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editorial

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The ambivalent place of ethics in European regulatory documents

Introduction

It is by now widely known that the field of bioethics was born from scandal: the Nuremberg Code was a response to the Nazi atrocities and the Belmont Report to the Tuskegee Syphilis experiments [1]. With the birth of bioethics came the push for a universal consensus on the necessity of ethics in research. Thus, by the mid of the 20th century, ethics, i.e., that study that looks into the ''moral permissibility of specific actions and practices [2],'' has been soldered as a necessary companion of clinical development, or research in general. Concretely, this means a universal acknowledgement of a set of imperatives that guide actions and practices meant to ''promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research [3]''.

Working within this framework, within the EU, regulators responsible for clinical development programs are required to take ethics into consideration. Documents such as *Points to consider on GCP inspection findings and the benefit-risk balance* oblige regulators to evaluate the ethical aspects of a clinical development program and to make sure that these ethical aspects are weighed in during marketing authorization application (MAA) deliberations [4]. This role of ethics in MAA deliberations is not only instrumental, i.e., ethics must be considered not only because the unethical aspects of a clinical trial may affect data integrity and scientific value but because upholding ethics is a basic obligation of these regulators. To quote,

> ***It should be noted that extensive non-compliance with ethical principles may indicate more widespread problems also affecting aspects of direct relevance to the benefit-risk assessment. But even if not, they should have consequences for the final conclusion on approvability of the application [4].***

This should not come as a surprise. GCP, the very framework used by these regulators, is defined as both a scientific and ethical document: ''GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects [5].'' However, this is where clarity ends. In this manuscript, we shall demonstrate that though ethics has a place in clinical development programs, exactly what its place is remains unclear in EMA documents pertinent to clinical development programs. By demonstrating such, this manuscript hopes to contribute by pointing to directions for future improvements in terms of clarifying and

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making explicit the place of ethics in clinical development programs.

Specifically, the ambiguous place of ethics in regulatory documents will be demonstrated by showing the following: ethics is a part of and not a part of GCP; the undefined role of ethics in GCP; and the mixed signals on which ethical imperatives are relevant to regulators.

Ethics is part of and not a part of GCP

As we have seen above, GCP is defined as both a scientific and an ethics document. This means that within this context, ethics is a subset of GCP and treating GCP and ethics as two separate entities means forcibly separating a subset (i.e., ethics) from its superset (i.e., GCP). Simply, such a distinction constitutes a logical contradiction.

This contradiction is something that we observe in relevant regulatory documents. In the EC directive 726/2004, for example, referring to clinical trials done outside the European Community, it is said,

> ***. . . it should be verified that these trials conducted in accordance with the** principles of good clinical practice **and** the ethical requirements **equivalent to the provisions of the said Directive (italics and bold mine) [6].***

Or, in the *Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorization applications to the EU Regulatory Authorities*, we read,

> ***. . . clinical trials conducted in countries outside EU/EEA (should be) conducted in accordance with the** principles of Good Clinical Practice **and** equivalent ethical standards **as those applied/requested in the EU (italics and bold mine) [7].***

In these documents, GCP and ethical standards are enumerated, i.e., they are presented as two distinct factors, and thus the contradiction we explained above. Typical of a contradiction, the message we get is, ''ethics is and is not a part of GCP.''

The undefined role of ethics in GCP

Within the ICH-GCP document [5], the very framework of the regulation of clinical development programs, and thus the framework used by regulators, ethics has no clear place. In the entire document, the term 'ethics' or 'ethical' has been used only in four different instances: to define GCP, to state that clinical trials must be conducted in accordance with principles of the Declaration of Helsinki, to talk about the nature and tasks of an independent ethics committee (IEC), and as a topic content of a protocol.

Since the document adopts the Declaration of Helsinki as the source of what is ethical in clinical trials, it does not define what constitutes ethical conduct in clinical trials. To a certain extent, what is ethically acceptable in a clinical trial is left for the IEC to discern. For example, when talking about non-therapeutic trials on individuals incapable of consent, GCP states the following:

> ***When a non-therapeutic trial is to be carried out with the consent of the subject's legally acceptable representative,** the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns **and meets applicable regulatory requirements for such trials (italics mine) [5].***

Or, on a more general note,

> ***The IRB/IEC should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial [5].***

This is the same message when we consult what GCP says must be included in the topic, 'ethics' in protocols. Under that topic, GCP says, ''Description of ethical considerations relating to the trial'' [5].

With these, we are left only with questions. Are IEC's the only body responsible for the ethics of a clinical development program? What about the other regulatory bodies? Could we say that the main responsibilities of the IEC constitute everything that is stated in the Declaration of Helsinki or only those sections of Helsinki that are relevant to the sections of the GCP? What, ultimately, is the role of ethics in GCP?

Mixed signals on which ethical imperatives are relevant to regulators

Precisely because what is ethically relevant in GCP is too implicit if not undefined, in a previous article, we wrestled with the question of the role of ethics in GCP by identifying which GCP articles are also ethically relevant [8]. By looking at the intersection between international ethics guidelines and GCP documents, we have identified the following areas as constitutive elements of the ethics subset of GCP:

TABLE 1

Correspondences between ethical imperatives and GCP guidelines and/or regulations.

Correspondences between ethical imperatives and GCP guidelines and/or regulations
Basic principles (preambles) The interests and the welfare of the research participants prevail over the sole interest of science and society
Scientific validity Scientific design, protocol compliance, and the qualifications of the research staff
Favorable benefit-risk ratio
Independent review REC composition/requirements, REC rights and responsibilities, and the responsibilities of the investigator and/or sponsor
Informed consent Securing consent, information given to the participants, comprehension and voluntariness of the participants, and the use of data outside the protocol
Respect for participants Participant safety, privacy/confidentiality, dissemination of results, compensation, and the responsibilities of researching physicians to the research participants
Publication and registration
Special populations Vulnerable populations in general, persons not able to consent, emergency research, and pregnant or breastfeeding women

We wanted to think that this finally defines the ethics subset of GCP, and hence, the scope of the ethical responsibility of clinical development regulators. But then again, the *Reflection paper on ethical and GCP aspects* [7], i.e., the EMA document which to date is most explicit in terms of the place of ethics in clinical development, includes the following ethical imperatives to the obligations of regulators: ethics committee and national regulatory authority oversight; informed consent procedure; confidentiality; fair compensation; vulnerable populations; placebo and active comparator; access to treatment post-trial; and applicability of data to EEA population.

By quickly looking at this list and comparing it to Table 1 above, clearly, the last three topics, i.e., placebo and active comparator; access to treatment post-trial; and applicability of data to EEA population, obviously are not included in the original ethics subset of GCP. Simply, these three topics were not in the original ethics mandate of regulators, if by mandate we refer to the contents of GCP. Hence, the question, should placebo and active comparator, access to treatment post-trial, and applicability of data to EEA population, as ethical aspects be included in the ethics mandate of regulators? This means that above and beyond their responsibility to look at these issues from a scientific perspective, they also have to judge their ethical acceptability? Which ethics imperatives truly form part of the ethics subset of GCP?

Conclusion

The modest goal of this manuscript is to point to the need to define and specify the place of ethics in the regulation of clinical development programs. We have seen that ethics has an ambiguous place in regulatory documents specifically because ethics is a part of and not a part of GCP; ethics has an undefined role in GCP; and the lack of clarity which ethical imperatives are truly relevant to regulators. This ambiguity most definitely has repercussions on how the term 'ethics' is used in clinical development programs, but also on how ethics imperatives are implemented and regulated on such programs. The need to look into the repercussions of this ambiguity is heightened by the globalization of clinical trials: as clinical trials quickly go global, the role of regulators in upholding ethical standards must be specified and harmonized.

Conflicts of interest

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