Ethical implications of procedural or protocol adjustments to clinical research involving the participation of human subjects during the COVID-19 pandemic

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Abstract

The current coronavirus disease 2019 (COVID-19) pandemic has led to essential adjustments in clinical research involving human subjects. The pandemic is substantially affecting most procedures of ongoing, as well as new clinical trials related to diseases other than COVID-19. Procedural changes and study protocol modifications may significantly impact ethically salient fundamentals, such as the risk-benefit profile and safety of clinical trial participants, which raise key ethical challenges the subject-matter experts must face. This article aims to acquaint a wide audience of clinical research professionals, ethicists, as well as the general public interested in this topic with the legal, ethical and practical considerations in the field of clinical trials during the COVID-19 pandemic and to support the clinical researchers and study sponsors to fulfil their responsibilities in conducting clinical trials in a professional way that does not conflict with any legal or ethical obligations.

Keywords: clinical research, clinical trials, COVID-19, ethics, medical ethics, regulatory adjustments, research ethics, risk management

Introduction

Clinical research professionals are generally well aware of applicable regulatory guidelines, scientific standards and ethical principles (i.e., beneficence, nonmaleficence, respect for autonomy and justice), and they are used to conduct clinical trials in compliance with all pertinent requirements. Neither study sponsors² nor clinical investigators were prepared for the disruption triggered by the current COVID-19 pandemic that was caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 virus), which significantly impacted the conduct of clinical trials globally. The necessity for strict social distancing to impede transmission of the coronavirus, as well as the scarcity of research resources affected clinical researchers' ability to successfully continue or complete clinical trials, they were conducting prior to the current pandemic. According to a project supported by the National Center for Advancing Translational Sciences and National Institutes of Health, the COVID-19 pandemic had an indisputable impact on the number of completed clinical trials in 2020. The project assessed the impact of the COVID-19 pandemic on the number of both, submitted and completed interventional clinical trials by analysing 117,000 clinical trials across different regions and sectors that had been registered on the ClinicalTrials.gov database. Data from the December 1, 2019 to the December 1, 2020 was compared. For given regions (United States, Asia and Europe) and sectors (pharmaceutical and academic clinical research), the COVID-19 pandemic had a stronger impact on the number of completed clinical trials in 2020 with a decrease ranging from 13% to 23% depending on the region, sector and whether COVID-19 related clinical trials were included (Hawila & Berg, 2021).

General considerations that led to modifications of the clinical trials conduct should have been based on a risk assessment in order to address prioritization of the safety, confidentiality and privacy of clinical trial participants, as well as to prevent, reduce or minimize missing data, and thus, to ensure data integrity and reliability. According to the Guideline for good clinical practice E6(R2), study sponsors “should implement a system to manage quality throughout all

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² Sponsor means “an individual, company, institution or organisation which takes responsibility for the initiation, for the management and for setting up the financing of the clinical trial” (EMA, 2014, p. 12).

stages of the trial process. Sponsors should focus on trial activities essential to ensuring human subject protection and the reliability of trial results. Quality management includes the design of efficient clinical trial protocols and tools and procedures for data collection and processing, as well as the collection of information that is essential to decision making” (EMA, 2016, p. 30).

Ethical frameworks for clinical research

Ethical concerns play a significant role in establishing the processes and procedures for conducting clinical trials in a way that protects human subjects and minimizes risks while still advancing the public interest and enhancing benefits to individuals and society. Ongoing attention to the ethical concerns is crucial to ensure that clinical trials remain moral, and the research results will be valid.

Essential ethical frameworks are included in the following influential documents, and provide ethical guidance for clinical research ethics: The Nuremberg Code (1947) was based on universal principles of natural law and human rights, and established the fundamental principle that the participation in research requires the voluntary informed consent of the participating subject. The Declaration of Helsinki is an official policy of the World Medical Association (WMA) that was adopted for the first time in 1964 and has since undergone a number of revisions. The declaration established the first official set of guidelines for maintaining ethical standards in clinical research and emphasized the need to protect the health and interests of research participants. The Belmont Report, that was published in 1979 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, is known for establishing a framework of basic ethical principles – respect for persons, beneficence, and justice – which should assist scientists, subjects and reviewers to understand the ethical issues inherent in research involving human subjects.³ In 1993 the Council for International Organizations of Medical Sciences (CIOMS) published the International Ethical Guidelines for Biomedical Research Involving Human Subjects which superseded Proposed Ethical Guidelines (1982).⁴ There are also many further guidelines provided by the directives of the Council of Europe and the European Commission, and last but not least by the regulatory authorities of individual states (Nardini, 2014). Since each of these guidelines emphasizes certain ethical requirements while eliding others, there were specified the following seven general ethical requirements that provide a systematic framework for determining whether clinical research is ethical: social or scientific value, scientific validity, fair subject selection, favourable risk-benefit ratio, independent review, informed consent, and respect for potential and enrolled subjects (Emanuel et al., 2000).

In 2018 a team of multinational subject-matter experts consisted of ethicists, methodologists, health system leaders, regulators, research ethics committees, research funders and community members initiated a new project in order to identify ethical issues in clinical research and based on their analysis to develop a new ethical guidance document rooted in internationally accepted ethical principles. The guidance will facilitate the conduct of research important to patients, clinicians, and the healthcare system, while upholding the highest ethical standards in research (Taljaard et al., 2018). In 2019 the team reported that new ethical issues were detected that need to be addressed, and that there is a need to discuss ethical topics in new ways. The substantive areas of discussion were consistent with topics in the clinical trials literature, including risk assessments, informed consents, the governance of research activities, the selection of clinical trials participants, the roles and responsibilities of different stakeholders, and the publication and reporting transparency of clinical trials. Their findings suggested that, despite existing guidance on minimal risk and consent approaches (Office for Human Research Protections, 2015), there is a need to develop practically applicable frameworks for the risk

³ For more information see Department of Health, Education, and Welfare (1979).

⁴ For information about the revision process see Delden (2016).

assessment in clinical trials, as well as the guidance with respect to alternative informed consent approaches. The team also stated that addressing the highlighted ethical issues and developing ethical guidance will require multidisciplinary input within a broader and more comprehensive analysis (Nicholls et al., 2019).

Regulatory adjustments to clinical research during the COVID-19 pandemic

Shortly after a public health emergency related to COVID-19 had been declared, regulatory authorities in almost all countries recognized that the public health emergency might seriously impact the conduct of clinical trials. During the COVID-19 public health emergency, clinical trial participants might not be able to travel to a clinical trial site location for study visits and study-specific research procedures or to receive the treatment that should be dispensed on a recurring prescription.

Not only travel limitations affecting clinical trial participants, but also quarantines, other urgent work commitments of clinical site staff, clinical trial site restrictions or closures, interruptions to the supply chain for investigational medicinal products (IMP),⁵ or the risk of an exposure to or acquiring COVID-19 infections of clinical trial participants or health care professionals, are a few examples of unprecedented situations that have arisen numerous new challenges. These challenges led to difficulties in meeting clinical trial procedures, including dispensing, administering or using the investigational medicinal products, in adhering to protocol-mandated study visits, conducting key safety assessments or laboratory and diagnostic testing, which could have an impact on the safety and well-being of human subjects⁶ (Akacha et al., 2020). Therefore, regulatory authorities that are responsible for regulation of clinical trials acknowledged that substantial study protocol modifications could be required and they promptly issued relevant guidance documents which addressed the COVID-19 public health emergency with the aim to support response efforts to the pandemic and to ensure human subjects protection, as well as the reliability of clinical trials results (FDA, 2020, pp. 1–3).

Regulatory adjustments of the European Medicines Agency

Due to the impact of the COVID-19 pandemic on the health care systems and society, as well as the impact it might have on conducting clinical trials and the safety and welfare of clinical trial participants, the European Medicines Agency (EMA) in cooperation with other working groups⁷ issued the guidance document entitled as ‘Guidance on the management of clinical trials during the COVID-19 (Coronavirus) pandemic’. The purpose of the recommendations specified in the guidance was to protect the safety and well-being of clinical trial participants and to maintain the integrity of the clinical trials data (EMA, 2021, p. 3).

Key recommendations of the guidance covered the following aspects:

- Conversion of physical study visits into telephone or video study visits, alternatively postponement, reducing frequency or complete cancellation of study visits;
- A temporary halt of clinical trials at some or all clinical sites;

⁵ Investigational medicinal product means “a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use” (EMA, 2016, p. 11).

⁶ Subject means “an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control” (EMA, 2014, p. 13).

⁷ Such as Good Clinical Practice Inspectors Working Group, the Clinical Trials Facilitation and Coordination Group, a working group of the Heads of Medicines Agency, the Clinical Trials Expert Group, a working group of the European Commission representing Ethics Committees and National Competent Authorities and the European Commission (EMA, 2021, p. 3).

- Interruption or slowing down of recruitment and enrolment of new clinical trial participants;
- Extension of the duration of clinical trials;
- Postponement of clinical trials or of activation of clinical sites that have not been initiated;
- Clinical site closures if it was not feasible for a clinical site to continue participation in a clinical trial. Site closures should be performed without compromising the rights, safety and well-being of clinical trial participants and data validity;
- If unavoidable (based on the risk-benefit assessment for clinical trial participants), transfer of clinical trial participants to clinical sites away from risk areas, or closer to their home could occur;
- In case there was a need for any critical laboratory tests, imaging procedures or other diagnostic tests to be performed for the clinical trial participant's safety or integrity of the clinical trial (e.g., blood specimens, radiographic images, biopsies, ultrasonography, etc.), however, the clinical trial participant could not visit the clinical site, it was acceptable that laboratory, imaging or other diagnostic tests were done at an accredited local laboratory or relevant authorised and certified clinical facilities.
- If shipment of blood samples or other clinical specimens to a central laboratory could not be maintained, analysis should be performed locally and then assessed and properly reported in the clinical study report (EMA, 2021, pp. 4–5).
- In case of a need to re-consent enrolled clinical trial participants, it should be avoided that they visited clinical sites for the sole purpose of obtaining re-consent. If re-consent was necessary for the implementation of new urgent changes in the clinical trial conduct for reasons related to the COVID-19 public health emergency or important safety issues, alternative ways of obtaining the re-consent should be considered. These could comprise contacting the clinical trial participants via telephone or video-calls and obtaining verbal consents. Approved updated patient information sheets and informed consent forms should be provided to clinical trial participants by e-mail, mail or courier before the re-consent is obtained. Alternative ways of obtaining the re-consent should be documented in the clinical trial participants' medical records and supplemented with e-mail confirmation. At the earliest opportunity when the clinical trial participants are able to visit clinical sites for the regular study visits, the re-consents obtained by means of alternative methods need to be confirmed by way of usual consent procedures (EMA, 2021, p. 11).
- Alternative distribution methods for investigational medicinal products to clinical trial participants to avoid treatment interruptions were acceptable. Larger amounts of IMP could be provided to the clinical trial participants than normally provided during regular on-site study visits. Alternatively, the IMP might be delivered to the clinical trial participants by a distributor. The guidance specified conditions of the alternative means, such as a contract between the study sponsor and the distributor should be in place, an agreement with the investigator should be signed, and an appropriate consent of clinical trial participants should be obtained. The consent should be documented in the clinical trial participant's medical records. It should be noted that the distributor should not store any personal data of the clinical trial participant (the participant's name, address and contact details) for a longer period than is required for the purpose of dispatching the IMP. The clinical trial participants' personal data should never be provided to the study sponsor, and the distributor should not have access to the clinical trial participants' health information (EMA, 2021, pp. 11–13).
- As part of the risk assessment, a risk-based approach to monitoring should be taken, focusing on certain clinical sites, data points and processes that are critical to ensure the rights, safety and well-being of clinical trial participants, as well as the integrity of the clinical trial and clinical trial data. As cancelling or postponing of on-site monitoring visits and extending of the period between monitoring visits were necessary, the role of centralised monitoring had an increasing importance during the public health emergency.

Additional off-site monitoring activities included phone calls, video visits, e-mails or other online tools in order to discuss the clinical trial progress with clinical investigators and site staff (EMA, 2021, pp. 14–15).

- Remote source data verification should focus on the quality control of critical data collected in the course of the clinical trial, such as primary efficacy data and safety data. Remote source data verification should only be carried out if adequate data protection, including data security and protection of personal data is ensured (EMA, 2021, pp. 16–17). According to the EMA guidance, “data subject to remote source data verification are likely to require re-monitoring, in particular if it was based on pseudonymised documents, which cannot be considered as source documents, and considering that remote monitoring is expected to only have focused on the most critical information” (EMA, 2021, p. 15).

EU member states were encouraged to implement the harmonised guidance to the maximum possible extent to mitigate the disruption of clinical research during the COVID-19 public health emergency. They should complement the EMA guidance to create additional clarity on specific national legal requirements (EMA, 2021, p. 3). Based on this recommendation of EMA, regulatory authorities of EU member states have swiftly released their own national guidance documents on clinical trial management during the COVID-19 pandemic.⁸

Adjustments of the regulatory authority in the US

The United States Food and Drug Administration (FDA)⁹ issued a guidance document for industry, investigators, and Institutional Review Boards entitled ‘Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency’,¹⁰ which provided general considerations to assist study sponsors in assuring the safety of clinical trial participants, in maintaining compliance with good clinical practice (GCP),¹¹ and in minimizing risks to the clinical trial integrity for the duration of the COVID-19 public health emergency. The guidance was implemented immediately, even without prior public comments, as the FDA determined that prior public participation for this guidance was not feasible (FDA, 2020, pp. 1–2). As large numbers of clinical investigators at European clinical trial sites signed the Statement of Investigators, so-called Form FDA 1572,¹² they also have to follow pertinent FDA regulations. For this reason, the general considerations for study sponsors and clinical investigators specified in the FDA guidance are also included in this paper.

The FDA pointed out that any decision should be based on ensuring that the safety of clinical trial participants can be maintained. Thus, the safety of clinical trial participants was of the utmost importance in determining if and what changes in the clinical trial conduct were needed. Study sponsors, in consultation with clinical investigators and relevant Institutional Review Boards (IRBs) or Independent Ethics Committees (IECs), should assess whether the protection

⁸ National guidance documents can be found here: https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2020_03_CTFG_Link_to_National_guidance_on_CT_management_during_the_COVID-19_pandemia.pdf

⁹ The FDA is a federal government agency in the United States responsible for protecting the public health by ensuring the safety, effectiveness and security of human drugs, vaccines and other biological products for human use, as well as of medical devices.

¹⁰ The document was issued in March 2020. Up to now, the FDA provided several updates to the guidance.

¹¹ Definition of GCP: “Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible” (EMA, 2016, p. 6).

¹² The Statement of Investigator, Form FDA 1572, is “an agreement signed by the investigator to provide certain information to the sponsor and assure that he/she will comply with FDA regulations related to the conduct of a clinical investigation of an investigational drug or biologic” (FDA, 2010, pp. 4–5).

of participants' safety, welfare, and rights might be best served by continuing clinical trial participants in the clinical trial as per the study protocol, or by discontinuing the administration or use of the investigational medicinal product, or even by discontinuing their participation in the clinical trial. Such decisions should depend on specific circumstances, including the ability to conduct appropriate safety monitoring, the nature of the investigational medicinal product, the potential impact on the investigational medicinal product supply chain, the nature and the seriousness of the disease or condition being treated, and the risks involved in switching to an alternative treatment of the disease (FDA, 2020, p. 3). Study sponsors should carefully consider the following aspects of the subsequent clinical trial conduct when deciding on any procedural changes or study protocol modifications:

- Assessing whether the limitations imposed by the COVID-19 public health emergency on protocol implementation pose new safety risks to trial participants, and whether it is feasible to mitigate these risks by amending study processes and procedures.
- Assessing the continued availability of the clinical investigator/sub-investigators to provide oversight of the trial and properly assess and manage safety issues that may emerge.
- Assessing whether there will be sufficient clinical trial support staff given the evolving COVID-19 situation and its impact on staff availability. Are there appropriately trained staff that could be available to handle the expected tasks? Is there adequate equipment and materials for clinical trial support staff?
- Assessing whether clinical investigator sites will remain open to trial participants for required in-person assessments or whether the clinical investigator has the ability to provide required in-person assessments at an acceptable alternate location(s), or whether such protocol-specified, in-person assessments can instead be conducted virtually.
- Assessing the continued availability of clinical trial supplies and continued operations of vendors, especially related to supply of the investigational product and/or to clinical trial supplies that are essential for maintaining appropriate safety monitoring or other key trial procedures. This should include consideration of product stability (shelf life) if the treatment schedule is revised, or if the clinical site is unable to properly store the product for the needed duration.
- Assessing the continued availability of, and support for, information technology systems and any other technological tools needed to support the trial (FDA, 2020, p. 8).

Modifications to study protocols and clinical trial related procedures should address the impact on the informed consent process, protocol-mandated study visits and procedures, data collection, processing and interpretation, clinical trial monitoring, adverse event reporting, and changes in clinical investigators, site staff, or monitors (FDA, 2020, p. 5). As emphasized in the FDA guidance: "In all cases, it is critical that trial participants are kept informed of changes to the study and monitoring plans that could impact them" (FDA, 2020, p. 3).

Adjustments to the study protocol and study-specific research procedures and their ethical implications

During the COVID-19 public health emergency study sponsors had to carefully consider how to mitigate safety risks to clinical trial participants and, therefore, they might need to modify protocol-specified procedures. Clinical investigators should meet all legal and ethical requirements, including all new study protocol or procedural adjustments. Modifications were made to protect the life, safety or well-being of clinical trial participants, however, from another perspective, some changes in study protocols and subsequently in clinical trial procedures had potentially effects on the ethics of conducting clinical trials. The impact of modifications on the clinical trial conduct may have numerous ethical implications that can be categorized into those

that are more related to the risk-benefit profile of clinical trial participants and, thus, to their safety, and those that are more related to the study sponsors and may affect the clinical trial integrity, data interpretability and scientific validity of the clinical trial results.

Although regulatory authorities in numerous countries worldwide published applicable guidelines to support study sponsors and clinical investigators in their decision-making process, it should be emphasized that determining the risk-benefit ratio remains the responsibility of the clinical investigators and study sponsors. This needs to be performed in compliance with the ethical principles of beneficence, nonmaleficence, respect for autonomy and justice (Beauchamp & Childress, 2019) that serve as a basic justification for ethical evaluations in clinical research, as well as in compliance with the seven ethical requirements mentioned above.

Ethical implications related to clinical trial participants and their safety

A clinical trial's risk-benefit profile for each individual clinical trial participant might significantly change during the COVID-19 pandemic. In case clinical trial participants were not able to come to the clinical trial site for protocol-mandated study visits, then such visits were done by telephone or video contact, and thus, study-specific procedures and assessments were either not conducted at all (e.g., vital signs measurements, blood samples collection), or performed by other means (e.g., by using alternative arrangements, laboratories or imaging centres). Reducing visit frequency was also a common study protocol modification during the COVID-19 public health emergency. Such significant protocol adjustments could have substantial impacts on the clinical trial participants safety.

Other ethical concerns and, therefore, risks related to the clinical trial participants safety may be caused by the following aspects:

- Waiting for postponed study-specific research procedures;
- Treatment discontinuation due to supply chain management issues during the COVID-19 public health emergency;
- Assessing investigational medicinal products' responses not performed by a responsible clinical investigator on a regular basis when clinical trial participants were unable to come to the clinical trial sites;
- Prohibited concomitant medication not detected in time;
- Clinical significance of out-of-range laboratory findings not determined when the procedures described in a clinical trial laboratory manual were not followed if clinical specimens' collection and handling were performed in local laboratories;
- Physical examination findings and/or their progression not identified in time;
- Disease progression not determined in a timely manner;
- Clinically relevant changes in health status not identified in time;
- Belated detection of serious adverse events (SAEs);
- Late determination of potential causal relationships of SAEs to the investigational medicinal products;
- Postponed follow-up of clinically significant adverse events and impossibility to perform follow-up until a medical condition stabilizes or is no longer clinically significant;
- Significant difficulties and subsequent risks could also arise from the informed consent interview and discussion conducted by telephone and if the informed consent was obtained by means of an alternative method. Investigators are obliged to discuss all new and important information influencing the clinical trial participants' consent and their willingness to continue to participate in the clinical trial with already enrolled participants. Accordingly, updated informed consent forms need to be provided to the participants and

their re-consent should be obtained before the investigator may conduct any clinical trial specific procedures. It is important to emphasize that in compliance with the ethical requirement of respect for autonomy, clinical trial participants are free to withdraw from the clinical trial treatment and/or the clinical trial for any reason and at any time without giving reason for doing so and without penalty or prejudice. In any case, investigators should allow clinical trial participants to assess the potential risks and to make their own decision about their continued clinical trial participation and provide them ample time and opportunity to inquire about details.¹³ It is questionable whether one telephone call enables enough time for such a decision.

- Last but not least, the risk of exposure to COVID-19 during the engagement in clinical trial-related activities, e.g., during study protocol-specified procedures or protocol-mandated study visits. Other risks with serious safety implications may also be caused by concomitant medication intakes due to the treatment of COVID-19 symptoms.¹⁴

Although not all of these individual risks may have the potential to modify the clinical trial's overall risk-benefit profile, all of them are important aspects to consider what study protocol modifications need to be implemented during the COVID-19 pandemic in order to avoid safety hazards to clinical trial participants and ethical implications they may have. All the ethical concerns listed above are based on experience emerged from the remote GCP audits carried out during the COVID-19 public health emergency by the author of this paper, who also acts as a clinical and research Quality Assurance consultant and auditor. The nature and significance of the concerns were discussed with clinical trial teams and responsible personnel of pharmaceutical companies in order to determine whether there is a risk of a potential ethical issue, to prevent ethical implications or to find ways how to solve situations when ethical impacts have already occurred. It is worth emphasizing that clinical investigators are crucial in identifying any changes in medical conditions of clinical trial participants that are potentially ethically consequential, as well as that the investigators are responsible for protecting the safety of clinical trial participants under the investigators' care and for the control of investigational medicinal products.¹⁵

Ethical implications related to study sponsors

FDA as well as EMA regulations allow modifications made to a study protocol without a prior review or approval by regulatory authorities, if the changes are intended to eliminate an apparent immediate hazard or to protect the life and well-being of trial participants.¹⁶ Therefore, changes in the clinical trial conduct that are necessary to assure the clinical trial participants safety can be immediately implemented with the subsequent submission of the study protocol amendment, its review and approval by IRBs/IECs and regulatory authorities. However, until the study protocol amendment is approved, all such changes are considered protocol deviations and need to be transparently documented. Protocol amendments that are not required to prevent imminent safety risks to clinical trial participants can be implemented after they were submitted to IRBs/IECs and regulatory authorities and their approval has occurred.¹⁷ Clinical investigators and study sponsors should therefore document as protocol deviations any modifications to study protocol-specified procedures that have occurred prior to the approval of the study protocol amendment implementing the modifications (FDA, 2020, p. 4; EMA, 2021, p. 8).¹⁸

¹³ See EMA (2016, p. 25).

¹⁴ All listed ethical concerns are based on personal experience of the author of this paper.

¹⁵ See Code of Federal Regulations (CFR): 21 CFR 312.60.

¹⁶ See 21 CFR 56.108(a)(4), 312.30(b)(2)(ii).

¹⁷ See 21 CFR 312.30(b)(2).

¹⁸ See 21 CFR 312.62.

The main challenging areas that have a significant impact on the ethical conduct of clinical trials for study sponsors are as follows:

- Safety of clinical trial participants and of investigational medicinal products.
The study sponsor is always responsible for monitoring the safety of investigational medicinal products, for evaluating all accumulating safety data, as well as for a sufficient oversight of required reporting of serious adverse events that occur in the course of clinical trials (including submission of expedited safety reports to the regulatory authorities, as necessary, e.g., reporting of suspected unexpected serious adverse reactions, known as SUSARs). However, adjustments that resulted from challenges related to the COVID-19 public health emergency could significantly limit safety monitoring, which represents a new potential risk associated with investigational medicinal products, particularly, if there is a reasonable suspected causal relationship between the IMP and the occurred SAE. This, without any doubt, may potentially affect the risks-benefit profile and the clinical trial's scientific integrity. According to the EMA guidance, study sponsors should continue to follow the safety monitoring and reporting requirements in adherence to EU and national legal frameworks. "When per protocol physical study visits were reduced or postponed, it is important that the investigators continue collecting adverse events from the clinical trial participant through alternative means, e.g., by phone calls or telemedicine visits, as appropriate" (EMA, 2021, p. 6).
- Likewise, belated primary endpoints assessments, as well as important secondary or safety endpoints assessments due to COVID-19 restrictions may affect the clinical trial's scientific integrity.
- Another important challenge that raises the ethical implications for study sponsors is limited or even no on-site monitoring, since monitors may not be able to access clinical trial sites to perform standard monitoring activities, which may result in delayed identification of GCP non-compliances.
Sponsors tried to arrange alternative methods how to maintain monitoring of the clinical trial participants safety and the clinical trial data integrity, such as telephone contacts with the clinical trial team to assess modified clinical trial procedures at clinical sites, or monitoring through video conferencing, alternatively remote monitoring. Compared to the FDA guidance, most regulatory authorities in Europe did not allow to conduct remote source data verification. This could significantly affect risk management processes. It is worth mentioning that study sponsors should document if monitors were unable to access a clinical trial site or if monitoring was postponed, and they should carefully consider further strategy execution.
- Supply chain complications pose another substantial risk and subsequent significant impacts on the safety of clinical trial participants. The public health emergency could affect the feasibility of delivery of investigational medicinal products to clinical sites and subsequently to clinical trial participants. The interruptions might cause problems, which may jeopardize or even harm the clinical trial participants, as well as they may compromise the integrity and interpretability of clinical trial data.
- A key component prior to any implementation of study protocol modifications is a thorough consideration of the consequences to the statistical analysis. Some adjustments may raise important statistical issues that may substantially affect clinical trial results on efficacy and safety of an investigational medicinal product and validity of the data collected during the conduct of the clinical investigation during the COVID-19 public health emergency. Study sponsors should carefully evaluate the extent of missing data as this could lead to a significant loss of important information. Unforeseen intercurrent events raise statistical concerns as they could lead to serious issues and, thus, need additional thorough

considerations. “Some of the unforeseen intercurrent events may even result in the need to change certain endpoints, if the ones originally specified cannot be collected or assessed as planned. Therefore, appropriate missing data handling approaches aligned with the estimand¹⁹ of interest and plausible sensitivity analyses need to be specified” (Akacha et al., 2020). Deaths due to COVID-19 infections could also raise statistical concerns on clinical trial data integrity and the interpretation of clinical trial results.

The ethical interpretation of clinical trial results is essential to ensure the reliability of new knowledge on efficacy and adverse events of any medical interventions for regulatory authorities, as well as for physicians and subsequently for their patients in routine medical practice. Failure to adhere to ethical principles may have serious safety implications for patients caused by overestimation of benefits or underestimation of risks and harms.

- And last but not least, we cannot omit potential issues related to data collected from clinical trial participants by electronic methods using the electronic Patient Reported Outcome (ePRO) systems, i.e., electronic patient diaries and questionnaires. These hand-held devices are designed to be used for symptoms or vital signs reporting on a daily basis and should be completed by the clinical trial participants at home. However, if there was no regular review of data entered into the ePRO devices during the COVID-19 public health emergency, this could represent a new potential safety risk.²⁰

Study sponsors should identify emerging risks or trends, recognize all potential concerns about the safety of clinical trial participants and the integrity of data collected, consider how to mitigate the risks and take appropriate measures to comply with applicable regulatory requirements and guidelines, as well as with the ethical principles. The safety of the clinical trial participants is of primary importance, and risks of involvement in the clinical trial, in particular with additional challenges due to the COVID-19 pandemic, should be weighed against anticipated benefits for the clinical trial participants and society. As mentioned above, according to the EMA guidance, the sponsor should implement a system to manage quality during all stages of the clinical trial process,²¹ and all decisions to modify the clinical trial conduct should be based on a risk assessment. All identified risks should be reassessed as necessary. During the current pandemic, it is expected that study sponsors perform a thorough risk assessment of each ongoing clinical trial, as well as clinical investigators perform a risk assessment of each individual clinical trial participant. The measures that prioritize the clinical trial participant safety and clinical trial data validity should systematically be implemented. It must be noted that in case these two aspects conflict, the clinical trial participant safety is always a matter of greatest importance (EMA, 2021, pp. 6–7).

The above listed ethical concerns may significantly affect the integrity of collected or generated scientific data and the scientific validity and reliability of clinical trial results. Therefore, there is a strong ethical necessity of a regular independent examination of clinical trial related activities and documents²² so as to identify potential ethical missteps and to avoid any non-compliance with regulatory requirements and ethical principles. It is the responsibility of study sponsors to develop evidence-driven strategies to ensure the safety of clinical trial participants and scientific integrity of clinical trials.

¹⁹ An estimand is “a precise description of the treatment effect reflecting the clinical question posed by a given clinical trial objective. It summarises at a population level what the outcomes would be in the same patients under different treatment conditions being compared. The targets of estimation are to be defined in advance of a clinical trial” (EMA, 2020, p. 6).

²⁰ All listed ethical concerns are based on personal experience of the author.

²¹ See EMA (2016, p. 30).

²² Such as independent remote GCP audits.

Practical aspects: GCP audits during the public health emergency related to COVID-19

A primary purpose of GCP audits²³ is to evaluate the clinical trial team²⁴ compliance with a study protocol and relevant regulations and guidelines, to verify that the rights and welfare of clinical trial participants have been adequately protected, to assure the integrity of scientific data reported to the sponsor, to verify that the investigational medicinal products have been maintained and used in accordance with the study protocol, and last but not least, to verify the clinical trial has been adequately monitored. In addition to the above stated purposes of GCP audits, the auditor's assessment of the impacts of modifications of the clinical trial conduct is during the COVID-19 pandemic crucial. Therefore, GCP audits are an effective way to verify and substantiate the compliance with study documents, and legal or ethical requirements.

Particularly in the case of none or very limited on-site monitoring activities during the public health emergency related to COVID-19, there are serious concerns about delayed identification of GCP non-compliance, including protocol deviations not caused due to the impact of the COVID-19 related adjustments. Based on experience raised in the course of remote GCP audits carried out during the public health emergency it can be confirmed that numerous ethical challenges were examined. Some of them led to major, in several cases even to critical nonconformances. Examples of observations, identified by the author of this paper, included, but were not limited to:

- Violation of adherence to GCP standards was observed in the following areas:
 1. Lack of a sponsor's oversight and inadequate management of the study
 2. Principle investigator oversight was inadequate
 3. Inadequate study management by the contract research organization (e.g., Failure to escalate issues)
 4. Lack of accuracy and completeness of data collected:
 - Multiple inconsistencies between source data and electronic case report forms (eCRFs)²⁵ inputs were observed
 - Lack of source data to support eCRFs entries
 - Investigators or another site designee did not review electronic patient diaries/questionnaires data on the applicable website to confirm the correct data entry procedures and ensure that all entries were clear, complete, timely and plausible
 5. Backdating of essential documents
 6. Insufficient informed consent process: No evidence was present that subjects were re-consented as required and that the re-consents were obtained verbally, or if the subjects signed and dated the revised version of the informed consent form with all new information related to study protocol adjustments
- Failure to adhere to study protocol discontinuation criteria
- Failure to report safety information: Numbers of SAEs were not reported to the sponsor and not followed up properly
- Lack of source documents and/or source data to substantiate eligibility criteria
- Critical eligibility protocol deviations were found: Protocol excluded subjects were

²³ GCP audit is "a systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)" (EMA, 2016, p. 7).

²⁴ Clinical trial team is usually comprised of a principal investigator, sub-investigators, study nurses, pharmacists, laboratory technicians and study coordinators.

Principal investigator is "the responsible leader of a team of investigators who conduct a clinical trial at a clinical trial site" (EMA, 2014, p. 13).

²⁵ Case report form is "a printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject" (EMA, 2016, p. 8).

randomized although they were not fully eligible per several inclusion and/or exclusion criteria

- Laboratory results outside of the reference range were assessed as clinically significant, however, no appropriate action was taken
- Failure to comply with study protocol adjustments
- Lack of procedural compliance
- A significant backlog in entering data into the eCRFs²⁶

This is not intended to be an exhaustive list of nonconformances observed during remote GCP audits. Rather, it serves as an overview of some of the serious issues all responsible personnel should be aware of. Most of the major and critical findings were related to monitoring, study management and data management, source documentation/source data, the informed consent process and study protocol compliance. There were also cases of fraud detected during the remote GCP audits. Remote GCP audits have shown that the incidence of fraud in conducting clinical trials is approximately the same as it was prior to the current pandemic. According to research on fraud in clinical trials, there were 13.1% cases of fraud in the total number of GCP audits carried out in 22 European countries during a research period of six years (Jedličková, 2015, p. 135). As these cases of fraud were detected only in clinical trials during on-site GCP audits, it is likely that there could be additional undetected cases of fraud in clinical trials that were not audited. On the basis of data and the experience gained during the further GCP audits conducted by the same clinical GCP auditor, it can be confirmed that the incidence of fraud was slightly increasing after the research had been finished and published.

Clinical research performed in developing countries poses another challenge and raises ethical concerns that might cause significant ethical implications as there are very limited reasonable means to assess compliance of clinical sites during the COVID-19 pandemic. Remote GCP audits are currently the only efficient method to mitigate risks to clinical trial participants and to ensure that vulnerable local research ethics is protected and applicable ethical principles are also respected in developing countries. Particularly, when according to the repeated experience of the author of this paper, as well as the experience of other authors (Tsutsumi et al., 2021), there were no additional observations identified at the subsequent on-site audits carried out at the clinical sites audited remotely.

Although EMA recommended not to perform on-site GCP audits during the public health emergency, or to postpone them, the seriousness of observations identified during remote GCP audits proves that a systematic examination of clinical trial related activities is necessary. The nonconformances observed during remote GCP audits have resulted in multiple safety and ethical risks and, furthermore, raise concerns about the overall accuracy of collected and reported clinical trial data during the public health emergency. Given the number and severity of the audit observations, it was evident that monitoring procedures using alternative approaches were not sufficient. It is therefore recommended that efficient monitoring activities (e.g., remote source data verification)²⁷ should continue during the COVID-19 pandemic to assure confidence that the clinical site's processes of source documentation/data and study protocol compliance are adequate, as well as to ensure issues at clinical sites are identified and/or escalated in a timely manner to allow for prompt corrective actions.

²⁶ All listed examples are based on the compilation of observations emerged from the remote GCP audits carried out during the COVID-19 public health emergency by the author of this paper, who also acts as a clinical and research Quality Assurance consultant and auditor.

²⁷ Remote source data verification was, however, not permissible during the public health emergency related to COVID-19 by majority of regulatory authorities in Europe due to data privacy and data protection regulations (e.g., GDPR).

The nonconformances may seriously impact the accuracy and completeness of the data collected and, therefore, pose a significant risk for the clinical trial participants safety and data quality or integrity. Critical or major nonconformances should be urgently addressed to minimize potential safety, regulatory or business risks. Since ethical implications could be serious, responsible professionals must be held accountable for all critical nonconformances with all potential consequences during the public health emergency as well. Therefore, it is without any doubt that regular independent auditing is essential not only to assure the safety and data quality or integrity, but also to prevent the potential loss of the data collected, particularly during the COVID-19 pandemic.

Given the current insights into the ethical issues, study sponsors have the indisputable responsibility to conduct regular quality assurance activities, such as on-site GCP audits, alternatively remote GCP audits if on-site audits are unfeasible, in order to protect the safety of clinical trial participants, as well as to ensure validity of the clinical trials data. Postponed GCP audits, as recommended by EMA,²⁸ may cause numerous serious nonconformances not identified in time, which may raise significant ethical issues. This leads to ethical dilemmas whether not to carry out any GCP audits during the public health emergency with all the above listed risks (including serious safety risks not detected or assessed in a timely manner), or, whether to conduct remote GCP audits, with all the limitations they may have. There is a clear evidence that remote audits undoubtedly represent an effective mean of performing a compliance assessment of a clinical site and, therefore, they may play an important role in mitigating risks to clinical trial participants. It should be noted that although some aspects of GCP audits cannot be analysed remotely and should be verified on-site, e.g., the evaluation of facilities or specialized techniques, remote GCP audits are considered as a valuable alternative (Geijo, 2020). This was also confirmed by verification experiments of remote auditing in Japan where the remote auditing model was found as feasible and useful as conventional on-site audits and can provide the same level of auditing in terms of the number of observations. In the verification experiments facility tours were conducted with direct viewing via combination of Information and Communication Technology (ICT) tools, e.g. smart glasses (Tsutsumi et al., 2021). Based on the experience gained it can be concluded that remote GCP audits as part of a sponsor's risk-based approach have added value on the quality of clinical trials and on the level of confidence in the GCP compliance status of clinical sites.

Conclusion

It is anticipated that the COVID-19 related adjustments to clinical research that we experienced during last months could be relevant for any other public health emergencies in the future and the current experience may serve as an important precedent. Regulatory authorities, study sponsors and clinical trial teams now have appropriate sets of guiding principles and instructions that can be used in a similar situation and together with the practical experience from the current pandemic may facilitate clinical research preparedness for future public health emergencies.

Due to the significant challenges quality improvement experts and safety professionals are being faced with, study sponsors should identify and realize all effects that the current COVID-19 pandemic may have on the conduct and quality of clinical trials, and how to deal with those challenges. It is highly recommended that study sponsors and contract research organizations have along with a risk management plan also a crisis management plan in place. For example a business continuity plan or a business contingency plan, which is designed to keep a business running in the event of any unexpected disaster. The crisis management plan should minimize

²⁸ According to the EMA guidance, during the COVID-19 pandemic on-site GCP audits, as well as remote GCP audits can be considered only for critical trials. Nevertheless, it was not specified further what clinical trials should be considered as critical trials (EMA, 2021, p. 17).

any potential disruptions and should specify critical items and procedures on how to implement an efficient disaster recovery strategy.

In the light of the acquired experience, it is without any doubt that research ethics continues to play a key role to address effects of the COVID-19 pandemic on clinical trials integrity. All responsible personnel should keep in mind that there is an urgent ethical imperative to conduct only reasonable and meaningful clinical research with the primacy of respect for the clinical trial participants' safety, rights, dignity, humanity and wellbeing. Only such approaches can be effective in efficient clinical trial management and can ensure that the clinical research professionals are well prepared to handle potential ethical issues in order to avoid any negative ethical implications. It is important to develop professional ethical reflection on research ethics in the context of the new unprecedented circumstances in conducting clinical trials. Based on such hindsight and reflections, there should be a wider discussion within subject-matter experts to address each area of concern, and to ensure ethical and scientific quality standards for designing and conducting clinical trials, including efficient methods of monitoring and auditing, as well as for the collection, processing, analysis and interpretation of the clinical trial data generated in the course of the clinical trials during any other public health emergencies. This is a way how to advance the ethical practice of clinical research, to strengthen its credibility, as well as the reliability and validity of clinical trial results, and to create the safe future of clinical research.

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