

## THE NEW EU CLINICAL TRIAL REGULATION (NO. 536/2014) AND INVESTIGATOR-LED STUDIES

Conducting clinical research in an academic environment is largely dictated by the availability of scarce resources. In contrast, clinical research in a commercial environment may avail of relatively generous funding. While both academic and commercial research often have fundamentally different objectives and risks (1), they are at present obliged to comply with the same standards of Good Clinical Practice (2, 3), including adherence to relevant national legislation. The result of such a “one-size-fits-all” approach is a fundamental mismatch between risk and risk-management, in which academic-led studies lose out due to soaring administration and compliance costs (4). A new Clinical Trial Regulation (Regulation [EU] No 536/2014), scheduled for application this year, should redress the current imbalances.

Academic trials and commercial trials generally have different objectives - academic trials are often focused on real world outcomes and routine clinical management, while commercial trials generally focus on assembling data to secure product approval and market authorisation (1, 5). Such distinct objectives lead to different study designs and different risk profiles, in turn leading to a potential wastage of scarce resources when the rules become misaligned.

While all stakeholders readily agree with the foundational principles of patient protection and safety, as articulated in the Declaration of Helsinki (6), differences often arise in how best to deliver such protections.

The current obligations for initiating, conducting, monitoring and reporting a clinical trial in the EU are set out in EU Directive 2001/20/EC (7), and laterally, EU Directive 2005/28/EC (8), and within the International Conference on Harmonization (ICH) of Good Clinical Practice (ICH-GCP E6 R1, June 10<sup>th</sup> 1996) (3). The latest addition, Regulation (EU) No 536/2014 of the European Parliament, will be applied as of May 28<sup>th</sup>, 2016 (9) however, applications under the new system will need to await introduction of an EU portal, scheduled for delivery sometime in 2018.

The purpose of the EU Directives on clinical trials is to set out the regulations and administration of GCP in the execution of trials conducted within the 28 Member States. However, a number of practices, including guideline ICH-E6, detailing the expected good clinical practice for human trials, has attracted significant criticism (10, 11), as have additional obstacles that un-necessarily hinder the progress of non-commercial studies (12, 13). In particular, concerns had arisen that ICH-E6 lacked transparency on the identity of the authors and the evidence-base upon which the guideline rests; the most recent implemented version of the guideline, from June 1996, had not been updated in over 10 years. Work on a new addendum is all but complete with a revised adopted guideline scheduled for implementation by June 2017; however, the current ICH-E6 has been criticised for creating costly and complex approval procedures, principally written with industry in mind and having little or no input from the academic research community (14). In addition, monitoring had been criticised as disproportionately focused on minutiae of trial conduct rather than centralized oversight, while drug safety appeared more focused on individual case reports than on the more material consideration of overall rates of adverse events.

While each of these criticisms is well-founded, I believe they overlie three (3) core methodological challenges which need to be addressed if application of the new EU Regulation is to be a success:

**(i) Recognition that current rules deal with different processes.** Academic and commercial trials are not the same however, current regulatory frameworks do not appropriately acknowledge the clear distinctions. A top-down imposed “one-size-fits-all” approach attempts to shoe-horn one constituency of the research community (academic researchers) into a process designed for a different constituency (the pharmaceutical industry). While these constituencies have much in common, they differ in respect of *why* they do research. Academic research is primarily conducted to drive improvements in patient care and treatment, or to assess approved treatments on a broad heterogeneous population, while pharmaceutical research, which has similar goals, is primarily driven by accelerating technology and new treatments forward, often with the objective of introducing new medicines into the marketplace. If current regulations persist in applying the same audit and management processes on both constituencies, then a significant body of research, of benefit to patients, clinicians and society, will increasingly struggle to find sufficient funding.

**(ii) Risk management needs to be proportionate.** Risk management must be proportionate to the actual risk. Any reasonable assessment of risk must acknowledge the differences between, for example, an aspirin study conducted across a number of rural populations, versus a virally delivered experimental gene therapy study in an orphan neurological indication. Current EU regulations (and interpretations thereof) generally fail to accommodate such a distinction. Clearly, the actual risks of aspirin use and gene therapy are logarithmically different however, a voluminous body of documentation may be required for both studies. Significantly, funding an academic-led aspirin study in rural communities can be close to impossible, while funding a gene therapy study may likely attract various commercial players (15). More importantly, the beneficiaries of the aspirin study may far out-number the beneficiaries of the orphan gene therapy study, resulting in a negative selection pressure against academic investigator-led research (16).

**(iii) All stick, no carrot.** Finally, there appears to be a fundamental contradiction in the basic message from the EU. The Commission stresses the importance of patient safety and validity of data, but remains silent on how to deliver same and on who is going to pay for it. The process appears to be all stick and no carrot. If the EU wishes to impose homogenous regulations for the control of clinical trials, regardless of risk and costs, and then enforce such regulations through national legislation obliging governments to uphold them, then such obligations should come with the necessary resources to meet those obligations. Academic funding for administration and compliance is close to non-existent and so, ultimately, the message from the EU becomes both contradictory and confusing as it simultaneously states: patient safety and validity of data are important, but not important enough to be paid for. The result is that patient welfare – positioned at the core of the Declaration of Helsinki – may become corroded.

The core criticisms of GCP derive from a misunderstanding of risk management, coupled with the ever-increasing costs required for full compliance. Access to funding is materially different in academic and commercial environments leading to an uneven playing pitch where universities and hospitals are being priced out of the clinical trial field due to increasingly burdensome obligations designed for industry. If such a trend remains unchecked, clinical trials may only be conducted by those with the deepest pockets, potentially resulting in an erosion of unbiased studies due to the inevitable conflicts-of-interest that may arise. A rebalancing of processes, risks and resources is required to produce a framework that maintains patient safety and data validity, but incorporates realistic management systems that protect and sustain a vibrant and independent clinical research environment.

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