proposed that it is important to look more broadly at what a trial aims to achieve, and work out how to make that

happen. They argued that the ultimate goal of a trial is to produce a result that is accurate, high-quality, safe and ethical. This quality then does not necessarily mean perfect data, but *'the absence of errors that matter'*.

This redefinition led to the CTTI's 'quality by design' project. This aims to shift away from tick-boxes and one-size-fits-all guidelines, towards encouraging researchers to fully understand the objectives of a particular trial and to identify the data that are crucial in that setting. Spending more time planning the design of trials to meet those objectives ensures that quality is built-in from the start.

Therefore the CTTI has now published recommendations on improving clinical trials. One is around creating a culture that rewards critical thinking and open dialogue about quality, and goes beyond sole reliance on tools and checklists. Another is to streamline trial design so that it directly addresses the questions being posed and the credibility of the trial. Finally, it is necessary to involve patients as equal partners.

The future: What does 'good' look like?

Delegates agreed on the need for appropriate, proportionate standards that focus on the things that matter. Beyond any revisions to the existing guidelines, or the creation of new sets of guidance, wider culture change is required to ensure that guidance is implemented appropriately.

There were different approaches to defining core principles of good clinical practice. One suggested starting point was: *'Look after the patients, and the results'*. Another perspective was: *'A good clinical research study should have a clear question; measure things to answer that question; and do this accurately, safely and ethically'*. In addition, the importance of avoiding *'errors that matter'* was emphasised: for example answering a question wrongly; doing something dangerous for patients (in the current study or in the future); or behaving unethically. Delegates generally suggested that broadly, the existing principles of the ICH GCP are appropriate, even if the guidelines themselves need updating.

There was support for a 'decision tree', perhaps through a computerised app, that could sit alongside the core principles and help relate them to a range of research settings. By answering a series of linked questions about trial type, setting and risk, researchers could understand what is, and is not, needed to conduct the trial safely. Keeping a repository of previous studies was also suggested, so that researchers can see how previous studies with a similar risk profile incorporated the core principles.

Participants emphasised the importance of future-proofing guidance. They noted that overly prescriptive guidelines can stifle innovation as technology advances and instead, describing 'what good looks like' will allow researchers to adapt this to different techniques and technologies. It was also felt that patients should be involved in defining good clinical practice, and suggested that outcome measures, in particular, should be defined by, and relevant to, patients.

Conclusion and next steps

Delegates acknowledged the importance of guidance to foster good clinical practice, but felt that over-interpretation and lack of clarity has caused compliance with existing ICH GCP guidelines to become a tick-box exercise (treating the guidelines as requirements to be followed, rather than advice to be interpreted). Instead, delegates called for guidance that does more to encourage critical thinking about which measures and processes are important in any particular trial while removing unnecessary bureaucracy.

Overall, delegates shared a commitment to improve patient outcomes through research of the highest quality, and agreed on the importance of engaging the broadest possible community, including patients. This may either involve redeveloping and redefining ICH GCP and the culture surrounding its application, or considering a new set of complementary guidance, formed around a bottom-up understanding of what basic scientific principles are important in different types of trials. For either of these options, there was a sense that rather than simply replacing E6, a broader framework to cover different study types and settings (such as adaptive trials, behavioural studies, or trials in low and middle-income countries) is required. This would fall outside the original remit of ICH GCP.

There were suggestions for short-term action: for example researchers to identify what unnecessary or inappropriate processes they could stop doing now, and funders to consider how to support the use of the most appropriate good clinical practice guidance for the trial being conducted. However, beyond this further debate is needed. This is a crucial time, with major developments occurring in trial design as well as technological advances in how data are stored, collected and shared; the coming artificial intelligence (AI) revolution may also transform the design and implementation of clinical trials. The Wellcome Trust, Bill & Melinda Gates Foundation and Academy expressed willingness to continue supporting this debate.