Recommendation of the Council on the Governance of Clinical Trials

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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.

The Recommendation's focus on harmonising regulatory requirements across and between countries is key to accelerating the launch of critical and robust clinical trials during emergency health crises, such as the COVID-19 pandemic. As such clinical trials are usually run by the public research sector and often need to be multi-national in order to produce reliable results, the diversity of national regulations can be a major challenge in these situations. This is particularly the case for public research institutions that do not have the resources to rapidly file multiple applications for authorisation and address different national requirements, but are at the frontline for the testing and discovery of effective treatments.

For more information, see:

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

For further information please consult:
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.

Related documents

EXPLANATORY MEMORANDUM FOR THE RECOMMENDATION OF THE COUNCIL ON THE GOVERNANCE OF CLINICAL TRIALS[1]

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[1] This explanatory memorandum was approved by the Global Science Forum by written procedure on 1 February 2013 [DSTI/STP/MS(2012)2/ADD/REV1].

INTRODUCTION

OECD Members have over time developed large arrays of legislations and administrative processes to regulate clinical trials for the development and improvement of drugs and treatments before they can be used for patients. These regulatory processes have taken on different forms in different countries, and many countries or regions are currently revising or adapting them in response to the evolution of science as well as to ethical or practical demands. Clinical trials are increasingly evolving from projects conducted at single sites and sponsored by single institutions into global multi-site collaborative undertakings. However, the disparities in regulations between countries may create obstacles for the development of international co-operation in clinical research.

Although several regional and international initiatives have attempted to facilitate the conduct of trans-national clinical research, the increased administrative complexity of the system has often constituted a serious impediment for many of the stakeholders involved, particularly in the academic sector. An Expert Group of the OECD Global Science Forum led the work to develop an OECD Recommendation to facilitate international co-operation in clinical trials and proposed harmonisation solutions. Following review by the Global Science Forum and the Committee on Scientific and Technological Policy, this text became an OECD Recommendation upon its adoption by Council on 10 December 2012.

Considering the scope and the technical complexity of the principles included in the OECD Recommendation, Members considered it essential to issue an accompanying Explanatory Memorandum. Its purpose is to explain and elaborate on the principles and facilitate their implementation.

The first part of the Memorandum provides general background information in the areas which Members have identified as being of most concern, related to the existing clinical trial regulatory complexity and diversity. It explains the international dimension of the problem and summarises the work carried out by the OECD.

The second part contains comments and detailed information on the general features of the Recommendation’s principles as well as detailed comments on specific sections.

This Memorandum is an information document, prepared to explain the technical elements of the Recommendation principles. It is subordinate to the Recommendation itself and should not be regarded as changing its content, but it may help in its interpretation and application.

I. General Background

1. Problems

1. Independent clinical trials are key to the development of evidence-based medical practice, which constitutes a major goal for patients, health professionals, public health and health systems worldwide. Therefore, in addition to ensuring the safety and rights of patients, the regulatory framework for clinical trials should ensure that those trials can be conducted efficiently and lead to reliable results.

2. Although many clinical trials are still performed in a single country, over the years there has been a growing trend to perform large-scale clinical trials across borders. In the European Union, nearly 25% of all applications to carry out clinical trials are now for multinational clinical trials, *i.e.* clinical trials intended to be conducted in at least two Member States[2]. Furthermore, cross-border trials involve approximately two-thirds of all subjects enrolled in a clinical trial, so mono-national clinical trials are now largely limited to small studies with low recruitment targets.

3. International collaboration brings many advantages for all types of clinical trials. Trial participant recruitment is faster and, importantly, the results of the trial are more generally applicable because they have been obtained in different health care settings or different geographical areas and may encompass patients of different ethnicities.

4. On the other hand, multinational clinical trials are significantly more complex to perform than national ones due in particular to the difficulties arising from the diversity of legal frameworks. In a recent survey conducted by the OECD Global Science Forum among the various clinical trial stakeholder communities[3], the diversity and complexity of administrative requirements and procedures were found to be some of the main hurdles to be overcome by experts wishing to set up multinational trials. In large pharmaceutical companies, this complexity is usually managed by the in-house regulatory affairs departments. Furthermore, large companies often have subsidiaries in the different countries where trials are being performed, giving them access to local information and expertise. The pharmaceutical industry can also use its financial resources to take advantage of the services of Contract Research Organisations (CROs), which can help sponsors of clinical trials to perform the study. However, academic groups from hospitals and university centres usually do not have similar resources. As sponsors, they are in most cases performing trials on tight budgets, and cannot usually afford outsourcing to a CRO.

5. Such regulatory complexity has detrimental consequences. Many well-conceived clinical trials that are aimed at addressing important public health problems either cannot be conducted or are so delayed that their impact is dramatically reduced. This is particularly true for the conduct of international clinical trials which involve multiple centres, and for trials initiated by academic structures which do not have well-developed administrative support. Thus, the number of clinical trials, particularly those initiated by academic investigators for non-commercial purposes, has been falling in recent years in some regions. In the European Union for example, the total number of applications for clinical trials fell by 25% from 2007 to 2011[1]. There is also fear that administrative issues may lead to some clinical trials being moved away from countries with complex regulatory requirements to countries with less stringent regulatory systems, in particular to save cost. In addition to raising ethical concerns, such moves may result in bias in the trial results, which may not include all the types of patient ideally required.

6. In addition to the challenges presented by existing national regulatory complexity, clinical trial investigators have had to respond to administrative requirements that are not always adapted to the nature of their study. Existing regulations have largely been developed for traditional trials of which the objective is to test 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 require very controlled procedures. These are, however, often less suited to address the many academic trials which use already marketed products.

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[2] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2012:0369:FIN:EN:PDF

[3] www.oecd.org/science/scienceandtechnologypolicy/49344626.pdf

7. In recent years, there has been a growing demand for better ways of aligning regulations across countries. The idea of a new harmonised regulatory framework has therefore emerged, whereby requirements would be based on the risk associated with the clinical trial at stake (involving the introduction of a regulatory and management approach proportionate to the risk of the trial). Identification of key risks and subsequent mitigation of these risks should result in a more optimal use of resources, while enhancing protection of the participants in the trials. This risk-based approach could both facilitate international clinical trials and help streamline the procedures for low-risk clinical trials.

8. Such a new regulatory system , however, necessitates a consensus on a number of key issues such as how to define the risk, which institution should be in charge of defining and validating potential risk categories, and which existing regulatory and monitoring processes would be affected. Although there was a broad consensus among stakeholders for the adoption of a risk-based approach to clinical trials regulation, no mechanism yet existed that would help align the regulatory requirements for clinical trials worldwide, and to develop and validate the risk assessment tools and risk-adapted monitoring procedures needed for its use in international clinical trials. This Recommendation provides such a mechanism.

2. International context

9. To facilitate trans-national clinical research, initiatives such as the ICH-process[4] have aimed at harmonising existing rules in several regions, but were mostly focused on clinical trials performed by industry on medicinal products. In the European Union, the regulatory process of clinical trials for medicinal products was harmonised in 2001 by the adoption of Directive 2001/20/EC, the "Clinical Trial Directive" (CTD), which had to be implemented by EU Members by 1 May 2004. In response to concerns of the clinical research community, this Directive is now undergoing a revision process to improve the harmonisation and simplification of the administrative and regulatory aspects of clinical trials.

10. Such initiatives have significantly improved patient safety and data quality, but other challenges in the conduct of clinical trials remain, both at national and international levels. Scientific studies must be completed quickly to be scientifically relevant, and excessive regulatory delays interfere with the timely completion of studies that are in the public interest.

11. In its recent work on clinical research[5], the European Medical Research Councils (EMRC) at the European Science Foundation (ESF) identified a series of major impediments for conducting Investigator-Driven Clinical Trials (IDCT) in Europe, echoing a recent analysis of the US National Institute of Health on international collaboration on clinical trials[6]. Two major issues related to the regulatory environment for clinical trials have emerged:

- **Persisting differences in administrative processes**. Differences in interpretation of existing regulations and other processes have led to even higher levels of complexity – especially in multi-national clinical trials. The sponsor of a multinational clinical trial needs to have a very detailed knowledge of every country's requirements for clinical trial authorisation, imposed by regulatory authorities and ethics committees. It also has to integrate different national requirements to the protocol as applications must be submitted in parallel in all the countries involved. Ambiguous definitions add to the problem, as identical terms may be interpreted differently from one country to another or even within the same country.
- **Inadequate regulation for some clinical trials**. Setting up and managing clinical trials is hampered by the regulatory framework that adopts a "one size fits all" national approach. For instance in Europe, regulations that apply to higher risk clinical trials of investigational medicinal products (IMPs) have been applied to all trials regardless of the risk involved and

[4] The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH, www.ich.org) is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration.

[5] www.esf.org/fileadmin/links/EMRC/FL_IDCT.pdf

[6] "Enhancing Collaborative United States (US) -European Union (EU) Government and Academic Sponsored Research: Issues with the European Clinical Trials Directive and Potential Solutions", NIH report

the objective of the trial. Thus the requirements for low risk trials, for example, trials using already licensed drugs for similar indications – which are often almost indistinguishable from standard care – can be prohibitively onerous and time-consuming for academic institutions. One of the questions, which arises particularly in the context of clinical trials undertaken for non-profit purposes, is whether there might be a rationale for distinguishing different categories of clinical trials, using a risk-based approach.

12. In this context, several initiatives are currently exploring risk-based regulation due in particular to the ongoing work on to the preparation of a revised European legislation on clinical trials. The European Medicines Agency (EMA), together with the EU national competent authorities, released a consultation[7] on risk-based quality management in clinical trials in August 2011, with a proposal covering both risk identification and risk mitigation. At the same time, the US Food and Drug Administration (FDA) submitted a guidance document on a risk-based approach to monitoring for consultation[8], reflecting the discussions within the Clinical Trial Transformation Initiative (CTTI[9], supported by the FDA Critical Path programme). This latter initiative promotes the concept of quality by design: the protocol should clearly identify procedures and data that are critical to the reliability of the clinical trial results, and the monitoring plan should be designed to focus on these critical aspects. It is part of a broader initiative by the Department of Health and Human Services and the FDA[10] to rejuvenate the regulation governing research with human subjects in the US, which now includes a reference to a risk-based approach in regulation processes[11].

Models of regulatory frameworks

13. There are currently two main models (with a broad spectrum of particular situations) of regulatory frameworks for clinical trials across the world (Table 1):

i) a model centred on the use of data in the perspective of obtaining a marketing authorisation, with different requirements and regulations for clinical trials whose objective is the registration of a medicinal product ("IND" (Investigational New Drug) trials in the US, "chiken" trials in Japan) vs. other categories of clinical trials ("non-IND" studies, "non-chiken" studies). In this model, the data collected by non-registration trials cannot be used for drug registration purposes.

ii) a model that does not discriminate based on the registration or non-registration objective of the study, and ensures the same level of protection of trial participants in both cases. This is, for instance, the model in use in Europe since the 2001/20/EC Directive. In this model, data from all clinical trials can later be used for registration purposes, but in turn the requirements represent a major bottleneck for academic clinical research, which involves mostly lower-risk clinical trials using already marketed products.

14. The first model implicitly makes a risk-based distinction in clinical trial oversight, as the regulatory requirements differ for trials on medicinal products which have or do not have a marketing authorisation (the risk refers here to the safety of the participant in the trials, whereas the risks related to the scientific validity and credibility of the trial's results are not taken into consideration). Registration trials (IND or chiken) are supervised by the regulatory authority in charge of delivering the marketing authorisation (the US FDA, or the Pharmaceuticals and Medical Device Agency (PMDA) in Japan), and also require approval by ethics committees/institutional review boards. In turn, non-registration (non-IND, non-chiken) clinical research, including clinical trials on authorised medicinal products used within the marketing authorisation, is not regulated but merely subject to ethical guidelines. In practice, these studies are supervised by ethics committees/institutional review boards, but do not require approval by,

7 www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500110059.pdf

8 www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM26999.pdf

9 www.ctti-clinicaltrials.org/

10 Federal Register, Vol. 76, No. 143, 26 July 2011, Proposed Rules, pp. 44512-44531

11 Emanuel EJ, Menikoff J. Reforming the regulations governing research with human subjects. N Engl J Med. 2011, 365:1145-50

or notification to, the regulatory authority (except, for instance, when a post-marketing trial is required by the regulatory authority). Other countries have adopted this model with a more flexible trial oversight process. For instance, in Australia, for each individual trial protocol, the ethics committee examines the proposed usage guidelines for the medicinal product and decides whether it has the competence to approve the trial (this is called a "notification scheme"). Alternatively, the ethics committee may require approval of the trial by the Therapeutic Goods Administration (TGA) (this is the "exemption scheme"). The TGA is not involved when the medicinal product has marketing authorisation and is being used within its approved indications (although ethics committee approval is still required).

15. The second model does not make any difference between clinical trials based on the registration objective. The interpretation of the 2001/20/EC Directive in most European countries results in similar requirements for any trial on medicinal products: approval by ethics committees, approval by the regulatory authority, reporting of Suspected Unexpected Serious Adverse Reactions (SUSAR) to the ethics committees and competent authorities, need for a sponsor, need for an insurance/indemnification, etc.

Table 1. Simplified representation of the stratification and oversight requirements for clinical trials on medicinal products in various countries/regions

<table>
<tr><td rowspan="2">Marketing authorisation status of the medicinal products</td><td rowspan="2">Non-authorised medicine</td><td colspan="2">Authorised medicine, treatment regimen outside marketing authorisation</td><td rowspan="2">Authorised medicine tested within marketing authorisation</td></tr>
<tr><td>Not supported by established medical practice</td><td>Supported by established medical practice</td></tr>
<tr><td>USA</td><td colspan="3">IND trials
supervision by FDA
approval by IRB</td><td>non-IND studies
approval by IRB</td></tr>
<tr><td>Japan</td><td colspan="3">Chiken trials
supervision by PMDA
approval by IRB</td><td>Non-chiken studies
approval by IRB</td></tr>
<tr><td>Australia</td><td colspan="4">exemption scheme
approval by RA (TGA)
approval by EC

notification scheme
Approval by EC
(EC decides if TGA should be involved, based on trial protocol)</td></tr>
<tr><td>2001/20/EC Directive</td><td colspan="4">approval by RA
approval by EC</td></tr>
<tr><td>UK adapted 2001/20/EC Directive</td><td>approval by RA (MHRA)

approval by EC</td><td colspan="2">approval by RA (MHRA)
(adaption of application dossier)

approval by EC</td><td>notification to RA (MHRA)

approval by EC</td></tr>
<tr><td>Draft EU Regulation 2012</td><td colspan="2">co-ordinated approval by oversight bodies</td><td colspan="2">low intervention trials
co-ordinated approval by oversight bodies</td></tr>
<tr><td>OECD Recommendation</td><td>approval by regulatory authority

approval by EC/IRB</td><td colspan="2">approval by regulatory authority
(adaption of application dossier)

approval by EC/IRB</td><td>approval by EC/IRB

(notification to or approval by RA as an option only)</td></tr>
<tr><td></td><td colspan="4">IND: investigational new drug
EC: ethics committee
IRB: institutional review board
RA: regulatory authority

marketing ↑ authorisation</td></tr>
</table>

16. A majority of investigator-driven clinical trials considered that this undifferentiated approach resulted in unnecessary burdens and costs, hampering Europe's attractiveness and competitiveness in clinical research. Comparing the figures before and after the implementation of the 2001/20/EC

Directive, the ICREL project (Impact on Clinical Research of European Legislation[12]) demonstrated a major increase in the cost of administration, safety reporting, monitoring, trial management and insurance, particularly for the trials conducted by academic sponsors. This represents a critical issue as the number of academic trials increases in developed countries, as shown by the EMA registry, which indicates that the percentage of trials with non-commercial sponsors was in the range of 20% in 2006, and close to 40% in 2011. Although academic trials also include high-risk, early-phase trials on advanced therapy, biologics or biopharmaceuticals, the majority of the investigator-initiated clinical trials correspond to lower risk trials, either comparing therapeutic options within their marketing authorisation, or exploring new indications for already marketed products.

17. For this reason, the academic community raised serious concerns about the 2001/20/EC Directive. The EU Commission published in 2006 a guidance document for public consultation with a proposal for specific modalities for non-commercial trials, a concept that would have better aligned the European legislation with the non-European model. However, this was viewed as a two-tier model, suggesting a lower credibility for results derived from non-commercial trials – as, for instance, data from non-commercial trials would not have been accepted for later registration purposes. This guidance document was never adopted. Rather, the concept of a risk-based approach was promoted: adaptations should be made possible for clinical trial oversight and management, but should be based on the risk associated with the trial, and not on the nature of the sponsor nor the objective of the trial, and should not affect the credibility of the trial results.

18. It should be underlined that part of the problem was related to an overly stringent interpretation of the provisions of the 2001/20/EC Directive during its transposition into national legislations in Europe. In fact, the Directive also enables risk-based provisions, as demonstrated by the UK pilot initiative[13] which used the flexibility offered by the 2001/20/EC Directive to distinguish three categories of trials mostly based on the marketing authorisation status of the medicinal product. Switzerland (which is not a member of the European Union and therefore is not bound by the provision of the 2001/20/EC Directive) has also recently developed new legislation including risk-based provisions, with a similar stratification into three categories for the clinical trials on medicinal products. However, most European countries have transposed the 2001/20/EC Directive into legislations that are poorly adapted to a risk-based approach, resulting in a substantial burden for those investigator-driven trials which are comparing established treatment strategies or exploring new indications for authorised medicinal products. The new draft Regulation proposed by the European Commission to replace the 2001/20/EC Directive now contains explicit risk-based provisions, with a definition of low intervention trials as trials using marketed medicines within the marketing authorisation, or in a treatment regimen outside the marketing authorisation but supported by established medical practice.

19. Outside Europe, risk-based provisions already exist in some countries (*e.g.* Australia) or are currently being developed. Japan is considering the establishment of a new regulatory framework for the non-chiken clinical studies, whereas the clinical trial transformation initiative (CTTI) supported by the US FDA[14] includes risk-based quality management processes.

20. Adopting common principles for a risk-based approach to clinical trial oversight and governance would therefore result in two major improvements for international co-operation:

i) they would facilitate trials optimising the use of authorised medicinal products, for the benefit of patients, health professionals, health authorities; and

ii) they would ensure a better alignment of requirements for regulatory oversight and management of individual trials across the world regions.

3. Activities at the OECD

21. At the initiative of the Delegations of Germany and Spain, the OECD Global Science Forum approved the creation of a Working Group to Facilitate International Co-operation in Non-Commercial

[12] www.efgcp.be/downloads/icrel_docs/Final_report_ICREL.pdf

[13] www.mhra.gov.uk/home/groups/l-ctu/documents/websiteresources/con111784.pdf

[14] www.ctti-clinicaltrials.org/

Clinical Trials at its 21st meeting in October 2009. Following extensive work and a series of meetings and workshops, the Working Group submitted a final report to the GSF at its 25th meeting in October 2011 in Berlin. This report[15] contained a number of policy recommendations, including a specific one related to the introduction of a risk-based approach to clinical trial oversight in national regulatory procedures. The GSF agreed to extend the activity of the Working Group to follow up the implementation of the report's various recommendations, and in particular to refine the substance of the proposed risk-based adaptation of clinical trial regulation and to formulate a draft OECD Council Recommendation.

II. The Principles

1. Purpose and Scope of the Recommendation

22. This Recommendation is primarily driven by the need to facilitate international co-operation on multi-site clinical trials. Many such trials are driven by important public health issues and are undertaken by academic institutions, for which existing regulations have introduced over time excessive administrative hurdles. The objective of the Recommendation is to foster the establishment of a harmonised regulatory framework which includes/uses different requirements based on the actual risk associated with the study, which could both facilitate international clinical trials and help streamline the procedures for low-risk clinical trials.

23. The Recommendation focuses on clinical trials on medicinal products, for which a stratification based on the marketing authorisation status is possible. Clinical trials on medical devices are not currently included in the Recommendation as major divergences in the regulatory context (marketing authorisation or conformity assessment), and the heterogeneity of the devices create a more complicated picture[16]. Adherents may nevertheless explore the opportunity to transpose the principles of this Recommendation to other categories of clinical trials, including those related to traditional medicinal products, nutrition, radiotherapy or surgical procedures.

24. Whereas risk stratification based on the marketing authorisation status (or conformity assessment for medical devices in Europe) is in principle only valid for clinical trials on health products (medicinal products, medical devices), the trial-specific approach applies to every category of clinical trial and clinical research, and Adherents are invited to consider extending similar principles to the whole spectrum of clinical research.

2. Risk, risk assessment and risk adaptation

25. There is a fairly broad consensus to consider risk as the likelihood of a potential hazard occurring and resulting in harm to the participants and/or to the reliability of the results. There are three major components of risk that can be detailed as follows:

i) Risk to patients' rights: this relates to the information provided to the patients participating in clinical trials and to informed consent forms and procedures, as well as to personal data protection;

ii) Risk to patients' physical integrity and safety: this comprises the potential safety of the treatment intervention, the risk of the diagnostic procedures, and the vulnerability of the patient population (age, social environment, education, etc.); and

iii) Risk to data integrity and public health: this includes data quality, data management and analysis, accessibility of data, credibility and robustness of design and methods, and the potential impact of the trial results on public health.

26. In evaluating risk for clinical trials, one should focus on the additional or incremental risk that a patient or subject participating in a clinical trial may be exposed to, compared with the risk of non-participation, *i.e.* the risk of usual care for patients (or the risk of daily life for healthy volunteers). This

[15] www.oecd.org/dataoecd/31/8/49344626.pdf

[16] Kramer DB, *et al.*, Regulation of medical devices in the United States and European Union. N Engl J Med 2012, 366:848-855.

should be taken into account for a broad variety of processes, including for clinical trial insurance and indemnity.

27. Risk-based clinical trial supervision requires both risk assessment and risk mitigation strategies. Risk assessment is the process of identifying the potential hazards associated with a given trial, and assessing the likelihood of those hazards occurring and resulting in harm.

28. Risk assessment should be based on objective elements, rather than on the subjective/intuitive assessment made during the risk-benefit evaluation of every clinical study. Methods for objective risk assessment have been developed (see, for example, the systematic evaluation of research risks[17]), and these constitute interesting leads for a more global debate. Various risk-assessment strategies for clinical trials have been developed across the world, particularly with the objective of defining risk-adapted monitoring plans. These strategies include:

- an approach (described as a "stratified approach" in the Recommendation) based on the definition of discrete risk categories based on the marketing authorisation status and the conditions for use in the trial, although this captures only part of the risk items (mostly the hazard related to the safety of the medicinal product).
- an approach (described as a "trial-specific approach" in the Recommendation) based on a case-per-case assessment of each individual trial, using guidance and decision trees covering all the aspects of risks (risks to patient rights, to patient integrity and safety, to results and public health).

29. In fact, most of the currently available strategies[18] propose mixed systems that combine the stratified and trial-specific approaches. This is the case for the model developed by Hôpitaux de Paris[19], the Adamon[20] and Optimon[21] studies, or the UK pilot initiative[22]. However, the Recommendation distinguishes these two approaches as they require different implementation procedures. A finite number of risk categories is suitable for national regulation/legislation, allowing for harmonised alignment of regulatory requirements for multinational trials. In addition, complex decision trees are needed to assess the risk for an individual protocol, and harmonisation should be based on internationally validated tools for risk assessment and risk mitigation.

3. Stratified and trial-specific approaches

30. To respond both to the need for more harmonised and streamlined regulation and to the need for participant protection, the Recommendation proposes to generalise a harmonised two-pronged strategy, as described above, the strands of which should be used in combination to adapt the oversight and management of clinical trials to the nature and intensity of the risks.

- The stratified approach, which is a risk-based approach that uses the marketing authorisation status of medical products to define a finite number of categories which can be used for legislation or regulation purposes across nations, and which assigns each individual trial to one of these categories;

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17 Rid A*, et al.*, Evaluating the risks of clinical research. JAMA 2010, 304:1472-9.

18 www.ecrin.org/fileadmin/user_upload/public_documents/News/Activities/Report%20Roadmap%20Workshop%20on%20Risk-%20based%20regulation%20Barceona%2018%20Jan%202010-1.pdf

19 www.drrc.aphp.fr

20 Brosteanu O.*, et al.*, Risk analysis and risk adapted on-site monitoring in noncommercial clinical trials, Clin Trials 2009; 6; 585

21 Journot V.*, et al.*, on behalf of the Optimon Collaborative Group; Validation of a risk-assessment scale and a risk-adapted monitoring plan for academic clinical research studies - The Pre-Optimon study Cont. Clin. Trials, 32: 16-24, 2011.

22 www.mhra.gov.uk/home/groups/l-ctu/documents/websiteresources/con111784.pdf

- The trial-specific approach, which takes into account the whole spectrum of risk determinants for defining trial management and operations, including insurance coverage, safety reporting, quality control and management procedures.

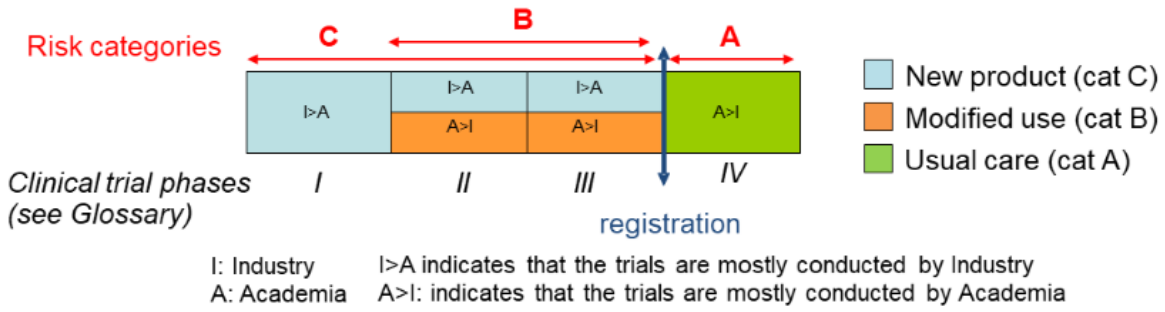
3.1 Stratified approach

Risk categories

31. This consists in defining categories of clinical studies associated with different levels of risk. Only a restricted number of finite categories can be defined, focusing on a single dimension of the risk definition, *e.g.* the risk to participants related to the safety of the product (this approach is not therefore valid for clinical trials that do not deal with medicinal products but focus instead on surgical procedures, radiotherapy, etc.). In the Recommendation, the stratification proposed distinguishes three categories, which can be related to the clinical development of medicinal products (Figure 1):

- Usual care (Category A): Clinical trials testing authorised medicinal products in accordance with the marketing authorisation;
- Modified use (Category B): Clinical trials testing authorised medicinal products according to treatment regimens outside the marketing authorisation, either supported (a), or not supported (b) by published evidence and/or guidance and/or established medical practice (note that categories Ba and Bb are not necessarily related to clinical trial phases II and III respectively, see Glossary);
- New product (Category C): Clinical trials testing non-authorised medicinal products.

Figure 1. Risk categories and clinical development of medicinal products



32. This three-category system allows for a good alignment of the requirements for international clinical trials (Table 2): category A roughly corresponds to the non-commercial (non-IND, non-chiken) trials outside Europe, where no oversight by the regulatory authority is usually required. This will facilitate the independent assessment by academic institutions of medicinal products and treatment strategies, which is a critical activity for the optimisation of healthcare and for cost containment. However, oversight by the regulatory authority is sometimes necessary for such post-marketing trials, in particular for clinical trials corresponding to post-marketing authorisation commitments (part of the risk management plan, post-authorisation safety or efficacy studies). This is made possible through the option of a notification to, or an approval by, the regulatory authority.

Table 2: Risk categories for the stratified approach

	C - New product	B – Modified use	A – Usual care
Medicinal product Based on Marketing Authorisation (MA) status, with modulating	Not authorised (according to national or regional regulation)	Authorised (according to national or regional regulation) Tested according to treatment regimens outside the marketing	Authorised (according to national or regional regulation) Tested in accordance with marketing authorisation

factors: (up/downgrade) - Novelty (new chemical entity/class) - Innovative nature - MA in other countries		authorisation (in terms of population, condition, administration, dosage) (a) supported by or (b) not supported by published evidence and/or guidance and/or established medical practice	

33. In turn, clinical trials on non-authorised medicinal products, or medicinal products used outside the licensed indication require approval by the appropriate regulatory bodies. Making an additional distinction between category B and category C takes into account the fact that, for category B, information is already available on the efficacy and safety of the medicinal product (although for a different disease indication or population), and the fact that the product is already manufactured, labelled, marketed and distributed. Compared with category C, category B is therefore associated with a lower risk, allowing for adapted requirements. This may facilitate the management of category B trials, conducted mostly by independent researchers to explore new indications, particularly in cancer and rare diseases.

34. Within the B category, a distinction should also be made between trials where the medicinal product is used according to treatment regimens outside the marketing authorisation, either supported (Ba) or not supported (Bb) by published evidence and/or guidance and/or established medical practice. As Ba trials explore conditions that represent the standard of care, this distinction makes sense with regards to insurance/indemnity, and to the recommendation that the cost of the treatment given as part of the clinical trial be borne, for investigator-driven trials, by the usual public or private health insurance schemes.

35. Modulating factors could be taken into account, even though they may complicate the categorisation and be subject to interpretation: the innovative nature of the treatment (for instance, the use of advanced therapy medicinal products/biologics,) could lead to a more careful supervision of the trial as the treatment use is still restricted and the safety issues more difficult to anticipate. Conversely, new galenic forms or minimal variations (new salts, enantiomers) from an existing drug or class of drugs have to be taken into account as low novelty. Similarly, marketing authorisations obtained in other countries or regions have to be considered.

36. The risk categorisation for an individual trial should be proposed by the investigator and/or sponsor, and should later receive validation by an appropriate approval/oversight body (for instance, an ethics committee/Institutional Review Board, and/or competent or regulatory authority). Risk stratification should impact the oversight and management processes of the clinical trial and result in adapted provisions.

Risk adaptation

37. The stratification of clinical trials in categories, based on the marketing authorisation of the medicinal product, is used to adapt the oversight and governance processes to the risk posed by those various categories.

Trial approval by regulatory bodies

38. The role of the regulatory body is usually assigned to the authority in charge of delivering the marketing authorisation. However, in some cases, the ethics committees (or other bodies) may have the mission and competence to act as the regulatory body supervising the use of medicinal products in clinical trials.

39. Clinical trial approval by the regulatory bodies is considered as necessary for categories B and C trials (with a possible adaptation of the content of the dossier for category B), since such trials involve the use of new drugs or of medicinal products outside their authorised indication.

40. Such regulatory authority approval may, however, not be required for the lower risk (A) category. The absence of such a requirement would simplify trial oversight and promote harmonisation with countries like the US and Japan where no approval by the regulatory authority is required for non-IND or non-chiken studies. Notification to (or approval by) the regulatory body could be considered as an option for countries that consider the involvement of the regulatory body as necessary, in particular for appropriate processing of adverse events. This may concern the proposal for a new clinical trial regulation in Europe which takes the approach of providing for a co-ordinated assessment of multinational clinical trials among Member States. In such a situation, addressing different ethics committees separately would be much more burdensome for the sponsor than the proposed co-ordinated joint assessment procedure in which the regulatory bodies manage the consultation of the ethics committees.

41. Regulatory authorities should, however, have oversight on some Category A trials, conducted as part of the post-marketing commitment given by the marketing authorisation holder (part of the risk management plan, post-authorisation safety or efficacy studies).

42. In any case, improvement in the clinical trial registration system should enable regulatory bodies to access information on Category A trials through trial registries, to request further information if needed, or to perform inspections. For this reason, the Recommendation encourages public registration of the key items (including the 20 WHO ICTRP[23] 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.

Ethical review and informed consent

43. The ethical review and informed consent should not be affected by the risk category. In agreement with the Declaration of Helsinki, Adherents should require ethical review and approval of the trial by a research ethics committee or institutional review board for every trial involving human participants, whatever the nature and extent of risk. Informed consent from every trial participant should be required, whatever the risk category, except for example when the research is prospectively planned and approved by a research ethics committee or institutional review board and trial participants are unable to give prior consent, consistent with the provisions of the 2008 Declaration of Helsinki describing situations where consent may be given by a third person or a waiver of consent may be granted:

> *Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorised representative.*

Safety reporting

44. Although the proposed stratification is based on the knowledge of the safety of the medicinal product, it is not possible to propose a consistent set of risk-adapted provisions based on these categories. This is due partly to the discrepancies in the current definitions, reporting processes and oversight bodies involved across the world regions and partly to the fact that possible adaptations

[23] www.who.int/ictrp

depend on the individual trial rather than on its category. The Recommendation therefore states that, regardless of the risk category, safety reporting should include periodic reports of serious adverse events and expedited reporting of unexpected serious adverse reactions to the appropriate oversight bodies having the capacity to detect safety signals. Under legislation which requires periodic safety reporting from the marketing authorisation holder of authorised medicinal products (such as the EU pharmacovigilance legislation), additional trial-specific periodic safety reporting may not be required for trials in risk category A (testing authorised medicinal products in accordance with the marketing authorisation). Adaptations may be possible based on the protocol of each individual trial (section 3.2 under the trial-specific approach).

Indemnification and insurance

45. The major risk determinant to be considered for insurance and indemnity purposes is the risk to patient safety and integrity. In turn, such risk depends on the risk to safety associated with the medicinal product which is the basis of the proposed stratification. Therefore, regulatory frameworks should take into account the risk categories for the purpose of indemnification and insurance. However, patients and healthy volunteers should not bear the cost of any negligent or unforeseen harm related to their participation in clinical trials.

46. When the treatments tested correspond to usual care (category A) or modified use in established treatment regimens (category Ba), the Recommendation calls for countries to explore how the national health services or insurance systems could provide indemnification in investigator-driven trials. This is expected to save a substantial amount of public funding. Importantly, this provision should also apply to investigator-driven trials initiated in other countries to facilitate multinational trials.

Management of the medicinal product

47. For investigator-driven trials using medicinal products tested within its marketing authorisation (category A), or in a modified use in an established treatment regimen (category Ba), countries should provide a mechanism to have the cost of treatment borne by the usual procedure (*i.e.* public or private health insurance schemes) – as the patient would have been treated anyway in the absence of the trial, the only difference being the trial setting. In such cases, the costs of use of the medicinal product should be neither the responsibility of the sponsor, nor of the trial participant. Some countries have already implemented such a system, and disseminating this principle would have a considerable impact on the conduct, and multinational expansion, of independent trials for comparative assessment of established treatments, for the benefit of patients, health professionals, and healthcare systems.

48. For trials using authorised medicinal products (categories A and B), and depending on the nature of the trial, measures should be taken to allow for simplification of the labelling, tracing, accountability and distribution of the product. For instance, hospital pharmacies should be able to repackage and re-label medicinal products without specific Good Manufacturing Practice (GMP) authorisation in categories A and B trials. Cost-effective alternative techniques for the labelling and tracing of investigational medicinal products should be made possible for category A or B trials. When relevant and depending on the trial objective and protocol, treatment distribution should be made possible from the shelf, with or without a trial-specific label.

Documentation

49. For trials using marketed products (categories A and B), and depending on the nature of the trial, measures should be taken to allow simplification of the trial documentation in various ways: the trial master file could be adapted; the investigator brochure could be replaced by the summary of product characteristics; the Investigational Medicinal Product (IMP) dossier should not be required for category A, and cross-reference should be allowed for category B.

Quality management

50. The stratification into categories based only on the marketing authorisation status of the medicinal product is not relevant for the quality management and trial monitoring, which should consider

the whole spectrum of risk determinants, particularly data quality, the robustness of the results and the impact on public health, and be driven by the trial-specific approach.

Table 3: Impact of risk categorisation on clinical trial oversight and management

	C - New product	B – Modified use	A – Usual care
Ethical review	Approval consent	Approval consent	Approval consent
Regulatory bodies	Approval	Approval (trial specific provisions for content of dossier)	Approval may not be required (option: notification or approval)
Adverse event reporting	Periodic serious adverse event reporting. Expedited report of Unexpected serious adverse reactions to oversight bodies with capacity to detect signals	Periodic serious adverse event reporting. Expedited report of Unexpected serious adverse reactions to oversight bodies with capacity to detect signals	Periodic serious adverse event reporting. Expedited report of Unexpected serious adverse reactions to oversight bodies with capacity to detect signals
Indemnification/insurance		Indemnification mechanism by the public health system (for established use, Ba) for investigator-driven trials	Indemnification mechanism by the public health system for investigator-driven trials
Medicinal product		Cost of medicinal product covered by usual procedure for IIT (for established use, Ba) Adaptation of labelling, tracing, distribution, accountability possible Repackaging and relabeling without GMP-authorisation	Cost of medicinal product covered by usual procedure for IIT Adaptation of labelling, tracing, distribution, accountability possible Repackaging and relabeling without GMP-authorisation
Documentation		Adaptation of Trial Master File Investigator Brochure replaced by Summary of Product Characteristics Where possible, cross reference to Investigational Medicinal Product (IMP) dossier	Adaptation of Trial Master File Investigator Brochure replaced by Summary of Product Characteristics No IMP dossier
Quality management	Trial-specific	Trial-specific	Trial-specific

3.2 Trial-specific approach

51. The “trial-specific approach” refers to operational processes that cannot be captured by the stratified approach (focusing on the risk associated with the safety of the medicinal product), nor be part of the legislation. It consists of guidance on how research oversight and governing bodies should perform risk assessment and risk mitigation of each individual clinical trial, evaluating the risks inherent to the research procedures set out in the protocol and impacting either the trial participants themselves or the robustness of the data collected. Considering the whole spectrum of risk determinants (including risk to patient - or healthy volunteer - rights and integrity, risk to results and to public health) requires a comprehensive risk assessment based on the trial protocol. Adoption of common principles will result in a substantial facilitation of multinational trials. This trial-specific approach, used in combination with the stratified approach, should help refine the oversight and management of the trial, with a particular impact on data quality and credibility of results, and therefore on its consequences on public health.

Risk assessment

52. “Risk assessment” consists of assessing, on a case-per-case basis, the risk associated with an individual trial protocol. It takes into account the various dimensions of the risk as previously defined: risk to the patient rights, to the patient safety and integrity, to the results and to the consequences for public health, preferably supported by a decision tree or a guidance document. Risk assessment also considers the experience and training at the investigation site, as well as the robustness of procedures, as determinants for data credibility. The concept of quality-by-design broadens this approach, stating that the trial should be designed to maximise the robustness of data collection and analysis. In particular, it aims at ensuring that the protocol identifies the critical data and procedures, and that the monitoring plan focuses on these critical points.

53. Although many risk assessment tools may be developed, the risk assessment should be based on common principles describing the risk determinants:

I. Risk to patient (or healthy volunteer) rights, more specifically:

   1. patient information, informed consent, process for obtaining consent
   2. personal data protection

II. Risk to patient (or healthy volunteer) physical integrity and safety, more specifically:

   1. known and unknown safety of the treatment intervention, administration, dosage (incremental risk compared to usual care), risk of decisions made on cumulated data (*e.g.* dose escalation)
   2. risk, burden and intrusion of non-treatment (diagnostic) intervention and clinical procedures specified by the protocol (incremental risk compared to usual care)
   3. vulnerability of the patient population and risk related to its health and healthcare environment

III. Risk to data quality, results, and public health, more specifically:

   1. data quality (in particular the reliability of data collection), data management, investigation sites, (including training and experience of investigator and staff), quality assurance, trial management and governance, transparency and access to raw data
   2. credibility of results, in particular robustness of design and methods, complexity of the trial, potential source of bias (including conflicts of interest)
   3. impact of trial results on healthcare practice and public health

54. Interestingly, these risk determinants could be valid whatever the category of clinical trial (clinical trials on medicinal products; clinical trials on medical devices, therapeutic trials without medicinal product, *e.g.* surgery, radiotherapy, psychotherapy; diagnostic trials, other interventional or observational clinical studies). Therefore, Adherents are encouraged to explore the possibility of

extending the application of the principles of trial-specific risk adaptation of clinical trial oversight and management to every category of clinical trials.

55. Risk assessment should be flexible, but the training of assessors and a methodology to objectively assess the risk are viewed as key issues to prevent divergent assessments. Appropriate training modules for investigators, clinical trial professionals, ethics committee members, competent authorities, insurance and health industry staff are to be developed to ensure the reliability, consistency and harmonisation of the assessment.

56. Risk assessment should be made by the investigator and the sponsor, and the trial oversight and governance bodies should consider the nature and extent of risk in determining the trial oversight and management processes.

Table 4. Risk adaptation following the stratified and the trial-specific approaches, as described in the Recommendation

Process	Stratified approach	Trial-specific approach
Ethical review	As specified in the Declaration of Helsinki and in the International Conference of Harmonisation (ICH) E6 guideline, Adherents 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).	Adherents 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.
Approval by regulatory bodies	Adherents should require approval by the appropriate regulatory bodies, for instance the Competent Authority, for category B and C clinical trials. Adherents may decide not to require prior approval from regulatory bodies for category A clinical trials. Adherents 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: Adherents 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.	It should be possible to adapt the content of the application dossier based on the protocol of the individual trial.
Safety reporting	Adherents 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.	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

Process	Stratified approach	Trial-specific approach
		bodies, to include specific provisions in the trial protocol for the reporting of some types of foreseeable adverse events to be waived. No waiver should however be possible for post-authorisation safety studies and post-authorisation efficacy studies. The requirement for a Data Safety and Monitoring Board should also be linked to the nature of the trial.
Indemnification and insurance	Adherents should ensure that their regulatory framework takes into account the risk categories for the purpose of indemnification and insurance. Adherents 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.	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.
Management of medicinal product	Adherents 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. Adherents 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 trial objective and protocol, it should be possible to distribute the medicinal product from the shelf, with or without a trial-specific label. Adherents should allow pharmacies to repackage and re-label medicinal products without specific Good Manufacturing Practice (GMP) authorisation in category A and B trials.	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.
Documentation	Adherents 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.	
Quality management		Trial quality management should adapt to the particularities of the trial and to

Process	Stratified approach	Trial-specific approach
		the nature and extent of risks. Risk assessment should identify the key trial parameters. Quality management plans should focus on mitigating key risks.
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.

Risk mitigation

57. The specific risk of a clinical trial should determine what adaptations should be made in the trial governance and oversight processes, such as safety reporting, management of the medicinal product, documentation, and insurance/indemnity. Above all, the nature and extent of risk affects the monitoring of data quality and the robustness of results. Monitoring can be adapted to the risk (as stated in ICH E6 guideline), however, the scientific community lacks globally-validated strategies for risk-adapted quality management in multinational trials.

58. Risk assessment should therefore result in adapted provisions to mitigate the risks. In addition to those listed in the Recommendation (for clinical trials on medicinal products), additional provisions could be proposed for other categories of clinical trials (as countries are encouraged to implement similar principles for all categories of clinical trials).

Ethical review and informed consent

59. As already mentioned for the stratified approach, clinical trials on medicinal products should receive approval after full ethical review whatever the nature and extent of risk. The collection of informed consent should not be affected by the nature and extent of risk, and should follow the provisions of the Declaration of Helsinki describing situations where consent may be given by a third person or a waiver of consent may be granted.

60. In turn, for clinical research which does not focus on/involve health products, an expedited ethical review may be considered. For instance, this could be the case for low risk studies involving the collection of blood samples, of data obtained through non-invasive procedures routinely employed in clinical practice, of data obtained from voice/video/digital recordings, of prospective biological specimens obtained by non-invasive means, of data on individual or group characteristics or behaviour; or for research employing the use of surveys, interviews, oral histories, etc.

Approval by regulatory bodies

61. The need to obtain approval by a regulatory body is mostly determined by the stratified approach. However, the content of the application dossier could be adapted based on the nature of the trial.

Safety reporting

62. The nature and extent of risk may have a strong impact on the safety reporting procedures for an individual clinical trial, based on the protocol, the nature of the intervention and cumulated previous experience, and the medical condition of the patient population. The trial protocol may contain specific provisions indicating a waiver on the reporting of some adverse events to the sponsor or specific oversight bodies, in agreement with the appropriate regulatory bodies (however, no waiver should be

given to post-authorisation safety or efficacy studies required by regulatory authorities). The requirement for a Data Safety and Monitoring Board should also be linked to the nature of the trial.

Management of the medicinal product

63. Based on the trial protocol and objectives, alternative and cost-effective methods for traceability may be used and labelling could be adapted based on factors such as blinding, the administration procedure, or the nature of the patient population. Methods to ensure compliance to treatment and drug accountability could also be adapted based on the trial design and objective. Depending on the protocol, the medicinal product could be made available on prescription at community/retail pharmacy outlets.

Indemnification/insurance

64. The risk assessment principles described earlier (section II 3.2: risk assessment) to capture the risk determinants should be used to determine the indemnification/insurance provisions and costs (where required), which should be proportionate to the risk to the patient's (or healthy volunteer's) integrity and safety. In addition, use of common tools would reduce discrepancies between countries.

Quality management

65. Clinical trial quality management should adapt to the particularities of the trial and to the nature and extent of risks. A quality-by-design approach is recommended to increase the robustness of data collection and analysis while designing the study protocol. Risk assessment should identify the key trial parameters and focus the quality management plans on the mitigation of those key risks. Education and exploitation of information technology may lead to a reduction in the amount of monitoring, including site visits.

Control procedures

66. Both the risk inherent to an individual trial and the risk mitigation procedures have to be considered during inspections and audits.

4. Comments for implementation

67. The stratified approach is appropriate for legislation or regulation purposes, as it defines a finite number of risk categories based on the marketing authorisation status of the medicinal product. Its implementation should therefore follow a “top-down” transposition into the national or regional legislation, and/or into regulations and guidelines produced or overseen by the appropriate trial oversight bodies.

68. By contrast, the trial-specific approach cannot be captured in national legislation or regulations. Adoption and implementation of common principles and guidelines by the oversight bodies supervising individual trials (ethics committees/institutional review boards, competent/regulatory authorities), and governance bodies managing the trial (sponsors), will contribute to the harmonisation of oversight and management procedures for a single protocol.

69. Implementation of the trial-specific approach therefore requires the “bottom-up” development of risk assessment tools and risk mitigation strategies suitable for multinational studies and validated for use in multiple countries. Expert groups from various countries, including representatives of the main stakeholders involved in clinical trials (patients, investigators, sponsors, ethics committees, regulatory authorities, insurers) should therefore be invited to develop a set of common tools and guidelines for objective risk assessment based on facts and data, on the one hand, and on common strategies for risk mitigation, including in particular safety reporting, insurance, monitoring, audits and inspections, on the other hand.

70. Some initiatives have already started developing such instruments (section I.2), including risk-adapted monitoring strategies or quality-by-design approaches. An umbrella organisation is now expected to take on the co-ordination of such activities to ensure a consistent and co-ordinated

development of global tools, receiving global validation, and available for use by the global clinical research community for international trials. Multiple tools, based on well-identified concepts and strategies, could be made available to the scientific community. The sponsor or investigator of a given trial would select among these tools the one that is best adapted to that trial.

71. Such tools should include two components:

- guidelines and decision trees supporting the definition and assessment of risk; and
- subsequent procedures and strategies to mitigate the risks identified.

72. This raises questions regarding:

- the general principles governing the development and implementation of such tools;
- the international panel of stakeholders involved in this development (academic and industry sponsors, investigators, regulators, ethics committees, patients), and their country of origin;
- how best to take advantage of established regional or national initiatives; and
- who should validate these tools (worldwide/nationwide).

73. To ensure appropriate and harmonised understanding and use of these tools, efficient and global training curricula will be a critical success factor. It will strengthen the consistency of risk assessment across countries, and across stakeholders (ethics committee members, regulators, investigators, sponsors, insurers). Similarly, the training of staff involved in the design, management and oversight of clinical trials in the field of risk mitigation procedures will be key to the quality of trials, the credibility of trial results, and the security of trial participants.

GLOSSARY

Terminology	Definition
Adverse event (AE)	Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. *(Directive 2001/20/EC)* An adverse event can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease in any subject in a clinical trial (including those in an untreated control group), whether or not considered related to the investigational medicinal product. *(Complement of the definition from Directive from ICH topic E6 1996)*
Adverse reaction (AR)	Any untoward and unintended responses to an investigational medicinal product related to any dose administered. (Directive 2001/20/EC) An unwanted effect caused by the administration of drugs. Onset may be sudden or develop over time. *(Source: clinicaltrials.gov)*
Approval and notification	Approval: Explicit approval: explicit positive opinion to initiate the trial granted by an oversight body following the submission of an application supported by a dossier. Implicit approval is achieved through a "tell and wait" notification, *i.e.* application and supporting dossier submitted to the oversight body and presumed approval in the absence of non-acceptance signals in a given time frame. Notification ("tell and do") refers to the submission of an application and supporting dossier to the oversight body followed by initiation of the trial without delay.
Clinical research	Clinical research refers to: 1. Patient-oriented **research**: research conducted with **human participants** (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly **interacts** with human participants. Excluded from this definition are *in vitro* studies that utilise human tissues that cannot be linked to a living individual. Patient-oriented research includes: Mechanisms of human disease; Therapeutic interventions; Clinical trials; or Development of new technologies. 2. Epidemiologic and behavioural studies 3. Outcomes research and health services research *(Source NIH Glossary)*

Terminology	Definition
Clinical trial (CT)	Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy (*Directive 2001/20/EC*). A clinical trial is a research study to answer specific questions about vaccines or new therapies or new ways of using known treatments. Clinical trials (also called medical research and research studies) are used to determine whether new drugs or treatments are both safe and effective. Carefully conducted clinical trials are the fastest and safest way to find treatments that work in people. Trials are in four phases: Phase I tests a new drug or treatment in a small group; Phase II expands the study to a larger group of people; Phase III expands the study to an even larger group of people; and Phase IV takes place after the drug or treatment has been licensed and marketed *(Source:clinicaltrials.gov).* Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes *(Source: WHO).*
Clinical trial authorisation (CTA)	An authorisation of a clinical trial by the competent authority of a Member State will be a Clinical Trial Authorisation (CTA) and will only be valid for a clinical trial conducted in that EU Member State. This authorisation does not imply approval of the development programme of the tested IMP. (*EU Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial October 2005*)
Ethics committee (EC)	An independent body in a Member State, consisting of healthcare professionals and nonmedical members, whose responsibility it is to protect the rights, safety and wellbeing of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent (*Directive 2001/20/EC).* The EC Regulations require a single ethical opinion for multicentre trials; the Directive 2001/20/EC calls it “the concerned ethics committee”.
Good clinical practice (GCP)	A guideline written by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The ICH-GCP E6 document describes the responsibilities and expectations of all participants in the conduct of clinical trials, including investigators, monitors, sponsors and independent review boards. GCPs cover aspects of monitoring, reporting and archiving of clinical trials and incorporates addenda on the Essential Documents and on the Investigator’s Brochure, which had been agreed earlier through the ICH process.
Good manufacturing practice (GMP)	Good Manufacturing Practice (GMP) is that part of quality assurance which ensures that medicinal products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorisation (MA) or product specification. GMP is concerned with both production and quality control*.(Source: MHRA)*

Terminology	Definition
Incremental risk	Incremental risk refers to the additional risk related to the participation in a clinical study, when compared to the risk related to the standard of care or of non-participation in the clinical study.
Informed consent form (ICF)	A form detailing the decision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative; if the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation. (*Directive 2001/20/EC)* Informed consent: A person's voluntary agreement, based upon adequate knowledge and understanding, to participate in human subjects research or undergo a medical procedure. In giving informed consent, people may not waive legal rights or release or appear to release an investigator or sponsor from liability for negligence. *(NIH Glossary)*
Institutional review board (IRB)	1. A committee of physicians, statisticians, researchers, community advocates, and others that ensures that a clinical trial is ethical and that the rights of study participants are protected. All clinical trials in the US must be approved by an IRB before they begin. 2. Every institution that conducts or supports biomedical or behavioural research involving human participants must, by federal regulation, have an IRB that initially approves and periodically reviews the research in order to protect the rights of human participants. *(Source: clinicaltrials.gov)* An administrative body established to protect the rights and welfare of human research subjects recruited to participate in research activities conducted under the auspices of the organisation with which it is affiliated. The IRB has the authority to approve, require modifications in, or disapprove all research activities that fall within its jurisdiction. *(Source: NIH Glossary)*
Investigational medicinal product (IMP)	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form. (*Directive 2001/20/EC*)
Investigator	A doctor or a person following a profession agreed in the Member State for investigations because of the scientific background and the experience in patient care it requires. The investigator is responsible for the conduct of a clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the leader responsible for the team and may be called the principal investigator. *(Directive 2001/20/EC)*
Monitoring	Act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s). *(ICH-GCP 1996)*

Terminology	Definition
Participant	An individual who participates in a clinical trial as either a recipient of the investigational medicinal product or a control (*Directive 2001/20/EC*) .The term subject is also used.
Participant information sheet	A document informing the participant about a clinical research study in which he/she is being asked to take part. The intention is to provide the participant with sufficient information to let him/her decide whether or not he/she wish to take part in this study.
Personal data	Any information relating to an identified or identifiable natural person hereinafter referred to as 'data subject'; an identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his or her physical, physiological, mental, economic, cultural or social identity. (*Directive 95/46/EC*)
Protocol	A study plan on which all clinical trials are based. The plan is carefully designed to safeguard the health of the participants as well as answer specific research questions. A protocol describes what types of people may participate in the trial; the schedule of tests, procedures, medications, and dosages; and the length of the study. While in a clinical trial, participants following a protocol are seen regularly by the research staff to monitor their health and to determine the safety and effectiveness of their treatment. *(Source: clinicaltrials.gov)*
Quality Assurance (QA)	All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s) (*ICH GCP*).
Regulatory authority (RA)	Regulatory body having the power to regulate. Based on the ICH, their tasks include reviewing of submitted clinical trial applications and clinical data and conducting inspections.
Sponsor	An individual, company, institution, or organisation, which takes responsibility for the initiation, management, and/or financing of a clinical trial (*Directive 2001/20/EC).* *Sponsor* means a person who initiates a clinical investigation, but who does not actually conduct the investigation, *i.e.*, the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A person other than an individual (*e.g.*, corporation or agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators *(CFR - Code of Federal Regulations Title 21).*
Sponsor-Investigator	An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (*e.g.*, it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator. (*ICH Harmonised Tripartite Guideline: Guideline For Good Clinical Practice E6)*
Standard of care	Treatment regimen or medical management based on state of the art participant care. *(Source: clinicaltrials.gov)*

Terminology	Definition
Stratified risk-based approach	One of two oversight and management methodologies, along with the trial-specific approach, that is applicable to each clinical trial. It is a risk-based methodology that is centred on the marketing authorisation status of a medicinal product. The stratified risk-based approach can serve as a common set of principles to be applied to legislation or regulatory frameworks across countries and nations. It focuses on the foreseeable safety of the medicinal product.
Trial-specific risk-based approach	One of two oversight and management methodologies, along with the stratified risk-based approach, that is applicable to each clinical trial. It is an approach that consists of the ethical review and related considerations relevant to operational processes and including insurance coverage, safety reporting, quality control and management procedures. As each clinical trial is unique, these ethical review and operational processes are examined on a trial-specific, case-by-case manner.

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