Greater harmonisation of clinical trial regulations would help the fight against COVID-19

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This brief discusses the existing obstacles in developing international clinical trials that are critical to fight the COVID-19 pandemic. It provides information on relevant adaptations of regulatory requirements for clinical trials, intended to accelerate the processes, and highlights the need to harmonise further these regulations between national regulatory authorities. To this end, this brief describes the existing OECD Recommendation on the Governance of Clinical Trials issued in 2012 and how its implementation could greatly facilitate and streamline the registration and conduct of international clinical trials.

Key messages

- The urgent quest for safe and effective COVID-19 treatments requires international co-operation for conducting clinical trials to test and compare existing and new therapeutics.
- Many national regulatory authorities have set up streamlined and fast-track clinical trial approval processes. However, the lack of harmonisation between national regulations is slowing down the implementation of international clinical trials.
- In order to accelerate the rigorous testing of COVID-19 treatments, governments and regulatory authorities are encouraged to share information internationally and co-ordinate policies for COVID-19-related clinical trial approvals.
- Adopting harmonised risk categories – as provided for in the OECD Recommendation on the Governance of Clinical Trials – is a critical step in harmonising clinical trial regulations across countries, and accelerating the rigorous testing of potential treatments.

Adaptation of clinical trial regulatory processes for COVID-19

Since the global outbreak of SARS-CoV-2 (COVID-19) in early 2020, many research institutions, supported by public and private funders, have taken action to accelerate R&D on vaccines and treatments. As a result, many new pre-clinical research studies and clinical trials have been launched, and hundreds of clinical trials related to COVID-19 have been registered. While most of these are testing drug candidates, several potential vaccines are also being tested. Information on these clinical trials can be found on the World Health Organisation (WHO) website and in the OECD brief Treatments and a vaccine for COVID-19: the need for co-ordinating policies on R&D, manufacturing and access.

Confronted with a massive and urgent demand for new treatments, most national and regional regulatory authorities have developed accelerated clinical trial authorisation procedures for COVID-19 treatments and vaccines; these concern initial marketing authorisation applications as well as extension applications for authorised medicines that are being repurposed for the treatment of COVID-19 (see regulatory updates).

Adaptation of regulatory requirements and processes typically includes:

- Relaxation of the need to conduct a risk assessment for the trial
- Tolerance to deviating from the standard protocol[1]
- Possibilities to delegate part of the trial to sub-investigators and to local sites
- Use of electronic alternatives to paper documentation
- Flexible drug delivery processes to patients[2]
- More flexible and proportionate oversight and monitoring of the trial (using remote mechanisms), and
- More flexible conduct of ethical reviews (although no change to patient safety rules).

[1] Trial protocols are documents that describe the objectives, design, methodology, statistical considerations and aspects related to the organization of clinical trials. Trial protocols must meet a standard that adheres to the principles of Good Clinical Practice in order to obtain ethics approval by local Ethics Committees or Institutional Review Boards.

[2] Allows for the use of commercially available treatments where a subject is unable to receive the investigational drug from the trial site but where the product is approved for other uses.

Some international initiatives have been developed to facilitate exchanges between regulatory authorities on adapted clinical trial registration requirements. The Trial Master File Reference Model (TMF Reference Model), managed under the auspices of the Drug Information Association (DIA) Document and Records Management Community, has conducted a very informative review of national Health authorities' guidance on COVID-19. Efforts have been made to facilitate a common approach and recommend good practices, but the reality remains that complying with the multiple different requirements of different national and regional authorities is delaying the implementation of important studies.

Obstacles remain to conducting international clinical trials during the COVID-19 crisis

Many of the clinical trials for COVID-19 treatments and vaccines have been launched at the national level, and are being conducted by health research institutions within a single country, having only to fulfil the (often accelerated and streamlined) regulatory requirements of a single national regulatory authority. However, the medical community indicated early on that many of these national initiatives, often of limited amplitude, do not provide the robustness that is necessary to effectively validate treatments.

For this reason, a number of international trials have been launched with the goal to recruit enough patients in hospitals from multiple countries to test a diversity of potential treatments and posology and come up with robust enough statistical data to inform relevant regulatory and health authorities.

Solidarity is probably the largest international therapeutic trial initiative and is being fostered by the WHO. The Solidarity Trial will compare four treatment options against standard of care to assess their relative effectiveness in managing patients with COVID-19. By enrolling patients in multiple countries, the Solidarity Trial aims to rapidly discover whether any of the tested drugs slow disease progression and/or improve survival. Other drugs can be added into this trial as it progresses based on emerging evidence of potential usefulness.

Solidarity is not conceived as a traditional single, double-blind clinical trial, but instead provides simplified procedures to enable any interested hospitals to participate, with very little paperwork required. It relies on the overall number of patients enrolled to provide statistically credible data, even if all tests are not centrally controlled and managed, which allows for some protocol variation between hospitals. Nevertheless, and despite its flexibility, Solidarity has run into delays due to the fact that individual national authorities have different views on the protocol and plans. Organisers have indicated that a more efficient and internationally harmonised regulatory approach would have greatly facilitated the trial.

At the same time, a large clinical trial called Discovery is focussing on several antiviral drug treatments. It is led by the French National Institute for Health and Medical Research (INSERM) within the European REACTing consortium, and was planned to link up to the Solidarity initiative. The Discovery trial was expected to enrol several thousand participants across France, Austria, Belgium, Germany, Luxembourg, the Netherlands, Spain, Sweden and the United Kingdom. However, this trial has run into serious difficulties in achieving its initial patient recruitment goals. Obstacles have included differences in regulatory requirements between countries and the unwillingness of some national authorities to cover treatment costs per patient. As a result, patient recruitment as of mid-May 2020 was still largely restricted to France and the trial has come short of its expectation.

Improving harmonisation of regulatory processes for clinical trials is particularly relevant in the context of the COVID-19 crisis

These examples show that, despite the efforts of the clinical trial regulatory authorities to streamline national procedures, there is an urgent need for better international harmonisation of regulatory requirements and processes.

In addition to the challenges presented by the existing national regulatory complexity, clinical trial investigators have to respond to administrative requirements that are not always adapted to the nature of their studies. Existing regulations have mostly been developed to deal with trials which have as their objective the development of new medicines. Because of the novelty of the drug or of the process involved, such trials present an unknown risk for the patients who participate in the studies and therefore necessitate strictly controlled procedures. Those are however often less suited to address trials, which use already marketed products. Such trials, which often attract less commercial interest, are often supported by public funding and led by academic researchers.

The challenges to conducting international trials are not new and there has been a growing demand for better ways of aligning regulations between countries, from both academic researchers and industry. The idea of a new harmonised regulatory framework was behind the development of the OECD 2012 Council Recommendation on the Governance of Clinical Trials (see Box 1).

The Recommendation seeks to improve consistency among national regulations and their interpretations, and to streamline procedures for the oversight and management of clinical trials by introducing a proportionate regulatory approach, while enhancing the protection of participants in research trials.

This harmonisation of regulatory procedures has taken an increased importance with the COVID-19 crisis. In a normal situation, the pharmaceutical industry, which conducts the majority of clinical trials on novel drugs, often uses the support of specialised companies (Clinical Research Organisations, CROs) which are experienced in dealing with national regulations in multiple countries. Even if this may take more time than carrying out trials at the national level only, these companies have the experience and resources needed to carry out international trials when these are necessary.

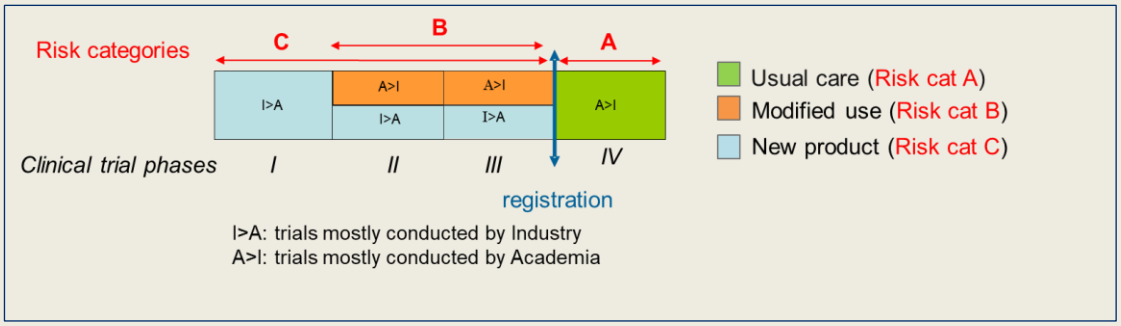
In emergency situations, the diversity of national regulations becomes a real challenge. This is even more the case for public research institutions which do not have the resources to file multiple applications and address multiple different national requirements, but are at the frontline for the testing and discovery of effective treatments. The first action when confronted with new infectious diseases is to test and compare existing drugs and therapeutics (see Repurposing existing drugs for COVID-19 offers a more rapid alternative to a vaccine), and such trials are usually run by the public research sector, while the pharmaceutical industry concentrates on the development of new treatments, which are likely to have a greater financial return.

The OECD Recommendation, which advocates the adoption of a standardised risk-based approach that would streamline clinical trial regulation for existing drugs and therapeutics, and help harmonise regulatory requirements, is thus particularly relevant to the current COVID-19 pandemic.

Governments and key regulatory authorities are encouraged to seize the opportunity provided by the current exceptional situation to significantly advance the international harmonisation of multiple aspects of clinical trial regulations, working with the International Council for Harmonisation (ICH) – which has developed a number of guidelines for the harmonisation of the technical requirements for pharmaceutical products and could facilitate discussion on regulatory standardisation using the lessons learned from the COVID-19 crisis. Other international networks, such as the Clinical Research Initiative for Global Health (CRIGH) whose members represent the needs of public health research institutions, could also make a valuable contribution to this work.

Box 1. OECD Recommendation on the Governance of Clinical Trials

- The OECD Recommendation on the Governance of Clinical Trials is a policy instrument adopted in 2012 that defines a framework for better oversight of clinical trials. It is intended to facilitate international co-operation in clinical trials on medicinal products, particularly for trials initiated by academic institutions.
- Countries adhering to the Recommendation are invited to implement a risk-based oversight and management methodology for clinical trials reflecting a series of principles for risk assessment. These principles combine (A) a stratified approach, generally based on the marketing authorisation status of the medical product that can be applied in legislation or regulation in a common manner across countries, with (B) a trial-specific approach that considers a number of other issues such as additional diagnostic procedures, specific populations concerned, or informed consent.
- Adherents should introduce a definition of risk categories for clinical trials in their legislative or regulatory framework, in line with the following three categories that use the marketing authorisation status of medicinal products to determine the level and uncertainty of risk:



Further reading

OECD (2020), "Treatments and a vaccine for COVID-19: the need for coordinating policies on R&D and access", OECD, Paris,

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OECD (2018), *Pharmaceutical Innovation and Access to Medicines*, OECD Health Policy Studies, OECD Publishing, Paris, https://dx.doi.org/10.1787/9789264307391-en.

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