



Recommendation of the Council on the Governance of Clinical Trials

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Background Information

The Recommendation on the Governance of Clinical Trials was adopted by the OECD Council on 10 December 2012 on the proposal of the Committee for Scientific and Technological Policy. 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 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 ICTRP¹ 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.

¹ www.who.int/ictrp

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