COMMENTS

The revision of the ICH Good Clinical Practice guidelines: a missed opportunity?

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Abstract

The Guideline for Good Clinical Practice (GCP) of the International Conference of Harmonisation (ICH) is an international standard for the ethical and scientific quality of the designing, conducting, recording and reporting of trials that involve the participation of human subjects. Today, most regulators and funding agencies follow the ICH guidelines. These were drawn up by a small number of regulatory agencies and drug companies from high-income countries and do not pay sufficient heed to the problematic aspects of clinical trials in the low- and middle-income countries. A recent process of revision of the ICH GCP, which focused mainly on improving the use of technology and quality systems in clinical trials, did not remedy the pre-existing divide between the guideline, ethics and the challenges of globalised clinical research. It is not clear whether another, newly announced "renovation" of the ICHGCP (a "reflection paper" was open for public comment until March 11, 2017) will succeed in addressing this divide.

Background

The Good Clinical Practice (GCP) guidelines are "an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible" (1). The first international GCP guidelines were issued by the World Health Organisation (WHO) in 1995 (2) and were followed in 1996 by the GCP Guideline of the International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (1). The ICH brings together regulatory authorities from the European Union, the United States of America and Japan (founding regulatory members), Canada and Switzerland (standing regulatory members), and since very recently, Brazil and South Korea (regulatory members). The ICH E6 GCP Guidelines are part of a process meant "to improve, through harmonisation, the efficiency of the process for developing and registering new medicinal products" across ICH members. In the light of the ICH mandate, it could be expected that the ICH GCP code was applicable mainly or only in the ICH region. Nonetheless, most research actors in low- and middle-income countries (LMICs) today refer to the ICH rather than the WHO GCP codes (3).

The ICH GCP guidelines have not been spared by critics over time. They were reportedly written on the basis of informal consensus (described as the weakest approach to the development of guidelines) and no systematic, up-to-date search for the relevant literature was carried out (4, 5). Further, they were drawn up by a small number of regulatory agencies and drug companies from high-income countries (HICs), with little input from LMICs (6). In addition, the guidelines have been criticised for failing to take into account the challenges facing clinical researchers in LMICs (3,7, 8). This is not surprising, since they were issued before the so-called "globalisation of clinical trials" (clinical trials are being increasingly delocalised to LMICs) (9, 10). The process of revising the ICH GCP, started in 2015, had the potential to overcome these shortcomings, by bringing the guidelines up to date, with inputs from the literature on ethics and from field experience in LMICs.

The "consensus draft text" of an "integrated addendum" was published on the ICH website on June 11, 2015, and then transmitted to the National Regulatory Authorities of the ICH region for internal and external consultation. It was immediately apparent that the scope of the addendum was limited to the improved use of technology in clinical trials (3). Nonetheless, the process was public, even though poorly publicised, and comments could be submitted to the ICH Secretariat by January 31, 2016. The addendum was finalised and eventually adopted by the Committee for Medicinal Products for Human Use of the European Medicines Agency on December 15, 2016. It was published as EMA/CHMP/ICH/135/1995 (11). To the best of our knowledge, the external contributions have not been made publicly available, nor has a list of the external contributors.

Integrated addendum to the ICH GCP guidelines and further plans for renovation

Changes have been integrated directly into several sections of the parent guideline and clearly identified as "addendum" (11).

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To cite: Ravinetto R. The revision of the ICH Good Clinical Practice guidelines: a missed opportunity? *Indian J Med Ethics*. 2017 Oct-Dec; 2(4)NS:255-9. DOI: https://doi.org/10.20529/IJME.2017.057

Published on May 23, 2017.

Manuscript Editor: Sunita V S Bandewar

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In case of a conflict between the previous and the new version, the latter will prevail. The main focus of the changes is on (the improved) use of technology and quality systems, as explained in the introduction:

"Since the development of the ICH GCP guideline, the scale, complexity and cost of clinical trials have increased. Evolutions in technology and risk management processes offer new opportunities to increase efficiency and focus on relevant activities. When the original ICH E6 text was prepared, clinical trials were performed in a largely paper-based process. Advances in the use of electronic data recording and reporting facilitate implementation of other approaches." Most changes concern procedures aimed at ensuring the integrity of trial-related duties, functions, and data. For instance, "detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed"; and "if non-compliance that significantly affects or has the potential to significantly affect human subject protection or reliability of trial results is discovered, the sponsor should perform a root cause analysis and implement appropriate corrective and preventive actions".

Sponsors are requested to implement an explicit system of quality management, with a major focus on the identification of risk, evaluation and control, including "the design of efficient clinical trial protocols and tools and procedures for data collection and processing, as well as the collection of information that is essential to decision-making…." The system of quality management should use a risk-based approach, including *Critical Process and Data Identification; Risk Identification; Risk Evaluation; Risk Control; Risk Communication; Risk Review;* and *Risk Reporting*. The whole process must be documented.

The integrated addendum introduces the concept of "risk-based" clinical monitoring: "The sponsor should develop a systematic, prioritised, risk-based approach to monitoring clinical trials. The flexibility in the extent and nature of monitoring described in this section is intended to permit varied approaches that improve the effectiveness and efficiency of monitoring. The sponsor may choose on-site monitoring, a combination of on-site and centralised monitoring, or, where justified, centralised monitoring. The sponsor should document the rationale for the chosen monitoring strategy (eg in the monitoring plan)."While the traditional on-site monitoring is performed at the study sites, centralised monitoring is "a remote evaluation of accumulating data, performed in a timely manner, supported by appropriately qualified and trained persons". Sponsors must develop an explicit "monitoring plan", describing the monitoring strategy and responsibilities, the methods to be used and the rationale for their use, and emphasising the monitoring of critical data and processes.

The integrated addendum also introduces changes in the storage system, which should "provide for document identification, version history, search, and retrieval". Interestingly, "Essential documents for the trial should be supplemented or may be reduced where justified (in advance of trial initiation), based on the importance and relevance of the specific documents to the trial," and, "The sponsor should ensure that the investigator has control of and continuous access to the CRF data reported to the sponsor. The sponsor should not have exclusive control of those data."

It is to be noted that on January 12, 2017, the ICH announced plans to further modernise the GCP and related guidelines. A "reflection paper" has been published on the ICH website and was open for public comment until March 11 (http://www.ich.org/products/gcp-renovation.html). The proposed renovation is planned in two steps: first, through the moderniation of the *ICH E8 General Considerations for Clinical Trials*, and second, by further renovation of the *ICH E6 GCP* "to anticipate and address a broader range of study types and data sources, while retaining the current E6 focus on good clinical investigative site practices". It is, in particular, proposed that tailored approaches be developed for different kinds of trials, ie "traditional interventional trials of investigational unapproved or approved drugs"; "non-traditional interventional trials and/or data sources", including pragmatic, clinical trials; and "non-traditional trial designs", such as observational studies, patient registries, etc.

Discussion

The effort to ensure the traceability and integrity of data is surely laudable. In addition, by limiting the large quantities of paper usually generated in clinical trials, the use of electronic systems will hopefully have a positive environmental impact. The other positive elements in the integrated addendum are the willingness to rationalise the probably excessive resources that have been dedicated to external monitoring up to now (12); and the explicit cross-referencing to the other ICH guidelines that should be used in conjunction with the ICH GCP, ie those on the management of data on clinical safety, reporting of clinical studies, geriatric populations, general considerations for clinical trials (that include an explanation of the different trial phases), statistical principles and paediatric populations. Nonetheless, the scope of the addendum remains quite limited to the use of technology and the adoption of sophisticated quality systems. The opportunity to integrate inputs from the literature on ethics and from the LMICs' experience in clinical research has been missed (8). This may be illustrated by a few examples.

With the globalisation of clinical trials, more and more studies are being undertaken in a host country, but being sponsored, financed and conducted by an external organisation (13). Various ethical guidelines and some research groups recommend that "externally sponsored trials" should be subject to the "double ethical review" In other words, a research protocol should be submitted for ethical clearance both in the country or countries where the research takes place and in the country of the sponsor and/or funding agency. This would help one get a complete and balanced review that takes into account the different perspectives and regulations

(13, 14). We suggested elsewhere that in the absence of a pre-existing harmonised regulatory framework between the host and the sponsor countries, the international GCP code could incorporate the notion of double ethical review for externally sponsored trials. It could also recommend measures to make review more efficient, for example, by promoting direct dialogue between the committees involved (3,8). Unfortunately, the integrated addendum ignores the debate and challenges concerning the ethical review of externally sponsored trials. This is despite the fact that externally sponsored clinical trials are increasingly being carried out in LMICs, and also as a part of the clinical development of new medicinal products that will be registered in ICH countries.

The integrated addendum is also silent on some problem areas related to the process of informed consent for children and minors. In the case of orphans and unaccompanied children, for instance, the ICH GCP still exclusively requires the consent of a "legally acceptable representative". *Per se,* this is a sound and logical rule, aimed at protecting the interests of the minor. Unfortunately, the concept of "legally acceptable representative" is not consistent with that in many LMICs, where guardians are not formally nominated by a tribunal but are instead, endorsed and acknowledged informally by the community (15–17). The ICH has preferred to ignore the problem, rather than considering alternative definitions that take into account the customary laws in various settings in LMICs.

Over recent years, the practical implementation of the assent of minors, commonly required in addition to parental consent so as to respect the autonomy of minors, has generated diverging opinions and contradictions in regulatory guidance, both in HICs and LMICs (18–22). In this case, too, the ICH preferred to ignore the debate and left the previous general text unchanged ("…..the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent").

Guidelines on research ethics concur that research maybe conducted in a given population only if it is "pertinent", and if there is a reasonable likelihood that its results will be available to that population (13). Thus, innovative products developed through clinical trials should be made available to all those in need in the countries where the trials were conducted, on the basis of the principle that the participants in trials and their communities should share both the burden and benefits of the research. Unfortunately, in the context of the rapid globalisation of clinical trials (9), there is a lack of adequate and structural strategies to make new medicines available and affordable in all countries involved in trials, including LMICs (3,23–25). With more and more trials being conducted in LMICs, including as part of the clinical development of medicines to be registered in the ICH countries, it is regrettable that the ICH GCP guideline continues to ignore the principle of "benefit-sharing" (8).

Over the last two decades, the importance of engaging with the communities has been increasingly understood and promoted in clinical research, particularly in the fields of HIV-AIDS (26) and tuberculosis (27). Unfortunately, there is no national or international regulation on community engagement yet (28). The ICH GCP could have helped to fill this gap (8), but the integrated addendum did not introduce any changes to the previous list of research stakeholders (ethics committees/institutional review boards, the investigator and the sponsor), and has persistently ignored the role of communities and/or patients' associations in research. Thus, the choice of whether or not to engage with the community is wholly at the discretion of the sponsor.

On another front, the integrated addendum pays no heed to the external funding agencies, which are not mentioned among the research stakeholders, despite their important role in shaping the agenda and standards of non-commercial research (29).

The integrated addendum is silent on a number of topics which have increasingly been at the core of the scientific and ethics debate, and on which sponsors and investigators still have no concrete regulatory guidance. These include the ethical and operational issues related to biobanking (30,31), the export of biological samples from the countries where the trials have been conducted (32–34), and data sharing (35–40). Recently, the World Medical Association issued the Declaration of Taipei on Ethical Considerations on Health Databases and Biobanking (41), which dwells on the ethical principles underlying the design, set-up and use of "health databases" and "biobanks", and the related governance principles and requirements. The words "biobanking", "health database" and "data sharing" do not even appear in the integrated addendum.

We have seen that the focus of the integrated addendum is on improving the use of technology. However, this is mainly or exclusively addressed from the point of view of HICs (and possibly of commercial sponsors that can rely on quality assurance services that enable them to develop sophisticated quality systems). For instance, the addendum has not introduced any changes to the parent guideline in terms of the informed consent process, laboratory quality systems and the quality assurance of investigational medicinal products (IMPs). It must be noted, though, that newly available technologies, such as multi-media and other tools, may improve the understanding and recall of informed consent among illiterate individuals and communities (42–44). As for the quality systems of laboratories, the integrated addendum does not include a cross-reference to the Good Clinical Laboratory Practices (GCLP) guideline (45), which provides detailed guidance on the analysis of biological samples from clinical trials. The GCLP are especially helpful for clinical trials in the LMICs, where the upgradation of local laboratories and harmonisation of the quality systems of laboratories may represent a major challenge (46). They are less relevant for the HICs, where triallists can rely on accredited laboratories. Last, to ensure the quality of IMPs, the integrated addendum still requires compliance only with the locally applicable Good Manufacturing Practices (GMPs). This criterion, which was

acceptable when the parent guideline was issued, has become insufficient today due to the variable quality of medicines on the international market (47, 48), with poor-quality medicines reaching even ICH countries (49).The unwanted use of poor-quality IMPs may bias the results of trials (50), so it is quite surprising that the integrated addendum does not make a more stringent reference to drug quality.

The "reflection paper", issued on January 12, 2017 to prompt the further renovation of the ICH GCP, does not mention any of these issues either.

Conclusion

The first principle of the integrated addendum is still the same as that of the parent ICH GCP guideline issued in 1996: "Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s). "On this basis, it might be argued that there was and there is no further need to integrate ethical principles and standards into the ICH GCP guideline. However, the reality is much more complicated. The ICG GCP guideline guides, *de facto,* most national legislators and funding agencies, so those principles and standards that are not explicitly mentioned in it are less likely to be considered by regulators, and the activities related to these principles are less likely to be funded by the funding agencies (8,29). For instance, as long as the "community" is not listed as a research stakeholder, there will be no obligation to engage with the communities or patients' associations. Also, it may be more difficult (in non-commercial research) to get external donors to fund activities aimed at engaging the community. In practice, it is entirely up to the research sponsors and funders how far they wish to apply the relevant principles that are not explicitly addressed in the ICH GCP, such as "community engagement" and "benefit-sharing".

Today, most regulators and funding agencies are influenced/guided much more by the ICH GCP guidelines than the ethics guidelines. In addition, it may be difficult for researchers to have a complete knowledge and understanding of the many other useful but not legally binding guidelines (13, 26,27,41). It is a pity that the manner in which the ICH GCP has updated its guideline has not been more collaborative, has not taken into account an analysis of the recent literature on ethics, and has not taken stock of the challenges of global clinical research. Instead, the divide between the ICH GCP guideline, ethics and the challenges in globalised clinical research remains as it was (13).

It could legitimately be argued that an instrument developed by a small group of regulators with a limited mandate should not have become the *de facto* global guidance. It is regrettable that the WHO GCP guidelines have not been updated since 1995, since the mandate of the WHO is far broader than that of the ICH, and a (revised) WHO GCP code could become an authoritative reference for research conducted outside the ICH region (3).

It does not seem likely that the ongoing ICH GCP "renovation" will aim at addressing the current divide between the ICH GCP guideline, ethics and the challenges in globalised clinical research. Nonetheless, it may be worthwhile to answer any future public calls for inputs so as to try to influence the process positively.

Acknowledgements

The ideas expressed in this article are, to a large extent, based on the experience of the Switching the Poles Clinical Research Network, funded since 2008 to 2016 by Belgian Technical Cooperation (DGD), and they have been described earlier in a doctoral research, carried out by the author, KU Leuven, Belgium. The latter worked under the supervision of Minne Casteels, Marleen Boelaert and Katelijne De Nys. The manuscript is available at https://lirias.kuleuven.be/handle/123456789/517274.

Funding

There was no external funding for writing this comment.

Conflict of interest *None declared*

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