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*Short communication*

# Regulatory framework for conducting Good Clinical Practice inspections - before, during and after the COVID-19 pandemic

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## Introduction

The Principles of Good Clinical Practice (GCP) define international ethical and scientific quality standards in the planning, implementation, monitoring and reporting of clinical trials conducted on humans. In this context, the protection of the rights, safety and well-being of respondents participating in clinical trials is a priority of regulatory agencies worldwide. Verification of compliance with GCP standards is done through audits and inspections as an exclusive right of the regulatory authorities (ICMRA, 2021). The COVID-19 pandemic have significantly affected the conduct of clinical trials (CTs) and posed unique challenges to all parties (sponsors, clinicians and regulators) involved in conducting of clinical trials. In this regard, deviations from the clinical trial protocol and / or protocol violations were inevitable and had a potential to significantly affect the safety of CT participants and the data integrity as most important aspects that defines the accuracy and reliability of the clinical evaluation (Park et al. 2021). In response to the new situation sponsors, researchers and regulators jointly adopted initial guidelines to ensure the safety of participants, data integrity, compliance with GCP principles (Sathian et al., 2020)

The overall aim of this study is to review and evaluate the effects of the COVID-19 pandemic on global legislation, practical experience and other allied information related to the planning, implementation, assessment and inspection of clinical trials. The specific objectives include review and analysis of the effect of the COVID - 19 pandemic on the local GCP legislation, guidelines and inspections.

## Materials and methods

We performed a systematic search of published evidence and guidelines for GCP and GCP inspection not favoring any type of product - drug, vaccine or medical device. The data and information were collected using public databases of global regulatory agencies - EMA, PMDA, MHRA and FDA. These regulators were selected because of their active involvement in inspection activities around the world and because of their pioneering acceptance of remote inspections during the COVID-19 pandemic. To supplement the findings and discussions, systematic reviews on this topic were retrieved from Medline via Pub-Med database and Google scholar, using the following predefined keywords: "COVID -19"; "Clinical trial", "good clinical practice", "regulatory agencies", "GCP inspections". Additionally, we searched the official websites of the national regulatory authority-Agency for Drugs and Medical Devices of the Republic of Northern Macedonia- MALMED, regarding the clinical trials approved by the Commission for Clinical Trials of drugs and medical devices in the period of January 2019 - April 2022 and inspections of CT conducted by the Commission for assessment of conditions for Good Clinical Practice at MALMED in the same period.

## Results and discussion

The initial search of the biomedical literature resulted in a total of 156 original scientific papers for further evaluation. The previously set criteria of non-preferences were met by total of 30 papers. Most of them, approximately 50%, were published in the second half of

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2020, which indicated the importance and need for a broad scientific, regulatory and professional discussion on the challenges and practical solutions in the regulation of clinical trials as a result of the pandemic. In the period 2020-2022, a total of 10 guidelines and regulatory frameworks for GCP and a total of 9 new guidelines for remote inspections have been published by regulatory agencies. Most of the GCP guidelines are published by the FDA and MHRA. Regarding GCP inspections, most of the guidelines and recommendations were published by FDA and PMDA Global regulatory authorities generally address the following aspects: initiation of new CTs, changes in current CT, reporting security data, risk assessment, communication with competent authorities, agreement with and communication between sponsors, research sites and CT participants, changes in: informed consent, distribution of the researched medical product, distribution of in vitro diagnostic and medical devices, monitoring, supervision, reimbursement of costs and Initiation of new CTs to test new COVID- 19 treatments. In parallel with the development of the pandemic and the need to continuously and proactively address data integrity and maintain the safety of CT participants, site staff and research team as published recommendations and guidelines are continuously being updated. In this context, they are flexible and can be tailored to individual locations, studies and participants based on their specific needs in CT design and methodology and generally apply to the logistics organization and management of CT participants. At national level, diversity has been identified in the readiness of national authorities in EU Member States in defining specific guidelines and recommendations for the implementation of CT.

Regarding GCP inspection, remote inspections were applied even before the COVID-19 pandemic, but their usefulness and implementation have not been documented due to the insignificant degree of practice. In the emerging situation, regulatory authorities and industry were equally quick to adapt to this type of alternative work methods. The requirement for remote assessment and inspection has to be determined on a case-by-case basis. This decision-making process is normally carried out by the lead inspector in consultation with operational management after taking into account the following factors: 1) local or international restrictions in force to deal with public health, emergency, 2) need to protect the health and safety of the inspector, the research team, including reducing the burden while dealing with the pandemic itself, 3) inspected entity's regulatory compliance history, for example, whether there is a history of repeatedly identified deficiencies or issues related to the information provided that could be potentially misleading to the inspector, 4) scope and objectives of the inspection, 5) specificity of the inspection site (e.g. research, bioanalytical, sterile manufacturing) and internal risks/suitability for remote assessment, 6) complexity of the activities that are undertaken and implemented at the location in terms of how challenging it is to observe and adequately assess from a distance, 7) regulatory compliance risks associated with the site, eg. Findings from recent on-site inspection, changes in site-location, delegated corrective measures, remote accessibility of electronic systems due to confidentiality rules, remote access to source documents while complying with regulations and/or institutional policies and the need to redact documents to protect privacy and confidentiality.

In the period from the beginning of the COVID - 19 pandemic until today, MALMED has not issued official national recommendations and guidelines for conducting and for inspection of clinical trials in emergency conditions due to the pending introduction of the new law on drugs and the law on medical devices that are being prepared and from which new bylaws emerge.

## Conclusion

Follow-up research is needed to analyze the effects and determine the best strategies for conducting research in times of widespread communicable disease. Although remote inspections are not a complete replacement for on-site inspections, they have proven their value and should accordingly remain an inspection tool in certain segments and situations of regulatory work with a need for alignment in methods and documentation covered by the inspection. The obtained results enrich the overall knowledge and are of great importance in relation to the need for regulatory standardization and harmonization of our national to the European regulations in the area of conducting clinical studies and inspection of good clinical practice.

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