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Improving Public Health by Improving Clinical Trial Guidelines and Their Application

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Improving Public Health by Improving Clinical Trial Guidelines and their Application

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Abstract

Evidence generated from randomized controlled trials forms the foundation of cardiovascular therapeutics and has led to the adoption of numerous drugs and devices that prolong survival and reduce morbidity, as well as the avoidance of interventions that have been shown to be ineffective or even unsafe. Many aspects of cardiovascular research have evolved considerably since the first randomized trials in cardiology were conducted. In order to be large enough to provide reliable evidence about effects on major outcomes, cardiovascular trials may now involve thousands of patients recruited from hundreds of clinical sites in many different countries. Costly infrastructure has developed to meet the increasingly complex organizational and operational requirements of these clinical trials. Concerns have been raised that this approach is unsustainable, inhibiting the reliable evaluation of new and existing treatments, to the detriment of patient care. These issues were considered by patients, regulators, funders, and trialists at a meeting of the European Society of Cardiology Cardiovascular Roundtable in October 2015. This paper summarizes the key insights and discussions from the workshop, highlights subsequent progress, and identifies next steps to produce meaningful change in the conduct of cardiovascular clinical research.

Key Words: clinical trials as topic; pragmatic clinical trials as topic; randomized controlled trials as topic; cardiovascular diseases

Introduction

Randomized controlled trials generate evidence on the benefits and harms of therapeutic interventions. Regulations and guidelines that govern clinical trials are intended to protect the rights, safety and wellbeing of the study participants and to provide assurance that the evidence generated can be relied on for individual patient care and the broader public health. However, there are concerns that these objectives are not being met due to significant problems with the interpretation and implementation of current regulations and guidelines.[1-5] Moreover, the over-interpretation of research governance requirements has inhibited methodological and technological innovation that could enhance the quality of cardiovascular trials. Moulding research to fit existing rules may not always be appropriate; instead regulations need to be flexible and allow proportionate approaches for each trial.[6;7]

The Cardiovascular Round Table of the European Society of Cardiology (ESC) convened a workshop to engender dialogue about improving the regulation and governance of clinical trials. Representatives from groups interested in clinical cardiovascular research (including patients, clinicians, regulators, funders, and trialists) collaborated to generate recommendations for optimal research and regulatory methods that would support rapid, reliable, and cost-effective evidence generation, while protecting the safety of clinical trial participants (see Figure 1).

Research Governance Challenges Facing Clinical Trials

The International Council for (formerly Conference on) Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice E6 (ICH-GCP) guideline was finalised in 1996 and has become established as the standard for the conduct of clinical trials worldwide.[8] Developed by a select group of regulatory authorities and

organizations representing the pharmaceutical industry (but without any input from non-commercial trialists or patient advocates), it was intended to provide consistency in the requirements for clinical trials conducted to support regulatory evaluations of new drugs across multiple countries. The guideline was not aimed at other types of clinical trials, such as non-registration trials, non-interventional studies, or trials of non-pharmacological interventions. However, it has been applied and, indeed, even mandated well beyond its original remit. For example, the European Union's (EU) new Clinical Trials Regulation requires that trial sponsors and investigators take account of ICH-GCP in all clinical trials of any medicinal product.[9] Similarly, the Gates Foundation requires grantees to adhere to ICH-GCP, even when they are conducting clinical trials in resource poor settings that are not intended for registration.[10]

Recently, ICH has acknowledged some of the problems with the GCP guideline[11] and initiated a public consultation on an E6 (R2) integrated addendum in 2015. Following comments from ESC and many other organizations interested in clinical trials,[12] ICH released a modified version in November 2016 for adoption and implementation.[13] However, concerns remain that this revision does not address fundamental problems with the ICH-GCP guideline and does not correct errors and inconsistencies in the original text (see Table 1).[14-16] ICH has also announced its intention to conduct a more substantial overhaul of guidelines that relate to GCP and clinical trial design, and have promised to publish a reflection paper outlining their plans in early 2017.[17]

Greater emphasis on the key scientific principles (e.g., maintaining the integrity of the randomization process, adherence to allocated study treatment, minimizing losses to follow-up) would have a greater impact on the quality of trial results than is achieved by the current focus on documentation and data checking in ICH-GCP,[15;16] but these aspects are not included in the proposed revisions and are not a focus of GCP inspections by regulators.[18] This failure can have

serious detrimental effects; for example, it was found that researchers did not consider it to be critical to minimize losses to follow-up after randomization (which allows unbiased "intention-to-treat" treatment comparisons) because it is not emphasized in ICH-GCP or included in ICH-GCP training.[15]

Quality Assurance and Risk-based Monitoring

The ICH-GCP guideline is intended to ensure the credibility of clinical trial results. For example, it states that those responsible for the trial (i.e., the regulatory "sponsor"; which is not necessarily the funder) should "ensure that trials are adequately monitored" and "determine the appropriate extent and nature of monitoring", and it emphasizes that "in general there is a need for on-site monitoring".[8] These statements have been over-interpreted;[18] consequently, site-based monitoring with extensive checking of source documentation is the prevailing method used in many trials and by many regulatory inspectors.[18;19] On-site monitoring is amongst the most costly operational activities in a clinical trial,[20] and there are serious concerns about its ability to detect important errors or improve quality, particularly of larger trials.[21-26]

Central statistical monitoring of trial-related data, in combination with targeted site monitoring informed by statistical analysis, has been proposed as a more effective and efficient method of detecting material errors during the conduct of a trial and identifying opportunities for improvement prospectively.[26-28] Regulatory authorities, particularly in the US and Europe, have now issued guidance documents that focus on a risk-based approach to monitoring, emphasizing "quality-by-design" concepts.[29-31] The ICH-GCP Addendum includes similar language but the contradictory text in the original guideline remains.[32] Widespread improvement seems unlikely

unless consistency is achieved in the guidance across all regulatory agencies, as well as in the approach used by regulatory inspectors and those who conduct trial monitoring.

Safety Reporting

A fundamental principle of clinical trials is the protection of clinical trial participants. However, the regulations and guidelines relating to safety reporting are unnecessarily complex and confusing, and frequently mis- or over-interpreted. Hence, important safety signals may get lost in the large volume of uninformative reports to regulatory authorities, ethics committees and investigators about adverse events.[32] Recent EU and US legislation indicates that the nature and extent of adverse event reporting should be tailored to each trial protocol, and FDA guidance discourages excessive expedited adverse reaction reporting.[9;33-35] However, this position is not well articulated in the ICH guidelines.[36;37]

In early phase trials of new treatments, rigorous ascertainment of adverse events is necessary[37] but, as knowledge of the safety profile of the treatment increases, the level of adverse event recording should decrease.[24] However, there is a widespread misunderstanding that it is required to record all non-serious adverse events even in late-stage trials of treatments when this may be neither scientifically justified nor required by regulators. Attempting to record information on all adverse events in a large late-stage trial may distract attention from systematic ascertainment of those serious health outcomes that might matter clinically and in public health terms.[24;38;39] Furthermore, clinicians view excessive reporting activities (including the frequent demand from sponsors to provide detailed narrative descriptions for common events not believed to be related to the study treatment) as burdensome and a disincentive to participation, which may result in fewer, smaller trials and less reliable evidence to guide patient care.[18]

Much of the emphasis in clinical trial guidelines is on expedited reporting of individual serious adverse events that are believed to be due to the study treatment ("reactions") and not previously recognized as being caused by the treatment ("unexpected").[36] There is good evidence that focus on these requirements, combined with the subjective nature of the attribution of adverse effects to the study treatment, can lead to excessive uninformative reporting.[32] Reports of such suspected unexpected serious adverse reactions (SUSARs) only have to be expedited if they have occurred among patients who were allocated the active study drug, so it is hard to draw meaningful conclusions about causality. Attribution of individual suspected adverse reactions to a treatment is only likely to be a reliable source of evidence about causation when both the effect is large and the particular adverse event would be expected to occur rarely in the type of patient being studied.[40;41] In all other circumstances, adverse events need to be compared collectively between the randomized treatment arms to determine their relationship to treatment.[34;42] In on-going trials, such comparisons are best conducted by an unblinded Data Monitoring Committee (DMC), adequately firewalled from those responsible for conducting the study in order to protect the integrity of the trial results.[43;44]

Despite introducing a new regulation that emphasised these points, a review conducted by the FDA's Office of Hematology and Oncology Products found that there had been little improvement in the rate of expedited event reporting (with, if anything, an increase); only 14% of all such reports were considered to be appropriate, with the remainder not providing any useful information about the safety profile of the drug under investigation.[32] Commercial sponsors have identified a lack of international harmonization, concerns about liability risks, and confusion about the rules for aggregated reporting as barriers to improving their adverse event reporting to regulatory authorities.[45]

Thus, although there have been advances in guidance about safety reporting issued by some regulatory authorities, modifications to ICH guidelines and the way that they are applied are clearly needed (see Figure 1). Changing guidance alone is unlikely to be sufficient; a more rational approach to safety monitoring will also need to be communicated widely and applied consistently by all involved – including trial sponsors, investigators, and regulatory authority reviewers, auditors and inspectors – so that there is a change in the mind-set.

Promoting Innovation

There is intense interest in the implementation of innovative clinical trial models for cardiovascular research. For example, many therapies for acute coronary syndromes have been developed in randomized effectiveness trials comparing a new treatment versus the current standard treatment. Increasingly, randomized trials are using existing clinical infrastructure (including electronic healthcare records and registries)[45-48] or collecting outcome information directly from patients (e.g., through smartphones and wearable sensors), without the involvement of a typical clinical research site. Overly cautious attitudes to innovation in trial design and the use of novel technologies may be the consequence of concerns about informed consent, privacy, information security, and data quality[49] or uncertainty about whether such approaches will be accepted by regulators.[50;51] However, it is important that clinical trial regulations (and the way in which they are interpreted and applied) keep pace with such innovation.[52]

Transparency

The public disclosure of clinical trial results ensures that the valuable contributions of study participants serve a meaningful purpose and advance the science and practice of medicine. Greater clinical trial transparency has been achieved through the use of clinical trial registries and requirements to report results.[9] Although some trial funders and journal editors are keen to promote sharing of individual participant data,[53-55] the potential benefits and challenges of doing so are the subject of ongoing debate.[56-60] Access to patient-level data might offer unprecedented opportunities for confirmatory or novel analyses, design of future trials, and methodological research. However, it also carries potential risks (for example, data-derived subgroup analyses may yield unreliable conclusions and lead to inappropriate treatment decisions) and opportunity costs (diverting resources away from new trials of cardiovascular treatments), so moves in this direction should be considered carefully.[61;62]

Education and Engagement

The fundamental importance of conducting well-designed randomized trials in cardiovascular disease is often under-appreciated. Ensuring that the public, patients, physicians (particularly in medical school curricula or early career), and policy makers are better informed in the value and key principles of clinical trials is a priority. Such initiatives should emphasize both the value of integrating clinical trials into routine practice[63;64] and the need to facilitate the reliable evaluation of existing treatments, some of which may not be as effective[65] or safe[66;67] as they are thought to be. Similarly, informing patients about the ways in which they can participate in clinical trials, the measures that are taken to ensure that their data are secure, and the value this information provides to the quality of care should help to reduce their concerns.

Patient advocacy groups can provide perspectives on disease or treatment burden and provide advice on the feasibility of specific aspects of a clinical trial, informing study design. Collaboration between patient groups and clinical trialists should be the norm rather than the exception. Likewise, patient perspectives should be included in the development of new guidelines and regulations, as has been done effectively in projects conducted by the FDA-funded Clinical Trial Transformation Initiative but is notably absent from ICH processes.

Ethics Review and Informed Consent

The importance of ethics committees for the protection of the rights, safety and wellbeing of study participants is not a matter of debate. However, some of the other processes intended to achieve these protections are of questionable effectiveness or efficiency, especially for later phase studies of new drugs or pragmatic trials of well-known treatments. Informed consent is an essential component of recognizing patient autonomy and respect for a person's right to make decisions about their participation in a clinical trial. However, in many cases, consent processes have become cumbersome, fail to provide study participants with the information necessary to allow them to make properly informed decisions, and are disproportionate to the level of risk involved. In particular, a streamlined approach should be adopted for pragmatic trials conducted in the setting of routine care. Such approaches are currently being considered in the proposed revisions to the Common Rule, which is the regulation that guides federally- supported human research in the US.[68]Although the EU Clinical Trials Regulation includes provisions for low-(risk) intervention trials and cluster randomized trials,[9] ICH-GCP does not currently address these issues.[13]

Conclusion

Cardiovascular therapeutics is built on a foundation of evidence-based practice created from decades of high-quality randomized trials. The ESC supports regulations and guidance that promote quality protections for clinical trial participants and meaningfully improve the reliability of the results of trials. However, regulations should be based on scientific principles, should be proportionate for the type of intervention and the extent of prior experience with it, and adaptable to the choice of trial design (including use of registry, electronic health record or sensor data). Regulations and guidance should also be internally consistent to avoid apparently conflicting requirements, which could lead to poor adoption of improved standards.

The ESC has set out a number of priority initiatives to improve the quality of GCP guidelines for clinical trials and their appropriate implementation (Table 2). The ESC is sharing views generated by the workshop and has already contributed to the public consultation on the ICH-GCP addendum. The ESC is committed to partnering with patients, investigators, sponsors, and regulators to create a clinical trial environment fit for the 21st Century, one that provides appropriate protection for trial participants, encourages innovation, operates efficiently, and leads to better care and improved outcomes for patients with cardiovascular disease.

Figure Legend

Figure 1: Key elements of Good Clinical Practice for randomized clinical trials

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Table 1. Examples of unclear, inconsistent and contradictory definitions within ICH-GCP (E6)

Term	ICH-GCP Definition	Concern
Adverse Event	"Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment…"	Implies that those not administered a pharmaceutical product (e.g. control group) cannot have adverse events
Adverse Drug Reaction	"…All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product and an adverse event is at least a reasonable probability, ie., the relationship cannot be ruled out"	The meaning of "is at least a reasonable probability" is very different from "cannot be ruled out"
Serious Adverse Event or Serious Adverse	"Any untoward medicinal occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect"	This is intended to define what is meant by "serious". However, the text is confusing and can be interpreted as suggesting that Serious Adverse Event and Serious Adverse Reaction are synonymous.

Table 1. Examples of unclear, inconsistent and contradictory definitions within ICH-GCP (E6) (continued)

Term	ICH-GCP Definition	Concern
Drug Reaction:		
Sponsor	"An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial."	Not consistent with other regulations: US 21 CFR 312.3: "Sponsor means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization."[69] EU Clinical Trials Regulation: "Sponsor means an individual, company, institution or organisation which takes responsibility for the initiation for the management and for setting up the financing of the clinical trial."[9] Note: EMA and FDA are both members of ICH

Note: These definitions are presented in the original ICH-GCP (E6) text and were left unaltered in the E6 (R2) Addendum.[8;69]

Table 2. Priority Initiatives of the European Society of Cardiology to Improve the Feasibility and Quality of Cardiovascular Clinical Trials

Priority Initiative	Aim
1. Support research on the utility of clinical trial activities	Support approaches to evaluate specific clinical trial activities to determine their effectiveness, value, and impact on safety of trial participants and the reliability of the results.
2. Make the case for improved regulation of clinical trials and participate in their development	Contribute actively to the development of regulations and guidance that facilitate high quality clinical trials, working in collaboration with all relevant stakeholders (including academic trialists, patient advocates, regulators, non-commercial funders, and industry)
3. Share best practice for translating regulatory requirements to practice	Support collaborative efforts among academic trialists, patient advocates, regulators (including auditors and inspectors), non-commercial funders, and industry to establish a consensus on methods to translate regulatory guidance into modern clinical trials.
4. Promote initiatives to reduce the over-interpretation and excessive application of reasonable regulatory requirements	Promote initiatives that encourage interaction among academic trialists, patient advocates, regulators (including auditors and inspectors), non-commercial funders, and industry to identify and rectify examples of over-interpretation regulatory requirements (i.e., activities that are conducted out of conservative interpretation of regulations rather than actual requirements).

Table 2. Priority Initiatives of the European Society of Cardiology to Improve the Feasibility and Quality of Cardiovascular Clinical Trials (continued)

Priority Initiative	Aim
5. Promote widespread understanding of the role of clinical trials in high quality cardiovascular healthcare	Provide mechanisms for educational initiatives targeting patients, practicing physicians, and policy makers on the importance of clinical trials for developing new therapies and for establishing the effectiveness of available therapies used in the setting of routine care. Through education, shift thinking towards a realization that, in the absence of such evidence, the most ethical approach is often to conduct a randomized trial.
6. Encourage and facilitate effective engagement of patients and their advocates in the clinical trial enterprise	Encourage patients and patient advocacy groups to become involved in decisions related to clinical trial design (e.g., ensure that trials are answering questions relevant to patients) and/or regulatory standards (e.g., regulations that protect patients while also enabling quality research to be conducted)

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Figure 1

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