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Regulatory sanctions for ethically relevant GCP violations

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Although EU inspectors and clinical assessors are mandated to identify and act upon ethical issues, regulators lack guidance on how this can be done. Hence, we propose a four-step regulatory approach on ethically relevant GCP violation findings. The first step is identification of the ethical issue. Next is analysis [i.e., identifying the gravity (intensity or severity) and the magnitude (amount and duration) of the ethics violation as well as the responsible person(s) or entity or entities]. The third step is evaluation, (i.e., the process of deliberating to determine the significance of the ethics violation, with the intention of identifying the most reasonable sanction and/or corrective or reparative action). Last is decision-making or the process of choosing and implementing a regulatory course of action.

Introduction

The contemporary history of ethics in the regulation of human experimentation brings us back to the Nuremberg Code, which was then followed by several other guidelines such as the Helsinki Declaration [1] and the Council for International Organizations of Medical Sciences (CIOMS) [2] guidelines. Foundational among these research ethics guidelines is the principle of respect for human rights. The latest version of the Declaration of Helsinki, for example, states 'although the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects' [1]. The CIOMS guidelines in effect uphold this same respect for human rights: 'researchers, sponsors, research ethics committees and health authorities have a moral obligation to ensure that all research is carried out in ways that uphold human rights . . . ' [2].

Integral to the upholding of human rights is accountability [3]. In the sense that these ethics guidelines uphold human rights in the practice of human research, these guidelines are all accountability measures. By 'accountability' we refer to 'the relationship of . . . duty bearers to the rights holders affected by their decisions and actions' [3]. Accountability has three elements: responsibility, answerability and enforceability. By 'responsibility' we refer to the existence of 'clearly defined duties and performance standards' of those in a position of authority, thus enabling the rights holder to assess the duty bearer transparently [3]. 'Answerability' refers to the requirement that the duty bearer provides 'reasoned justifications for their actions and decisions' to the rights holders [3]. Lastly, 'enforceability' refers to the requirement of public institutions to provide the following mechanisms: monitoring of the compliance of the duty bearer to standards;

sanctions to duty bearers in case of noncompliance; and corrective and remedial actions [3].

Guidelines specifically fall within the responsibility element of accountability (i.e., in the case of clinical trials they provide a specification of the responsibilities of the sponsor and the principal investigator immediately to the participants but probably also to the larger patient population). Nevertheless, these ethics guidelines would not be effective when the answerability and enforceability elements of accountability are lacking. To ensure that guidelines would have the assistance of the force of laws [4], aspects of these guidelines were incorporated into laws and regulations such as 45 CFR 46 (USA) and the E6 Good Clinical Practice (European Union, Japan and the United States), the latter being an 'ethical and scientific quality standard for designing, conducting, recording and reporting trials

that involve the participation of human subjects' [5].

The incorporation of ethical mandates into regulation must be followed by the provision of specific indications to make it possible for the sponsors to provide reasoned justifications for their actions (i.e., answerability) and for public institutions, in our case the pharmaceutical clinical trial regulators, to monitor compliance, provide sanctions to noncompliance and impose corrective and remedial actions (i.e., enforceability). To a certain degree, in the EU, there are already means in place for the sponsor to be answerable: sponsors provide inspectors with responses to the latter's initial findings. Insufficiencies, however, are more obvious when it comes to enforceability: although monitoring is already being done (including, to a certain extent, the monitoring and inspection of unethical conduct), at least within the EU, the provision of sanctions and corrective or remedial actions by regulators on retrospectively discovered unethical conduct are still works in progress.

In a previous publication, we demonstrated that, because pharmaceutical regulators use GCP as a framework, they are mandated to do (at least some) ethics assessments and identified which of the GCP articles are also ethical imperatives [6]. We also showed which ethical issues are frequently encountered by European drug regulators, post-trial [7]. In this manuscript, we wish to address the task of regulators to act upon ethical issues in clinical trials (i.e., their task to provide sanctions – imposing penalties – and/or corrective and remedial actions). Because regulators usually encounter ethical issues during clinical inspection or marketing authorization evaluation [7], we wish to respond to the question: how could regulators approach retrospectively identified unethical conduct during clinical assessment? Assuming that decision making is a fourfold approach of analysis-evaluation-treatment decision-making [8], and that data and scientific issues have already been cleared by the regulators, we propose the following four-step method.

Identify what the ethical issue at hand is

Before analyzing the problem at hand, it is first important to identify the nature of the ethical issue. Is this an informed consent issue or perhaps a participant safety issue? At this point, it is likely that regulators will identify more than one ethical issue. In which case, the act of defining or framing the ethical issues becomes important [9]. For example, the ethical issues present are: lack of sufficient information about risk in the informed consent form in one site; lack of follow-up on severe

adverse events on 50% of the sites; the fabrication of data by some clinical trial staff in some of the sites; and lack of adequate monitoring in all the sites. Regulators can choose to address these issues individually or frame these issues as part of a bigger ethical issue. If regulators choose to see these issues as part of a bigger issue, they might probably choose the issue of lack of efficient monitoring in all the sites, for example, with the other ethical issues as consequences. This means the deliberation process that will ensue will see the lack of monitoring as focal, with the other ethical issues as inputs in the analysis and evaluation.

Analysis: identify the gravity and the magnitude of the ethics violation as well as the responsible person(s) or entity or entities

If the decision-maker decides that the violation is an ethical issue, analysis should ensue. Analysis refers to the 'systematic use of information' [10], which in our case is meant to enable the possibility of ethical evaluation. But, what sort of information is necessary for this evaluation? When analyzing ethics violations, it is best to make a distinction between gravity and magnitude because we are not only dealing with ethical violations of various intensities (i.e., gravity); these violations can be systemic or isolated, multi-site or only in one site (i.e., the magnitude).

Note that inspectors are required to grade a discovered GCP issue during inspections either as critical, major or minor, depending on the probability of how 'conditions, practices or processes' might 'adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data' [11]. If the decision-maker identifies a GCP issue also as an ethical issue, because inspectors are not necessarily analyzing the issue from an ethical perspective, the inspectors' grade of major or critical should be taken more as a signal to the decision-maker that this issue might also be grave or intense (or both) from an ethical vantage.

Gravity

Gravity refers to the intensity or severity of the violation using ethics standards. There are two main types of human rights violations: coercion and harm [12]. Coercion is threatening or violating another person's freedom [12] (some prefer the term: voluntariness) [13], whereas harm involves 'removing or threatening the basic, nonsubtractive or additive goods to which all persons have rights...' [12]. Note that, although the traditional decision-making literature makes a distinction between certain and probable harm, we will not adopt that distinction in this approach. Because the very threat of

removing a 'good' or violating one's freedom is sufficient to consider an act as a violation of human rights, there is no sense in making a distinction between certain or probable harm.

The three goods, in descending order of importance, refer to the following: basic goods are essential preconditions for human actions such as life, freedom and physical integrity; nonsubtractive goods are abilities and conditions that maintain one's level of purpose-fulfillment and capabilities for particular actions; and additive goods are abilities and conditions that increase one's level of purpose-fulfillment and capabilities for particular actions [12].

Human rights violations can then be assessed for their gravity using these categories. For example, coercion, a violation of one's freedom that is essential for 'having a continuing long-range effective ability to exercise control over one's behavior by one's unforced choice' [12], by virtue of its direct threat to human action in general, is usually grave. Second, because well-being consists of the hierarchy of the three goods [12], this hierarchy is reflected in harms as well (i.e., the violation of basic goods is graver than the violation of nonsubtractive goods, which in turn is graver than the violation of additive goods).

Going back to ethically relevant GCP findings [7], examples of findings that are grave in the sense that they are either coercive or are basically harmful are the following: trials with no informed consent (coercion); severe adverse event not reported nor clinically evaluated (harm to a basic good, i.e., physical integrity); lack of performance of safety procedures (harm to a basic good, i.e., life or physical integrity). Using this standard, we can say that not following up on participants' reports of serious adverse events (harm to the participants' basic good, i.e., physical integrity) is graver than providing them with an informed consent that insufficiently informs about the possible benefits of a study. We shall use 'low', 'moderate' or 'high' to calibrate gravity, with high referring to violations that harm basic goods and low referring to violations that harm additive goods (Table 1).

Magnitude

Magnitude, by contrast, refers to the amount and the duration of the damage [14]. Amount of damage refers to the number of persons who were harmed relative to the total number of participants (one person as opposed to damage due to systemic causes). Duration refers to the length of time of the damage. Thus, the systemic lack of patient follow-ups during severe adverse events is greater in magnitude than an isolated case, and a sustained isolated case is greater in magnitude than an isolated case of a limited

TABLE 1

Gravity scale

High	Harm to a basic good (e.g., threatening loss of medical care without research participation; not following up on a participant's serious adverse event)
Moderate	Harm to a nonsubtractive good (e.g., lying to participants by, for example, denying or minimizing a considerable risk)
Low	Harm to an additive good (e.g., not sufficiently informing the participants about the benefits of a study; in some situations, lack of access to ancillary care)

time. Low, moderate or high shall also be used to calibrate magnitude, with high referring to ethical violations that are systemic and multisite given a considerable amount of time and low referring to ethical violations that are time-limited isolated cases. Fig. 1 demonstrates the magnitude scale with some of the possibilities in between the two extremes.

Responsible person or entity

Finally, ethical evaluation will be pointless without knowing who is responsible for the ethical violation; hence, the responsible person(s) or entity or entities must be identified. Inspection reports also aid in this process because responsible persons are identified in these reports (i.e., it could be the CRO, the IRB, the investigator, the sponsor, the laboratory or a combination of these various actors) [15].

Evaluation: deliberate on possible courses of action

Evaluation for our purposes refers to the process of deliberating on the given information gathered

during analysis to determine the significance of the ethics violation with the intention of identifying the most reasonable sanction and/or corrective or remedial action. Justice demands restitution or compensation when human rights are violated. The purpose of such an action is primarily to correct the injustice but also to prevent future violations (i.e., it includes the third step in decision-making: treatment, the process of deliberating on and selecting harm or risk mitigation measures) [10]. Hence, the question regulatory decision-makers need to answer is: which sanction and/or corrective or remedial action demands the least from the responsible person or entity but at the same time restores justice and deters future violations efficiently?

When deliberating on sanctions and corrective or remedial actions for the sponsor or the CRO, for example, we ought to relate the list of possible sanctions and corrective or remedial actions to the magnitude and the gravity of the ethical violation. Box 1 contains a nonexhaustive list of possible sanctions and corrective or remedial actions for the sponsor or CRO, in

descending order. Assuming that magnitude and gravity are of equal weight, the sanctions and/or corrective or remedial actions could reflect those shown in Table 2.

As can be seen from Table 2, assuming the reparative concept of restorative justice that requires the repairing of the harm to people and relationships [16], restitution should be prescribed when either gravity or magnitude is at least moderate (i.e., in terms of gravity, at least a nonsubtractive good has been harmed, or in terms of magnitude, the ethics violation is more than an isolated case within a limited timeframe). Because the violation of a nonsubtractive good means diminishing a pre-existent ability or condition that is meant to maintain one's level of purpose-fulfilment, the goal of restitution is to 'restore' or make-up for the diminished abilities and conditions. Because the violation of an additive good does not diminish any pre-existent good, we cannot speak of any form of 'restoration'. The same could be said for magnitude – gravity aside, an isolated violation within a limited timeframe is negligible relative to a consistently robust functional system. Hence, an ethical violation that violates an additive good such as insufficient information about the study's benefits in an isolated case would not require restitution but could be a warning. At the same time, any ethical violation that is above moderate, either in magnitude or gravity, could require graver sanctions on top of restitution.

The choice of the sanction and/or corrective or reparative action realistically would depend not only on the gravity and the magnitude but on other concerns such as the possible harm to (future) patients, the number of ethically relevant violations and other subjective or objective factors that would sway the deliberation process from the minimum possible to the maximum. In any group decision-making, these other factors are of course expected and could be acceptable provided that their role is made explicit in the deliberation process and that their weight in the decision-making process does not unjustifiably tilt the decision-making process. The restrictions in terms of possible sanctions are safeguards against this unjustifiable tilting of the decision-making process. Note that our list of sanctions and corrective or reparative actions probably is not exhaustive. Also, apart from the sanctions, it might also be worth considering making the violations known to the public for transparency purposes. In any case, the principle of restitution when at least the gravity or the magnitude is moderate should be a default principle (i.e., it applies unless otherwise).

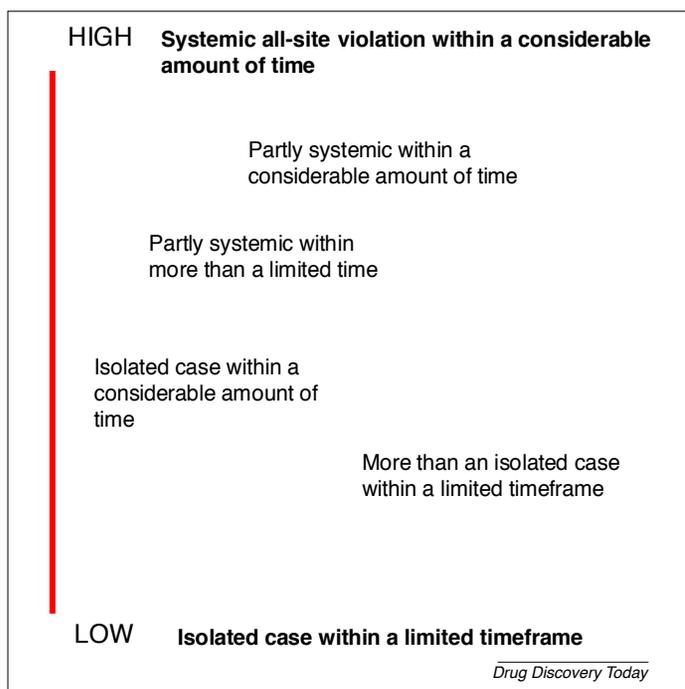


FIGURE 1

Magnitude scale showing some of the possibilities in between the two extremes.

BOX 1

List of possible sanctions and corrective or remedial actions for the sponsor or CRO

- Nonacceptance of data + restitution (NA + R)
- Legal sanctions + restitution (LS + R)
- Restitution before further consideration (R)
- Warning (W)
- Do nothing, considering the corrective and preventative actions response of the sponsor is satisfactory (DN)

TABLE 2

Possible sanctions for the sponsor or CRO given the gravity and the magnitude of the ethics violation

MAGNITUDE	High	LS+R R	NA+R LS+R R	NA+R LS+R R
	Moderate	R W	R	NA+R LS+R R
	Low	W DN	R W	LS+R R
		Low	Moderate	High
		GRAVITY		

Decision-making: decide on the course of action

The last step is the agreement among the regulators on what the sanction and/or corrective or reparative action ought to be and the consequent imposition of the sanction and/or the action. Apart from the agreement, the regulators should also decide on how the sanction and/or action must be implemented (i.e., questions such as what timeframe, which regulatory agency should do the implementation, which restitutionary actions have priority, among others, must be settled).

Limitations

We acknowledge that combining regulatory and nonregulatory policy instruments (such as information and education, co-regulation, voluntary approaches, among others [17], could be the best means to improve compliance to GCP ethical mandates. In this manuscript, we limited ourselves to regulatory policy instruments. There is need for work in the future on the most efficient manner to combine regulatory and nonregulatory policy instruments. Also, we limited ourselves to regulatory action post-violation. It is of course best to avoid unethical conduct even before or at least during clinical trials. Future work is also needed to explore means to avoid unethical

conduct during clinical trials. Reflections on nonregulatory policy instruments should all be geared toward this avoidance.

Concluding remarks

Pharmaceutical clinical trial regulators are expected to act upon ethical issues. In this manuscript, we propose a four-step process: identification of the nature of the ethical issue, analysis, evaluation and decision-making. After the GCP issue has been identified as ethical in nature, regulators must then assess the ethical violation in terms of gravity, magnitude and the responsible person(s) or entity or entities. From which, the regulators must evaluate which sanction and/or corrective or reparative action is most justifiable (i.e., which one requires the least from the responsible person or entity but at the same time restores justice and deters future violations efficiently). Lastly, the choice of sanction and/or corrective or reparative action must be decided upon, imposed and implemented.

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