Recommendation of the Council on the Governance of Clinical Trials

OECD Legal Instruments

OECD

BETTER POLICIES FOR BETTER LIVES

Please cite this document as:
OECD, *Recommendation of the Council on the Governance of Clinical Trials*, OECD/LEGAL/0397

Series: OECD Legal Instruments

Photo credit: © iStock.com/ilyaliren

Background Information

The Recommendation on the Governance of Clinical Trials (hereafter, the "Recommendation") was adopted by the OECD Council on 10 December 2012 on the proposal of the Committee for Scientific and Technological Policy (CSTP). The Recommendation is intended to facilitate international co-operation in clinical trials on medicinal products, particularly for trials initiated by academic institutions. Its primary focus is on improving consistency among national regulations and their interpretations, and on streamlining procedures for the oversight and management of clinical trials, by introducing a proportionate regulatory approach, while enhancing the protection of participants in research trials.

The need for an international standard on the Governance of Clinical Trials

Clinical trials, including tests of new medicines or new therapies, as well as optimising existing medicinal products and procedures, are fundamental to improving health and welfare. This is especially important during worldwide emergency health crises, such as the recent COVID-19 pandemic, when these clinical trials have to be fast-tracked to produce results as quickly as possible. However, while medical investigators, particularly in the public research sector, are increasingly involved in international studies and collaboration, they continue to face a wide array of different regulatory mechanisms across countries. This, combined with the tight national regulations to ensure patient safety and methodological quality, has led to administrative complexity that has led many well-conceived clinical trials aimed at addressing important public health problems to either not be conducted or to be so delayed that their impact is reduced. This is particularly true for the conduct of international clinical trails that involve multiple centres, and for trials initiated by academic structures that may not have well developed administrative support.

It is with this in mind that the OECD Global Science Forum (GSF), a subsidiary body of the CSTP, has worked on a harmonised framework for the better international governance of clinical trials, in which requirements will be based on the risks associated with the study. The Recommendation was developed following extensive consultations and intensive work involving other OECD committees (Health Committee, Chemicals Committee, Environment Policy Committee), as well as relevant stakeholders such as Business at the OECD.

Scope of the Recommendation

The Recommendation contains a set of principles that Adherents should implement to develop a risk-based oversight and management methodology for clinical trials. These principles are built on two approaches:

- 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, and
- a trial-specific approach that considers a large number of other issues such as additional diagnostic procedures, specific populations concerned, or informed consent.

This risk-based approach intends both, to facilitate international clinical trials and to help streamline the procedures for low-risk clinical trials.

For further information please consult:
http://www.oecd.org/sti/inno/oecdrecommendationonthegovernanceofclinicaltrials.htm.
Contact information: gsforum.contact@oecd.org.

Implementation

The 2020 Report on the implementation, dissemination and continued relevance of the Recommendation on the Governance of Clinical Trials, was approved by the CSTP on 9 September 2020. It demonstrates a growing awareness regarding the need to adopt a risk-based approach to oversight and management methodology in clinical research regulation. Although Adherents may still have different interpretations of risk-based regulatory processes, a very high percentage of those Adherents have started to adopt this approach.

Another important and positive element is that Adherents usually adapted their whole regulatory procedures to take into account the consequences of risk categories in the various elements of the regulatory approval process.

However, the Report also reveals a lack of standardisation of regulatory processes between Adherents, even when they have adopted a coherent risk-based approach. This is a major concern as such heterogeneity will continue to considerably hinder the development of international clinical trials, which are essential for evaluating treatments for rare diseases or during emergency crisis, such as the COVID-19 pandemic. The development of common international standards and procedures should, thus, be one area of the implementation process on which Adherents' focus should be particularly in the coming years.

The Report was developed by the GSF through an online questionnaire in 2018 – 2019, but the finalisation of the Report took place after the COVID-19 pandemic started, which allowed for discussions between Adherents on the role of the Recommendation to address the crisis. The key message emerging from the Report that resonates particularly loudly in the context of the COVID-19 crisis is that adopting harmonised risk categories – as proved for in the Recommendation – is a critical step in harmonising clinical trial regulations across countries. The COVID-19 crisis has demonstrated that failure in this regard constitutes a major obstacle to conducting essential clinical trials in response to pandemics.

THE COUNCIL,

HAVING REGARD to Article 5 b) of the Convention on the Organisation for Economic Co-operation and Development of 14 December 1960;

HAVING REGARD to the 2008 Helsinki Declaration on Ethical Principles for Medical Research Involving Human Subjects, and to the E6 guideline of the International Conference of Harmonisation for Good Clinical Practice;

RECOGNISING that clinical trials play a critical role in the development and evaluation of new and effective treatments of human diseases and therefore have a significant effect on public health;

RECOGNISING that the welfare and safety of patients and healthy volunteers participating in clinical trials must be duly ensured and their rights respected, in agreement with internationally recognised ethical rules;

RECOGNISING that the reliability of scientific data generated by clinical trials must be guaranteed, in order to ensure that medical practice is based on sound evidence;

RECOGNISING that many clinical trials are driven by pressing public health needs in areas where diseases and conditions affect only a small number of patients worldwide, or where treatments are not commercially viable, or where trials aim to improve existing procedures and prescribing practices, and that they increasingly involve multi-site international collaboration;

RECOGNISING that differences in national and regional regulations and their interpretation have led to very complex administrative processes, especially for multinational clinical trials;

RECOGNISING that national regulations that adopt uniform approaches regardless of the risk involved and of the objective of the trial may hamper the development of clinical trials, particularly those sponsored by non-profit groups such as universities, hospitals and charities;

RECOGNISING that more coherent and simpler administrative procedures for multinational clinical trials would be of great benefit to public health;

On the proposal of the Committee for Scientific and Technological Policy;

I. **RECOMMENDS** that Members adapt their national regulations and procedures to incorporate a risk-based methodology for the oversight and management of clinical trials, taking into account the principles set out in the Annex to this Recommendation, of which they constitute an integral part;

II. **INVITES** non-Members to adhere to this Recommendation;

III. **INSTRUCTS** the Committee for Scientific and Technological Policy to monitor the implementation of this Recommendation, review it in light of its impact on the quality of clinical trials and on the safety of clinical trial participants, and to report to Council within four years of its adoption and as appropriate thereafter.

ANNEX

I. OBJECTIVES AND SCOPE

This Recommendation is intended to facilitate international co-operation in clinical trials on medicinal products, particularly for trials initiated by academic institutions.

Its primary focus is on improving consistency among national regulations and their interpretations, and on streamlining procedures for the oversight and management of clinical trials, by introducing a proportionate regulatory approach, while enhancing the protection of participants in research trials.

Although this Recommendation is primarily driven by the need to facilitate co-operation among academic groups for clinical trials undertaken for non-profit purposes, Members may wish to extend the implementation of this Recommendation to the oversight and management of all clinical trials, thus adopting principles similar to those enumerated below regardless of the objective of the trial.

II. PRINCIPLES

Members should implement a risk-based oversight and management methodology for clinical trials reflecting the following 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 large number of other issues such as additional diagnostic procedures, specific populations concerned, or informed consent.

A. Stratified approach

A.1. Risk categories

Members 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:

Category A concerns clinical trials on authorised medicinal products (according to national or regional regulations) tested in accordance with their marketing authorisation.

Category B concerns clinical trials on authorised medicinal products tested according to treatment regimens outside their marketing authorisation (in terms of population, condition, administration, or dosage):

1. supported by published evidence or guidance or established medical practice;

2. not supported by published evidence or guidance or established medical practice.

Category C concerns clinical trials on medicinal products without any marketing authorisation.

Members should also take into account the following product-related modulating factors when assigning one of the above categories or subdivisions thereof to a clinical trial, as they may impact the risk assignment, and result in an upgrade or downgrade of the risk level:

- novelty of the medicinal product and/or of its class (including new formulation of a marketed substance);
- innovative nature of the treatment (e.g. advanced therapy/biologics);
- marketing authorisation obtained in other countries.

A.2. Risk assessment

The risk categorisation for an individual trial should be proposed by the investigator and/or sponsor, and later validated by appropriate approval or oversight bodies. These approval or oversight bodies should have access, whenever needed, to external expertise, particularly through requests to the regulatory bodies regarding the status of the medicinal product, and through requests to clinical experts regarding the accepted standard of care.

A.3. Impact of risk categorisation on the oversight and management of clinical trials

Members should ensure that the oversight and management processes of the clinical trials are adapted to the risk category. More specifically:

A.3.1 Ethical review and informed consent

As specified in the Declaration of Helsinki and in the International conference of Harmonisation (ICH) E6 guideline, Members should require that ethical review and approval of the protocol by a research ethics committee or institutional review board be carried out for every trial, regardless of its risk category. Informed consent from every trial participant should be required as a rule regardless of the risk category (exceptions may be granted in specific situations, as described in the provisions of the 2008 Declaration of Helsinki).

A.3.2 Approval of trial by regulatory bodies

Members should require approval by the appropriate regulatory bodies, for instance the Competent Authority, for category B and C clinical trials.

Members may decide not to require prior approval from regulatory bodies for category A clinical trials.

Members should ensure that regulatory bodies are able to access information through trial registration and that they can request further information if needed, or perform inspections. Members should strongly encourage public registration of the key items (including the 20 WHO ICTRP items and the risk category) of every trial before enrolment of participants, providing open access to information on ongoing trials for patients, investigators, researchers, health professionals, sponsors, ethics committees, competent authorities, funding agencies, and health authorities.

A.3.3 Safety reporting

Members should ensure that safety reporting in clinical trials on medicinal products includes, regardless of the risk category, periodic reports to the appropriate oversight bodies of serious adverse events. They should also provide for expedited reporting of unexpected serious adverse reactions to the appropriate oversight bodies having the capacity to detect safety signals, regardless of the risk category. However, adaptations should be possible based on the protocol of each individual trial (see B.3.3).

A.3.4 Indemnification and insurance

Members should ensure that their regulatory framework takes into account the risk categories for the purpose of indemnification and insurance. Members should in particular explore how the coverage of patients in investigator-driven clinical trials in the lower risk categories (products being used in approved indications, or used outside licensed indications in established treatment regimens, corresponding to categories A and Ba) could be achieved through indemnification by the national health services or health insurance system, product liability (for category A), investigator or institution liability, without requiring a specific trial insurance. However, patients and healthy volunteers should not bear the cost of any negligent or unforeseen harm related to their participation in clinical trials.

A.3.5 Management of medicinal products

Members should ensure that the cost of medicinal products in categories A and Ba clinical trials is borne by the same bodies as those bearing the costs in cases where the therapy is used outside the context of a clinical trial.

Members should make it possible to use cost-effective techniques for the labelling and tracing of investigational medicinal products for category A trials (and optionally for category B). Depending on the study objective and protocol, it should be possible to distribute the medicinal product from the shelf, with or without a trial-specific label.

Members should allow pharmacies to repackage and re-label medicinal products without specific Good Manufacturing Practice (GMP) authorisation in category A and B trials.

A.3.6 Documentation

Members should allow for category A and B clinical trials to adapt the trial master file and replace the investigator brochure by the summary of product characteristics. No Investigational Medicinal Product (IMP) dossier should be required for category A and cross-reference should be allowed for category B.

B. Trial-specific approach

Members should implement a complementary trial-specific approach to guide the operational processes of each clinical trial in addition to the general stratified approach.

B.1. Risk assessment principles

Sponsors, service providers, investigators, patient representatives, ethics committees and health authorities should develop common risk assessment tools to support the risk assessment of individual trials, enabling their use in multinational studies. Risk assessment tools should cover the main risk determinants, including:

I. Risk to patients' rights:

1. information and informed consent
2. personal data protection

II. Risk to patients' physical integrity and safety:

1. safety of the treatment intervention
2. risk of diagnostic intervention
3. vulnerability of the patient population

III. Risk to data integrity and public health:

1. data quality, data management and analysis, data access and publication
2. credibility of results
3. impact on public health

Risk assessment in clinical trials should be considered as a dynamic process, and be continuously reviewed and updated during the conduct of the trial. This process should take into account, in particular, amendments, deviations, or safety events and results of relevant data generated outside the study.

To promote uniformity and coherence in risk assessment, Members should organise training of risk assessors such as sponsors, investigators, ethics committees or Institutional Review Board, competent authorities, insurance companies, or patients' representatives.

B.2. Risk assessment procedure

Assessment of risk in a trial should be undertaken early in the process, in parallel with the development of the protocol, to ensure that the trial design, risk mitigation, and trial management plans included in the protocol take risk fully into account.

The level of risk to patients' rights and physical integrity and safety for a given trial should be assessed in light of the potential benefit associated with the research.

The nature and extent of risks associated with an individual trial should be assessed by the investigator and/or the sponsor.

B.3. Risk-adaptation and risk mitigation

The nature and extent of risks associated with each individual trial should impact the supervision and management processes of the clinical trial, and result in adapted provisions for risk mitigation.

B.3.1 Ethical review and informed consent

As stated in A.3.1, Members should ensure that ethical reviews and the collection of individual informed consents are not affected by the nature and extent of risks and follow the principles articulated in the 2008 Declaration of Helsinki and the ICH E6 guideline.

B.3.2 Approval by regulatory bodies

It should be possible to adapt the content of the application dossier based on the protocol of the individual trial.

B.3.3 Safety reporting

It should be possible to adapt the adverse event reporting requirements to the individual trial, to the nature of the intervention and cumulated previous experience, and to the medical condition of the patient population. It should also be possible, in agreement with the appropriate regulatory bodies, to include specific provisions in the trial protocol for the reporting of some types of foreseeable adverse events to be waived. The requirement for a Data Safety and Monitoring Board should also be linked to the nature of the trial.

B.3.4 Management of the medicinal product

Given that the objective of the trial and the risk assessment may affect the traceability of the medicinal product, labelling should take into account the particularities of the trial, the blinding procedure, the way of administering the medicinal product and the characteristics of the patient population. Treatment compliance regimes should also be adapted in line with the objectives of the clinical trial.

B.3.5 Indemnification/insurance

Indemnification/insurance provisions and costs, where required, should be proportionate to the risk to participants' integrity and safety. Risk assessment principles similar to those described in principle B.1.II should be used to determine the nature and extent of risk to patients’ physical integrity and safety. Common risk assessment tools should be developed to help assess risks in a manner that is consistent across locales.

B.3.6 Quality management

Trial quality management should adapt to the particularities of the trial and to the nature and extent of risks. Risk assessment should identify the key trial parameters. Quality management plans should focus on mitigating key risks.

B.3.7 Control procedures

Inspections, audits and monitoring should be established in a manner that is proportionate to the risk stratification and trial-specific assessment, and take into account the provisions made to take these risks into account.

About the OECD

The OECD is a unique forum where governments work together to address the economic, social and environmental challenges of globalisation. The OECD is also at the forefront of efforts to understand and to help governments respond to new developments and concerns, such as corporate governance, the information economy and the challenges of an ageing population. The Organisation provides a setting where governments can compare policy experiences, seek answers to common problems, identify good practice and work to co-ordinate domestic and international policies.

The OECD Member countries are: Australia, Austria, Belgium, Canada, Chile, Colombia, Costa Rica, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Korea, Latvia, Lithuania, Luxembourg, Mexico, the Netherlands, New Zealand, Norway, Poland, Portugal, the Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Türkiye, the United Kingdom and the United States. The European Union takes part in the work of the OECD.

OECD Legal Instruments

Since the creation of the OECD in 1961, around 460 substantive legal instruments have been developed within its framework. These include OECD Acts (i.e. the Decisions and Recommendations adopted by the OECD Council in accordance with the OECD Convention) and other legal instruments developed within the OECD framework (e.g. Declarations, international agreements).

All substantive OECD legal instruments, whether in force or abrogated, are listed in the online Compendium of OECD Legal Instruments. They are presented in five categories:

- **Decisions** are adopted by Council and are legally binding on all Members except those which abstain at the time of adoption. They set out specific rights and obligations and may contain monitoring mechanisms.

- **Recommendations** are adopted by Council and are not legally binding. They represent a political commitment to the principles they contain and entail an expectation that Adherents will do their best to implement them.

- **Substantive Outcome Documents** are adopted by the individual listed Adherents rather than by an OECD body, as the outcome of a ministerial, high-level or other meeting within the framework of the Organisation. They usually set general principles or long-term goals and have a solemn character.

- **International Agreements** are negotiated and concluded within the framework of the Organisation. They are legally binding on the Parties.

- **Arrangement, Understanding and Others**: several other types of substantive legal instruments have been developed within the OECD framework over time, such as the Arrangement on Officially Supported Export Credits, the International Understanding on Maritime Transport Principles and the Development Assistance Committee (DAC) Recommendations.