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1 **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

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59 Introduction

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

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

77 Research Governance Challenges Facing Clinical Trials

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

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

92 Recently, ICH has acknowledged some of the problems with the GCP guideline¹¹ and
93 initiated a public consultation on an E6 (R2) integrated addendum in 2015. Following comments
94 from ESC and many other organizations interested in clinical trials,¹² ICH released a modified
95 version in November 2016 for adoption and implementation.¹³ However, concerns remain that
96 this revision does not address fundamental problems with the ICH-GCP guideline and does not
97 correct errors and inconsistencies in the original text (see Table 1).¹⁴⁻¹⁶ ICH has also announced
98 its intention to conduct a more substantial overhaul of guidelines that relate to GCP and clinical
99 trial design, and have promised to publish a reflection paper outlining their plans in early 2017.¹⁷

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

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105 serious detrimental effects; for example, it was found that researchers did not consider it to be
106 critical to minimize losses to follow-up after randomization (which allows unbiased “intention-
107 to-treat” treatment comparisons) because it is not emphasized in ICH-GCP or included in ICH-
108 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

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

129

130 **Safety Reporting**

131 A fundamental principle of clinical trials is the protection of clinical trial participants.

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

139 In early phase trials of new treatments, rigorous ascertainment of adverse events is
140 necessary³⁷ but, as knowledge of the safety profile of the treatment increases, the level of adverse
141 event recording should decrease.²⁴ However, there is a widespread misunderstanding that it is
142 required to record all non-serious adverse events even in late-stage trials of treatments when this
143 may be neither scientifically justified nor required by regulators. Attempting to record
144 information on all adverse events in a large late-stage trial may distract attention from systematic
145 ascertainment of those serious health outcomes that might matter clinically and in public health
146 terms.^{24;38;39} Furthermore, clinicians view excessive reporting activities (including the frequent
147 demand from sponsors to provide detailed narrative descriptions for common events not believed
148 to be related to the study treatment) as burdensome and a disincentive to participation, which
149 may result in fewer, smaller trials and less reliable evidence to guide patient care.¹⁸

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

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

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

180 **Promoting Innovation**

181 There is intense interest in the implementation of innovative clinical trial models for
182 cardiovascular research. For example, many therapies for acute coronary syndromes have been
183 developed in randomized effectiveness trials comparing a new treatment versus the current
184 standard treatment. Increasingly, randomized trials are using existing clinical infrastructure
185 (including electronic healthcare records and registries)⁴⁵⁻⁴⁸ or collecting outcome information
186 directly from patients (e.g., through smartphones and wearable sensors), without the involvement
187 of a typical clinical research site. Overly cautious attitudes to innovation in trial design and the
188 use of novel technologies may be the consequence of concerns about informed consent, privacy,
189 information security, and data quality⁴⁹ or uncertainty about whether such approaches will be
190 accepted by regulators.^{50;51} However, it is important that clinical trial regulations (and the way in
191 which they are interpreted and applied) keep pace with such innovation.⁵²

194 **Transparency**

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

206
207 **Education and Engagement**

208 The fundamental importance of conducting well-designed randomized trials in
209 cardiovascular disease is often under-appreciated. Ensuring that the public, patients, physicians
210 (particularly in medical school curricula or early career), and policy makers are better informed
211 in the value and key principles of clinical trials is a priority. Such initiatives should emphasize
212 both the value of integrating clinical trials into routine practice^{63;64} and the need to facilitate the
213 reliable evaluation of existing treatments, some of which may not be as effective⁶⁵ or safe^{66;67} as
214 they are thought to be. Similarly, informing patients about the ways in which they can participate
215 in clinical trials, the measures that are taken to ensure that their data are secure, and the value this
216 information provides to the quality of care should help to reduce their concerns.

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

223
224 **Ethics Review and Informed Consent**

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

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240 **Conclusion**

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

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

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257 Figure Legend

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

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The opinions expressed in this paper are those of the authors and cannot be interpreted as the opinion of any of the organizations that employ the authors.

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Conflicts of Interest

277 Martin Landray: Conducts clinical trials funded by charity, government, and industry in
278 accordance with contracts through the University of Oxford (which acts as the regulatory
279 sponsor) that ensure the independence of the research from the funders.

280 Jeroen J. Bax: None declared.

281 Laurence Alliot: Employee of Servier.

282 Marc Buyse: Personal fees from IDDI and CluePoints (employee and stockholder); US Patent
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286 Ethics Committee; Personal fees from CHDR Leiden (full-time employee of the non-profit
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332 **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 <u>administered a pharmaceutical product</u> 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.

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17 **Table 1. Examples of unclear, inconsistent and contradictory definitions within ICH-GCP (E6) (continued)**
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Term	ICH-GCP Definition	Concern
<p>21 22 23 Drug 24 25 Reaction: 26 27</p>		
<p>28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56</p>	<p>“An individual, company, institution, or organization which <u>takes responsibility for the initiation, management, and/or financing of a clinical trial.</u>”</p>	<p>Not consistent with other regulations:</p> <p>US 21 CFR 312.3: “Sponsor means a person who <u>takes responsibility for and initiates a clinical investigation.</u></p> <p>The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization.”⁶⁹</p> <p>EU Clinical Trials Regulation: “Sponsor means an individual, company, institution or organisation which <u>takes responsibility for the initiation for the management and for setting up the financing of the clinical trial.</u>”⁹</p> <p>Note: EMA and FDA are both members of ICH</p>

57 333 Note: These definitions are presented in the original ICH-GCP (E6) text and were left unaltered in the E6 (R2) Addendum.^{8;69}
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334 **Table 2. Priority Initiatives of the European Society of Cardiology to Improve the Feasibility and Quality of Cardiovascular**
335 **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
<p>5. Promote widespread understanding of the role of clinical trials in high quality cardiovascular healthcare</p>	<p>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.</p> <p>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.</p>
<p>6. Encourage and facilitate effective engagement of patients and their advocates in the clinical trial enterprise</p>	<p>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)</p>

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