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Reducing Bureaucracy in Clinical Research: A Call for Action

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The increasing administrative burden associated with conducting clinical trials is a threat to patient safety, independent academic clinical research, and access to affordable innovation. While the Clinical Trials Regulation[1]—adopted by the European Parliament in 2014 to replace the Clinical Trials Directive[2] (from 2001) and finally expected to become applicable in the course of 2020—will go some way in addressing bureaucracy overload, more action is needed. This article discusses the issues resulting from the exponential growth of regulatory and administrative requirements for the conduct of clinical studies and the impact this is having on researchers and patients. It also describes how the European Hematology Association (EHA) is coordinating a series of activities to advance potential solutions for these issues.

Issues of safety reporting

Nothing is more important than the safety of our patients in clinical trials and there is a need to communicate new and important safety data to investigators. However, researchers now receive a significant amount of information on (1) side effects that are already well known, (2) side effects alleged to be treatment-related that are not, or (3) suspected unexpected serious adverse reactions (SUSARs) that are revealed to be neither unexpected nor serious.[3] This large and uncontrolled volume of information is now diluting and masking the truly important SUSAR reports, thereby compromising patient safety. It is evident that this issue is due, in part, to the overinterpretation of regulations by Contract Research Organizations (CROs),[4,5] which require even minor events to be documented and reported to fulfill the frequent audits and inspections to which they are subjected.[6] A simplified and less ambiguous formulation of the laws would help to prevent the overinterpretation of legislation. However, it is important to stress that physicians should not be encouraged to under-report serious adverse events (SAEs), as seemingly minor events could be significant if they occur in large numbers of patients.

Another issue with regard to safety reporting during clinical trials is that reported adverse events (AEs) tend to reflect investigators' impressions of these events rather than actual patient experience.[7,8] The methods currently used for detecting AEs in clinical trials are recognized as having limitations.[9] It has been suggested that direct reporting of AEs by patients, as opposed to relying on data recorded by clinicians or trial practitioners, could be a better approach that would both improve the quality of safety information and allow the earlier detection of SAEs.[10,11] We envision the introduction of simplified risk adapted reports, integrating data from electronic medical records.

We strongly recommend that regulators involve the key stakeholders—clinical researchers and patients—in the drafting of guidance documents for safety reporting. It is promising that the latest revision of the questions and answers document on Clinical Trials Regulation by the Directorate-General for Health and Food Safety of the European Commission now includes a separate chapter on safety reporting.[12] Furthermore, the US Food and Drug Administration (FDA) is currently revising its guidelines for safety reporting[13] and has recently issued a related questions and answers document.[14]

Informed consent forms

Several issues have been identified with the current informed consent process for participation in clinical trials. Informed consent forms (ICFs) are often too complicated for trial participants to understand, use complex scientific terminology, and demonstrate poor readability.[15] In addition,

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they are often too long and cannot easily be translated into multiple languages.[16] As a result, many participants, especially those from less developed countries, may not understand the clinical trial despite having signed the ICF.[15]

In the USA, it is required to include a key information section summarizing the ICF, but patients are still expected to read the complete form.[17] We suggest that the key information page in an ICF be considered sufficient and only this page should be mandatory, with further details available for those who are interested. We also feel that ICFs should be critically reviewed by patient representatives and that their opinions should carry more weight than the opinions of lawyers, given that the document is aimed at patients.

Another issue is that re-consent is often required during the course of a clinical trial due to ICF amendments, but this can cause confusion and anxiety among some participants.[18] It has been suggested that the re-signing of consent forms should only be necessary for ethical reasons, such as to protect participants from harm in the event of new findings about AEs, to maintain participant autonomy, or in the case of legally defective ICFs. Additionally, research review committees such as institutional review boards should oversee the re-consent process to ensure that participants are not contacted unnecessarily.[18]

As a starting point to simplify ICFs, EHA is developing a European ICF template through discussion with multiple stakeholders, including patient representatives. Another solution to the issue could be to make clinical trial documents publicly available to enable patients and other interested stakeholders to provide input into the ICFs. Alternatively, ICFs could be developed through procedures used for the drafting of other patient-focused documents, such as package leaflets. The latter must strictly adhere to the European Medicines Agency (EMA) Quality Review of Documents template and official glossaries,[19] and their readability is validated and continuously reviewed.[20]

Regulatory challenges

The administrative demands associated with current regulatory processes for the conduct of clinical trials are time consuming, at times clinically irrelevant, and partly responsible for the rising costs of developing new drugs.[3] CROs are necessary to manage this increasing amount of administration, but their personnel are not always experts in the area under investigation. Consequently, researchers often receive numerous queries from CROs that are unimportant yet involve an inordinate amount of paperwork.[3] By law, clinical trial sponsors are ultimately responsible for the conduct of their clinical trials and, therefore, retain responsibility for the management of any contractor, including associated bureaucracy and any impact it may have. As a practical solution, regulators could set a framework for the conduct of CROs to prevent bureaucracy from spiraling out of control. If left uncontrolled, bureaucracy and the increasing costs of conducting clinical trials could lead to the disappearance of independent academic clinical researchers, particularly new researchers who may not have a supportive infrastructure to cope with these ever increasing administrative demands.[3]

Another channel for addressing these two interrelated issues—overinterpretation/over-reporting and an imbalanced relationship between CROs, sponsors and investigators—is the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH, which brings together regulatory authorities and the pharmaceutical industry, has released the E8 revised guideline on General Considerations for Clinical Trials for public consultation[21] and is also revising guideline E6 on Good Clinical Practice.[22] We are heartened to see that multiple stakeholders including healthcare providers, academia, and patient organizations, are being invited to participate in workshops organized as part of the revision process.

Role of EHA

EHA is identifying specific issues[23] and is facilitating discussions between clinical researchers, regulators, and other relevant stakeholders to address the issues resulting from the increasing administrative burden associated with conducting clinical trials. As a first step, a workshop was held at the EHA Executive Office in The Hague on June 27, 2019, to discuss bureaucratic obstacles in clinical research.[24] This workshop was attended by different stakeholders involved in the legislation and conduct of clinical trials, including clinical researchers, the European Commission, EMA, FDA, and patient organizations. As a follow-up to this meeting, EHA is actively participating in revisions of the ICH E8 and E6 guidelines and has provided input to the European Commission on the latest revision of the Clinical Trials Regulation questions and answers document.[12] EHA is also aligning with key stakeholders, including the Biomedical Alliance in Europe, to develop specific actions. These include the creation of a 'conduct of clinical research' roadmap and a consensus opinion document on ICFs (for sharing with the European Commission). In addition, EHA is engaging with clinical researchers and patients outside of the hematology community to encourage cross-disciplinary debate of the current challenges associated with the conduct of clinical research.

Call for action

We call on regulators to ensure structural involvement of patients and clinical researchers in the formulation of informed consent forms and guidance documents for safety reporting and other aspects of clinical studies. Regulators should also set a framework for the conduct of CROs to prevent bureaucracy from spiraling out of control.

Clearly, bureaucracy in clinical research is a challenge faced not only by hematologists and their patients. EHA therefore calls on medical societies and patient organizations across disciplines to work together to develop a 'roadmap towards patient-centric, bureaucracy-light clinical research' in close dialogue with industry, policymakers, and regulators. Collectively, we must ensure that the interests of patients and clinicians are placed back at the center of the design and implementation of clinical trials.

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