

COMMENTARY

Good Clinical Trials by removing defensive interpretation of Good Clinical Practice guidelines

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1 | INTRODUCTION

The International Conference on Harmonization–Good Clinical Practice (ICH-GCP)¹ guidelines are implemented worldwide, to ensure the well-being of trial participants and the quality of trials. However, we and others^{2–8} believe these guidelines are often defensively interpreted, contributing to the spiraling costs^{9,10} of trials and actually have a counterproductive effect on participant safety and trial integrity. These effects are unintended and the result of the complex environment in which trials are currently performed. Most trials have a multitude of stakeholders, some with commercial interests, others with scientific aims, and regulators and ethics committees. The results of many trials are used for market approval and therefore by itself have enormous stakes attached. The environment is risk-averse, and this has led to increased regulation, but above all the most stringent interpretation of these rules. This has generated a market, where billion-dollar contract research organizations (CROs)^{11,12} offer to provide support services to adhere to this defensive interpretation. The current best practice has made trials expensive and evaluation of older less commercially attractive treatments, for instance, the repurposing of existing treatments by others than pharmaceutical firms, difficult or impossible, with some notable exceptions like the Oxford Recovery trial that specifically states that they do not conform to the letter, but rather to the principles of GCP.^{13,14}

In this article, we share our investigations of the existing rules as applied to our context of a nonprofit clinical research unit connected

to a major university medical centre, in which approximately 40–50 early phase studies in patients (50%) and healthy participants are performed per year (www.chdr.nl). We assessed the ICH-GCP-R2 guidelines point-by-point. Peculiarities from practice are primarily driven by a defensive interpretation of the chapters (4) Investigator, (5) Sponsor and (8) Essential documents. These peculiarities are shortly discussed per ICH-GCP-R2 chapter, and more importantly, suggestions are provided on how to interpret the guidelines more effectively. The original ICH-GCP-R2 text is cited. All suggestions aim to reduce redundant bureaucracy and improve both participant safety and a reliable trial. Many short examples are given in the Supporting Information, that may be relatable to other researchers, illustrative of the counterproductive current practice.

2 | ICH-GCP-R2 CHAPTER 4. INVESTIGATOR

2.1 | ICH-GCP-R2: 4.1 Investigator's qualifications and agreements and 4.2 adequate resources

An investigator must have the right qualifications and adequate collaborators and resources.

Defensive interpretation: The usual practical approach to this has resulted in a document (delegation and training log) that must be completed prior to start of each trial and includes all potential sub-investigators. This can lead to many forms, which require additional staff even to manage them and a process that needs to be

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redone for each new study. Generally, these forms are incomplete or outdated (Example S1 and Figure S1).

Suggested solution: Similar to working in health care institutions, use of personnel records and relying on internal training procedures and documentation can capture authorization for standard procedures. Also, modern data capture systems drive much of the delegation already.

Relevant regulations cited from ICH-GCP R2

4.1.1: “The investigator should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority (ies).”

4.1.5: “The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.”

4.2.4: “The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.”

Addendum 4.2.5: “The investigator is responsible for supervising any individual or party to whom the investigator delegates”

2.2 | ICH-GCP-R2: 4.2 Adequate resources and 5.2 contract research organization (CRO)

Audits of audits generate large amounts of unnecessary work.

Defensive interpretations: A sponsor should ensure oversight, which in practice results in many double-checks, possibly due to a felt need to eliminate the possibility of being accused of lacking sponsor oversight (Example S2).

Solution: Audits that have been performed by another party recently (like another pharmaceutical company, CRO or governmental body), e.g., in a period determined by risk, should be mutually accepted and should provide ample documentation to prove the concerning sections were adhered to.

Relevant regulations cited from ICH-GCP R2

4.2.6: “If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.”

Addendum 4.2.6: “If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.”

Addendum section 5.2.2: “The sponsor 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 CRO(s).”

2.3 | ICH-GCP-R2: 4.5 Compliance with protocol

Management of protocol deviations.

Defensive interpretations: Any minor deviation is documented and explained in a ‘deviation log’. Managing deviations with a negligible impact, risks those that are actually important being over-looked (Examples S3 and S4).

Suggested solution: Deviations from protocol are explicitly allowed if these are minor (e.g., administrative), but it is also stated that any deviation should be documented and explained, which can at times be excessive. Prespecify in the protocol a risk-based assessment on (what is deemed) a serious deviation, instead of “any deviation.” Additionally, the rules should be unequivocal.

Relevant regulations cited from ICH-GCP R2

4.5.2: “The investigator should not implement any deviation from, or changes of the protocol ... except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).”

4.5.3: “The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.”

2.4 | ICH-GCP-R2: 4.8 Informed consent of trial subjects

Multiple reconsents of participants.

Defensive interpretation: Statement 4.8.2 is adequate: a participant should always be informed if new information arises that may influence their choice to continue participation in a trial. However, statement 4.8.11 is contradictory, stating the participant should be informed on any change. This forces investigators and participants to re-consent—sometimes frequently—to deal with minor updates that often do not contribute to the participant's choice to participate⁷ (Example S5).

Suggested solution: 4.8.11 should be removed and only relevant changes in the patient information should be communicated. This naturally produces a problem in the determination of what is relevant. However, this is not solved by communicating all irrelevant changes to the subject as well. The nature of these changes is adequately covered by 4.8.2. This situation can be seen as parallel to the requirements for information in clinical care where the decision about relevance is left to the physician. In a trial the principal investigator is in the best position for this decision.

Relevant regulations cited from ICH-GCP R2

4.8.2: “The written informed consent form and any other written information ... should be revised whenever important new information becomes available that may be relevant to the subject's consent. ... The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.”

4.8.11: “During a subject's participation in the trial, the subject ... should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.”

The consent form protects the sponsor rather than the participant.

Defensive interpretation: Despite GCP stating that the ICF should be understandable, these documents have become unreadable, often including elaborate legal language (Example S6).

Suggested solution: Similar to a medical specialist in patient care, who does not share all knowledge with a patient but decides what is relevant, a researcher should be able to do the same. This means going back to what GCP section 5.8.6 already states: an ICF should be understandable. An example from the Netherlands is a nationally implemented ICF template by the Dutch authority for health sciences (a practice that also speeds up the reviewing process for the EC). This same authority states that there is no added value in generally describing GDPR law in the ICF, but that a reference to a reliable source is sufficient (e.g., a website of the national authority on data protection).

Relevant regulations cited from ICH-GCP R2

4.8.6: “The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject”

3 | ICH-GCP-R2 CHAPTER 5. SPONSOR

3.1 | ICH-GCP-R2: Addendum 5.0 quality management

Conflicting statements regarding risk-based approaches.

Defensive interpretations: Guidelines on quality management are preceded by an addendum advocating a risk-based approach and to avoid unnecessary complexity. However, original language is still in place and contradicts this (“ensure that all data are reliable and have been processed correctly”), often resulting in the latter being applied (Examples S7–S9).

Suggested solution: A sensible risk-based approach based on principles like Quality by Design, would require a full rewrite of the guideline taking it back to the basic principles of good clinical trials, which do not necessarily imply undue attention to the individual data points, but rather to the reliability of the trial result.

Relevant regulations cited from ICH-GCP R2

Addendum 5.0: “The sponsor should ensure that all aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures, and data collection and processing, as well as the collection of information that is essential to decision making. ... The quality management system should use a risk-based approach.”

3.2 | ICH-GCP-R2: 5.3 Medical expertise

Involvement of outsiders in medical decisions during a trial.

Defensive interpretations: The interpretation of the rules has led to outside consultants having a role in the medical care of participants on behalf of the sponsor, even though both the sponsor and investigators already have qualified medical staff appointed to the trial (Examples S10–S12).

Suggested solution: Delegation of medical decisions regarding participants should stay delegated to the responsible physician-investigator as was originally intended and should not be outsourced without a good reason.

Relevant regulations cited from ICH-GCP R2

5.3: “The sponsor should designate appropriately qualified medical personnel who will be readily available to advise on trial related medical questions or problems. If necessary, outside consultant(s) may be appointed for this purpose.”

3.3 | ICH-GCP-R2: 5.14 Supplying and handling investigational product(s)

Time lost by withholding treatments.

Defensive interpretations: Sponsors hold back shipment of investigational products to the pharmacy of a research organization until all regulatory approvals have been obtained while they also aim for a timely execution of a trial (Example S13).

Suggested solution: Placing the investigational product in quarantine at the pharmacy should not interfere with the guidelines. Issues with the product and accompanying documentation can be resolved in parallel.

Relevant regulations cited from ICH-GCP R2

5.14.2: “The sponsor should not supply an investigator/institution with the investigational product(s) until the sponsor obtains all required documentation (e.g., approval/favourable opinion from IRB/IEC and regulatory authority (ies)).”

3.4 | ICH-GCP-R2: 5.18 Monitoring

Trial monitoring for the sake of trial monitoring, not related to integrity of the outcome or participant safety.

Defensive interpretations: ICH-GCP requires both a complete and a risk-based (and therefore partial) monitoring. Due to this conflict, often complete monitoring is performed. This results in an inordinate amount of time and effort spent by monitors on checking data that are of little relevance to the primary objectives of a trial or the safety of participants (Example S14).

Suggested solution: Contradictory language should be removed. Selection of monitoring approach should be driven/adapted by the framework wherein the clinical research is performed, e.g., by a fully dedicated research organization versus a hospital department that

infrequently participates in clinical trials or paper versus electronic data collection. Finally, collecting data that can be foreseen to have no impact whatsoever must be prevented.

Relevant regulations cited from ICH-GCP R2

5.18.1: “The purposes of trial monitoring are that: ... (b) The reported trial data are accurate, complete, and verifiable from source documents.”

5.18.3: “Extent and Nature of Monitoring. The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general there is a need for on-site monitoring, before, during, and after the trial; however in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators' training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified.”

Confused roles in communication.

Defensive interpretation: In industry-run trials, sometimes all communication is through a subcontracted monitor, without assessing relevance and necessity. The result of this is often not more than an extra interface of communication in the multiple disciplines that are involved in trials (Example S15 and S16).

Suggested solution: Only involve monitors when this is relevant and necessary as stated in GCP. Additionally, there could be smarter ways (e.g., central statistical monitoring) to monitoring trials than having people visit sites.

Relevant regulations cited from ICH-GCP R2

5.18.4 Monitor responsibilities: “Monitor(s) in accordance with the sponsor's requirements should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:

a) Acting as the main line of communication between the sponsor and the investigator.”

Drug (hyper)accountability.

Defensive interpretation: Monitors often do not only check the methods of control and documentation, but also repeat the checks carried out by both pharmacy and clinical staff, which are a local responsibility (Example S17 and S18).

Suggested solution: As already stated in the guidelines, a monitor must only assure that systems for drug accountability are in place and being followed.

Relevant regulations cited from ICH-GCP R2

5.18.4. c) iv. “That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.”

Checking everything that can be checked.

Defensive interpretation: A 100% source document verification is often performed, along with checks of many administrative documents, as opposed to the advised risk-based approach (Example S19).

Suggested solution: Implementation of the risk-based approach, as already described in the addendum language in section 5.18.3 and 5.0.

Relevant regulations cited from ICH-GCP R2

5.18.4 m) “Checking the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other.”

Explaining the protocol to the author.

Defensive interpretation: Even when the investigator has written the protocol and is an expert in the field, monitors often again inform the investigator about the study, sometimes including a GCP course (Example S20).

Suggested solution: Although there will be situations where a sponsor must deal with a site that is entirely naïve regarding GCP and the nature of the intended research, this is increasingly uncommon. A generalized approach should therefore be replaced by a customized site initiation, that can in special cases be absent.

Relevant regulations cited from ICH-GCP R2

5.18.4 g) “Ensuring that the investigator and the investigator’s trial staff are adequately informed about the trial.”

4 | ICH-GCP-R2 CHAPTER 8. ESSENTIAL DOCUMENTS

4.1 | ICH-GCP-R2: 8.1 Introduction

Excessive documentation.

Defensive interpretation: Guidelines regarding trial master files (other than ICH-GCP) differ and invariably the most extensive is chosen on cautionary principles (Example S21).

Suggested solution: Do not file everything that can be filed, but only documents that are actually essential.

Relevant regulations cited from ICH-GCP R2

8.1: “Essential Documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced.”

4.2 | ICH-GCP-R2: 8.2 Before the clinical phase of the trial commences

The use of curriculum vitae (CV) as proof of competence of all involved.

Defensive interpretation: Requesting a recently signed and dated CV of every sub-investigator (Example S22).

Suggested solution: Documentation of the qualifications of the principal investigator suffices, as representative of all sub-investigators. The principal investigator should be made responsible for the qualifications of supporting staff and often this is done by medical or nursing qualifications and personnel training records which are routinely maintained in health care organizations. The rules should just stipulate that a system for recording training and education is available.

Relevant regulations cited from ICH-GCP R2

8.2.10: “CV of investigator and sub-investigator. Purpose: To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects”

4.3 | ICH-GCP-R2: 8.3 During the clinical conduct of the trial

Logs chewing up paper.

Defensive interpretation: Separate paper logs of screening and enrollment are often requested on ongoing basis during a trial (Example S23).

Suggested solution: The rules should not stipulate more than that the flow of participants is adequately recorded.

Relevant regulations cited from ICH-GCP R2

8.3.20: “Subject screening log. Purpose: To document identification of subjects who entered pretrial screening”

8.3.22: “Subject enrolment log. Purpose: To document chronological enrolment of subjects by trial number”

5 | DISCUSSION

In this paper, we highlighted several dysfunctional interpretations of ICH-GCP and inconsistencies in the current guidelines. We also indicate that there are potential simplifications possible in the interpretation of the rules that may produce considerable relief of the operational burden of trials. Our potential solutions are based upon experience and based upon common sense, but other solutions may be possible. We hope that this paper elicits a discussion about this.

Although the principles of Good Clinical Practice on first sight appear good, they may in current practice not be, because of undue attention to the integrity of individual data points, as opposed to the integrity of the trial outcome. Consequently, the resulting practices are not the best possible. They have generated a self-inflating system of multiple checks that provide no support for reliable outcomes and often are counterproductive. This survey may look like a litany of small matters that can all be individually resolved, but we believe that the totality of all these defensively interpreted rules has a considerable effect on the efficiency of drug development and therefore the price of healthcare interventions and ultimately public health.

Several reasons can be thought of why this has come to be. Hippocrates' “first do no harm” is deeply embedded in all aspects of health care. Any defensive action might instinctively be in line with this principle, but it remains a just question how much harm is done by delaying drug development due to unnecessary administration. Secondly, there is fear of regulatory reprimands when not adhering to the guidelines, or due to different interpretations of the guidelines. Thirdly, this environment of defensive decision making, has created the possibility for billion-dollar CROs,^{11,12} generating a financial incentive to keep this system going.

The burden of proof has unjustly shifted to the point where data is required to show that a check is not necessary, instead of using common sense. An adaptive approach, where professionalism and experience with trials of an organization or hospital is taken into account may offer a way out of this quandary.

Most of the rules in ICH-GCP are about either safety of the participant or integrity of the data. The literal interpretation of the latter is, we believe, the fundament of much behaviour in practice that does not contribute to improving trials and thereby health care. The focus should not be on reliability of every individual data point in a trial, but on ensuring that the outcome of the trial is reliable. Most data are entered in computer systems that can take over many of the quality assurance tasks currently performed by monitors, and the GCP system has not yet taken these developments sufficiently into account. Although 100% perfect data will favour a reliable outcome, striving for this perfection comes at a high cost (financial and qualitative) and is not necessary.^{6,15} A randomized controlled trial is very robust against random error (quality by design).¹⁵ Only when error becomes systematic, this becomes an issue, but this is not efficiently captured with focus on individual data points or other aspects like event adjudication.^{5,6,16} A potential risk of overinterpretation is that much of the quality assurance effort in a trial is directed towards items that are irrelevant and this leads to a deterioration of the signal-to-noise ratio in the trial. The result of this would be that useful signals of low quality remain undetected. Extensive monitoring could therefore lead to a decrease in the integrity of the data that matter.

Based on five controlled pivotal cardiovascular trials (of FDA approved drugs 2015–2016), mean costs for these trials were estimated at \$157.2M (95% CI 113.5–200.9M),⁹ although there is uncertainty in the tools used to calculate these costs. For comparison, the 1980s ISIS II trial¹⁷ in about 18,000 patients, which predated ICH-GCP, without on-site monitoring, cost approximately \$1.5M. Although there are many factors that drive costs, this large difference proves that the increase in cost is among other things due to the process, and not the complexity of the scientific content.^{18,19} Clearly, there may be reasons why a new chemical entity may require more extensive monitoring since less is known about such compounds, but it seems unlikely that this explains the full difference. Interestingly, the RECOVERY trial, which established dexamethasone as one of the only effective treatments for COVID-19,²⁰ was specifically performed according to the principles of GCP but not the letter (e.g., only trial specific consent-training was needed for qualified staff to perform the ICF procedure, without needing a GCP training certificate).^{13,14}

After an open letter in 2016 to EMA and ICH by 119 health researchers in 22 countries,²¹ ICH published a reflection paper on GCP renovation in 2017.²² A working group to revise ICH-GCP (R2) was endorsed in 2019,²³ engaging many different stakeholders.²⁴ The Clinical Trials Transformation Initiative (CTTI), a public–private partnership that engages to increase the quality and efficiency of clinical trials,²⁵ performed a worldwide survey with research professionals, also determining that the current ICH-GCP chapters 4 (Investigator), 5 (Sponsor) and 8 (Essential documents) require most improvement, helping the ICH in its efforts to improve various topics within GCP.²⁶

While these are commendable efforts, there is a timeline of multiple years to create this new version.²⁷ Also, we are still anxious too much focus on data point integrity will remain in the guidelines, as opposed to reliability of the outcome of a trial.

A new guideline should suffice for any research on health care interventions, as already advocated by a collaboration of over 260 trialists from 35 countries and more than 70 research organisations.⁸ Importantly, these rules need not to be complex.

In June 2020, the Good Clinical Trials Collaborative was launched, based at the Wellcome Trust in the United Kingdom, aiming to publish a new set of guidelines in 2021.²⁸ This initiative is driven primarily by clinical researchers, and also includes a range of stakeholders, and aims to reduce regulatory complexity and enable efficient conduct of trials that are needed to improve patient care.

We support this initiative and urge to consider the examples and suggested solutions given in this paper. A final concern remains that despite a new concise set of guidelines, a behavioral change is needed within the drug development community, that will prevent a recurrence of the defensive interpretation. We stress that simple and clear basic principles do not automatically preclude overinterpretation.

In conclusion, we do not dispute the need for documented evidence of participant safety and reliable trial outcomes, but demonstrated an excess of such documentation, due to conflicting statements or frequent defensive interpretation of these regulations, that reinforce the need for a new simple regulatory system that should encompass all health care interventions. Such a system should be established transparently in an open discussion, that should include regulatory authorities, but above all, clinical researchers, patients and the public. Until such new guidelines exist, clinical trial efficiency may be improved on short term by a less defensive interpretation of the existing guidelines.

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COMPETING INTERESTS

The authors are active trialists and are often subdued to an excessive administrative burden. The research of the authors would greatly benefit from reducing this administrative burden. During the writing of this manuscript, JdH and AC joined discussions with the Good Clinical Trials Collaborative (GCTC) but wrote this manuscript independently from the GCTC.

CONTRIBUTORS

Review project: A. Conception, B. Execution; Manuscript: A. Writing of first draft, B. Review and critique. JdH: 1B, 2A,2B; JH: 1B, 2A,2B; HH: 1B, 2A,2B; AK: 1B, 2B; JvS: 1B, 2B; GG: 1B, 2B; JB: 1B, 2B; AC: 1A, 1B, 2A, 2B.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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