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COUNCIL

Council

REPORT ON THE IMPLEMENTATION OF THE RECOMMENDATION OF THE COUNCIL ON THE GOVERNANCE OF CLINICAL TRIALS

(Note by the Secretary-General)

JT03465098

1. This document presents a report by the Committee for Scientific and Technological Policy (CSTP) on the implementation of the Recommendation of the Council on the Governance of Clinical Trials [OECD/LEGAL/0397] (hereafter, the "Recommendation") and conclusions regarding the instrument's continued relevance, dissemination, and whether the instrument requires updating or revision.

Background

2. The Recommendation was adopted by the Council on 10 December 2012 [C(2012)167; C/M(2012)14] on the proposal of the CSTP. The objective of the Recommendation is to improve consistency among national regulations and to streamline procedures by introducing a proportionate regulatory approach that facilitates international co-operation in clinical trials.

3. 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) 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

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

4. The Recommendation provides that Member and non-Member countries having adhered to it (hereafter "Adherents")[1] adapt their national regulations and procedures to incorporate a risk-based oversight and management methodology for clinical trials, taking into account the principles set in the Annex of the Recommendation.

5. In the Recommendation, the Council invites the CSTP "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 thereon to Council within four years of its adoption and as appropriate thereafter".

Methodology

6. The monitoring was initially delayed to be fully integrated within the 2017 general CSTP action plan for reviewing its legal instruments [DSTI/STP(2017)23], developed following the OECD-wide standard-setting review.

7. A questionnaire was developed by the Secretariat and approved by the CSTP's Global Science Forum (GSF) at its 38th meeting in October 2018. It was then transformed into a check-box online questionnaire for facilitating responses and analysis.

8. A link to the questionnaire was sent at the end of 2018 to all Adherents, as well as to non-Adherents participating in meetings of the CSTP in view of their interest in the topic, for completion. The consultation was prolonged until fall 2019 to allow for late responses to be analysed. The analysis of the questionnaire's answers was conducted by the Secretariat with input from experts from the Clinical Research Initiative for Global Health (CRIGH), who provided qualitative information.

[1] To date, the Recommendation has one non-Member Adherent: Brazil.

Process

9. GSF delegates discussed the draft report [DSTI/STP/GSF(2020)5] at the 42nd Session of the GSF on 23-24 April 2020 and had until 22 May 2020 to provide further comments to the Secretariat. The draft was also submitted to the Health Committee for comments. A small number of precisions provided by Delegations were incorporated into the revised version sent to the CSTP for approval.

10. The CSTP approved the draft report and its transmission to the Council under the written procedure, on 31 July 2020, [DSTI/STP(2020)11], with a minor factual error corrected in paragraph 58 at Norway's request and reflected in the Report set out in the Annex to this document.

11. The Council is invited to note and declassify the report. Thereafter, a link to the report will be included in the public webpage of the Recommendation on the online Compendium of OECD legal instruments.

Dissemination

12. Initial dissemination to relevant national health authorities was carried out by GSF and CSTP delegates. In addition, considering the complexity of the issue and that such a global Recommendation required a significant follow-up effort and strong commitment from the relevant partners at national / regional level, a follow-up group was established within the GSF to explore options for facilitating its implementation.

13. This effort led to the launch, in 2017, of the Clinical Research Initiative for Global Health (CRIGH) as an international research consortium. CRIGH's mission is to serve as a support to international collaboration in clinical research, for the benefit of patients, healthcare professionals, and health systems worldwide. Its Secretariat is shared between the US National Institutes of Health and the European Clinical Research Infrastructure Network (ECRIN). CRIGH is based on a network of national / regional organisations acting as clinical research infrastructures, delegated by national governments, and has actively supported the implementation of the Recommendation, as well as the development of this report.

The Recommendation and the COVID-19 crisis

14. The survey on the implementation of the Recommendation was carried out in 2019, i.e. before the outbreak of the SARS-CoV-2 (COVID-19) pandemic. As such, it did not include questions regarding the relevance of the Recommendation to such crises and the report does not directly address such questions. Following the discussion at the 42nd meeting of the GSF in April 2020 during which this issue was raised, the Secretariat aims to provide such a perspective in order to complement the content and findings of the report, set out in Annex A to this document.

Summary and conclusions

15. This review of the implementation of the Recommendation has demonstrated a growing awareness regarding the need to adopt a risk-based approach to oversight and management methodology in clinical research regulation. Although countries may still have different interpretations of risk-based regulatory processes, a very high percentage of those Adherents that responded to the questionnaire (hereafter "Respondents") have started to adopt this approach. This should speed up the implementation of the Recommendation as it proposes a validated standardised framework. Indeed, Respondents who have recently or are in the process of modifying their regulation to incorporate a risk-based approach, have used or are planning to use the Recommendation.

16. Another important and positive element is that, whenever Respondents have set up a risk-based approach, they have usually adapted their whole regulatory procedures to take into account the consequences of risk categories in the various elements of the regulatory approval process. It is worth nothing that, as many Adherents have already adopted a risk-based approach, amending their existing national regulatory processes to fully implement the Recommendation would not require major changes in their system.

17. However, this review also revealed a lack of standardisation of regulatory process between Respondents, even when they have adopted a coherent risk-based approach. Even in the European Union (EU), where common regulation should have led to harmonisation, large differences in interpretation of the various elements and terms remain. This is a major concern as such heterogeneity will continue to considerably hinder the development of international clinical trials, an issue that the Recommendation seeks to address. Thus, although a majority of Respondents consider their existing regulatory process as satisfactory, which is understandable when considering clinical research carried out within a national context, the development of international clinical research requires the adoption of common standards and procedures.

18. This review demonstrates the high ongoing relevance of the Recommendation and its importance for countries in the process of revising their current regulations. Suggestions for updates were minimal and primarily reflected the need to continue assessing the relevance of the Recommendation in coming years as new health technologies that should be considered in clinical trial regulations evolve, especially in light of the current COVID-19 pandemic.

19. In conclusion, while some key elements of the Recommendation are being progressively implemented by Adherents, there remains further work to do. For this reason, Adherents – particularly those planning to adapt their existing regulatory frameworks – should focus on taking further steps to implement the provisions of the Recommendation in the coming years. One area on which Adherents' focus should be particularly concentrated is the development of common international standards and procedures. In addition, EU Member States could take into account the provisions of the Recommendation in the context of their discussions on regulations.

20. Furthermore, it is proposed that Adherents, individually as well as through the CSTP and the Secretariat, work with relevant national and international organisations to facilitate broader dissemination of the Recommendation among relevant stakeholders.

21. In view of the additional work to be done, it is proposed that the CSTP continue to review the implementation, dissemination, and continued relevance of the Recommendation and report again to the Council thereon in five years' time.

Proposed action

22. In the light of the preceding, the Secretary-General invites the Council to adopt the following draft conclusions:

THE COUNCIL

a) noted document C(2020)108, in particular the report set out in its Annex, and agreed to its declassification;

b) encouraged Adherents to the Recommendation to continue their efforts to implement and disseminate the Recommendation and to address the main findings and challenges identified in the summary and conclusions section of the report;

c) invited the Committee for Scientific and Technological Policy to:

   i) support Adherents in addressing the findings and challenges identified in the summary and conclusions section of the report;

   ii) report to the Council on the implementation, dissemination, and continued relevance of the Recommendation in five years.

Annex A. The Recommendation and the COVID 19 crisis

23. The survey on the implementation of the Recommendation was carried out in 2019, i.e. before the current SARS-CoV-2 (COVID-19) pandemic. As such, it did not include questions regarding the relevance of the Recommendation to such crises and the report does not directly address such questions. This issue was raised during the 42nd meeting of the GSF in spring 2020 and this annex prepared by the Secretariat aims to provide such a perspective in order to complement the content and findings of the report, set out in Annex B to this document.

24. 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 provided 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.

Emergency clinical trials in the COVID-19 crisis

25. Since the global outbreak of COVID-19 in early 2020, a wide range of researchers, supported by public and private funders, have taking actions to accelerate R&D on vaccines and treatments. As a result, many new pre-clinical research studies and clinical trials have been launched. Hundreds of clinical trials related to COVID-19 have been registered since the beginning of 2020. Most of them test drug candidates, but several vaccine candidates are also being tested. Information on these clinical trials can be found on the World Health Organization (WHO) website[2] and an analysis on the development of COVID-19 vaccines and treatments is provided in policy brief (Treatments and a vaccine for COVID-19: the need for coordinating policies on R&D, manufacturing and access, 2020) developed by the OECD Health division secretariat.

Adaptation of clinical trial regulatory processes for COVID-19

26. Confronted with a massive demand for new treatments as quickly as possible, most national and regional regulatory authorities have developed accelerated clinical trial authorisation procedures for COVID-19 treatments and vaccines; these concern **initial marketing authorisation applications** as well as **extension applications for authorised medicines** that are being repurposed for the treatment of COVID-19. Detailed information on adapted regulations from a large number of countries can be found at https://www.sunnikan.net/fr/essais-cliniques-et-covid-19/.

27. Adaptation of regulatory requirements and processes typically includes:

- The need to conduct a risk assessment for the trial
- Tolerance to protocol deviation
- Possibilities to delegate part of the trial to sub-investigators and to local sites
- Use of electronic alternatives to documentation
- Flexible drug delivery processes to patients

[2] https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov

- More flexible and proportionate oversight and monitoring (using remote mechanisms)
- More flexible conduct of ethical reviews (although no change to patient safety rules)

28. Interestingly, some international initiatives have been developed to facilitate exchanges between regulatory authorities on adapted clinical trial registration requirements. The Trial Master File Reference Model[3] (TMF Reference Model), managed under the auspices of the Drug Information Association (DIA) Document and Records Management Community[4] conducted a very informative review of national Health authorities' guidance[5] on COVID-19. Initiatives have been taken to facilitate a common approach and recommend good practices, but limited consultations appear to have been carried out between regulatory authorities before they each published their own adapted fast-tracked procedures for COVID-19-related trials.

Relevance of the OECD Recommendation

29. Many of the clinical trials for COVID-19 treatments and vaccines have been launched at national level and are conducted in health institutions within a single country, having only to fulfil the (often accelerated and streamlined) regulatory requirements of a single national regulatory authority. However, the medical community realised early on that these national initiatives, often of limited amplitude (in terms of number of patients recruited and the type or doses of treatments to be tested) would, in some cases, not provide enough statistical power to rigorously evaluate treatments.

30. A number of international trials have therefore been launched, their goal being to recruit enough patients in hospitals from several countries to test a diversity of potential treatments and posology and come up with sufficiently robust statistical data to inform relevant regulatory and health authorities.

31. Solidarity[6] is probably the largest international therapeutic trial initiative and is fostered by the World Health Organization (WHO). The Solidarity Trial will compare four treatment options against standard of care, to assess their relative effectiveness in managing patients with COVID-19. By enrolling patients in multiple countries, the Solidarity Trial aims to rapidly discover whether any of the tested drugs slow disease progression and/or improve survival. Other drugs can be added into this trial based on emerging evidence of potential usefulness.

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

[3] https://tmfrefmodel.com/

[4] https://www.diaglobal.org/

[5] https://tmfrefmodel.com/wp-content/uploads/TMF-RM-Meeting-30-MAR-2020.pdf

[6] https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments

33. Discovery is a large clinical trial focusing on several antiviral drug treatments. It is led by the French National Institute for Health and Medical Research (INSERM) within the European REACTing consortium, and was planned to link up to the Solidarity initiative. The Discovery trial was expected to enrol 3 200 participants across France, Austria, Belgium, Germany, Luxembourg, the Netherlands, Spain, Sweden and the United Kingdom. However, this trial has run into serious difficulties to achieve its initial recruitment goals. Obstacles include differences in regulatory requirements between countries and the treatment costs per patient that many national authorities have refused to cover. As a result, patient recruitment in mid-May was still largely restricted to France and the trial risks being characterised as a "European failure"[7].

34. These examples show that, despite the efforts of the clinical trial regulatory community to streamline procedures, there is a need for a better harmonisation of national regulatory requirements and processes, as provided for in the Recommendation.

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

36. In emergency situations, the diversity of national regulation becomes a real challenge. This is even more the case for public research institutions, which do not have the resources to file multiple applications and address multiple different national requirements, but are at the frontline for the discovery of treatments. The first action when confronted with new infectious diseases is to test and compare existing drugs and therapeutics, and such trials are usually run by public hospitals, while the pharmaceutical industry concentrates on the development of new treatments, which are likely to have a greater financial return.

37. Taken together, the above considerations and examples illustrate that the Recommendation's advocacy for the adoption of a standardised risk-based approach that would streamline clinical trial regulation for existing drugs and therapeutics and the harmonisation of regulatory requirements has only become more relevant in the context of international public health crises, such as the current COVID-19 pandemic.

[7] https://www.lemonde.fr/sciences/article/2020/05/01/covid-19-sur-les-essais-cliniques-l-europe-est-un-echec_6038383_1650684.html

Annex B. Report on the implementation of the Recommendation on the Governance of Clinical Trials

1. Background

1. Medical research involves testing new discoveries by carrying out carefully controlled investigations on patients - known as clinical trials. This includes testing new medicines or new therapies, as well as optimising existing medicinal products and procedures to improve health and welfare.

2. While many clinical trials are conducted by the pharmaceutical industry on new medicinal products, clinical trials initiated and driven by academic investigators for non-commercial purposes also form a substantial and critical element of medical research. Many of these trials are driven by pressing public health needs and scientific opportunities that do not offer a strong business case to private companies. This can be due to the small number of patients affected (e.g. orphan diseases), to insufficient profitability of the treatments (e.g. paediatric therapies, pathologies in developing countries) or because the objective is simply to optimise existing procedures and prescriptions (e.g. finding the optimal drug combination or timing).

3. Trials are also needed to address questions relevant to the health technology assessment, comparing marketed products to determine the treatment option with highest efficacy, safety and cost-effectiveness for a given disease condition, or for a subgroup of patients. To find the required diversity of trial participants as well as to enhance the likelihood that the research findings are broadly applicable worldwide, these clinical trials increasingly involve international studies and collaboration.

4. Tight national regulations have been introduced over time to ensure patient safety and methodological quality. Depending on the country and on the nature of the trial, supervision is either based on specific legislation, on rules originating from the competent authorities, or merely on ethical guidelines. As a result, applicable regulatory mechanisms differ widely across countries.

5. The current administrative complexity is such that it leads 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 dramatically reduced. This is particularly true for the conduct of international clinical trials that involve multiple centres, and for trials initiated by academic structures that may not have well-developed administrative support.

6. In addition to the challenges presented by the existing national regulatory complexity, many clinical trial investigators have to abide by administrative requirements that are poorly adapted to the nature of their study. Existing regulations have mostly been developed to guide the conduct of traditional trials for new medicines, which present an unknown risk for patients. They are often less suited to address many academic trials that use drugs that are already marketed and often present lower risks.

7. In recent years, there has been growing demand for better ways of aligning the regulations between countries. The idea of a new harmonised regulatory framework has therefore emerged, in which requirements would be based on the risks associated with the study. 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 requires 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 is broad consensus on the desirability of adopting a risk-based approach to clinical trials regulation, there is not yet a mechanism to help align regulatory requirements for clinical trials worldwide, or to develop and validate the risk assessment tools and risk-adapted monitoring procedures needed for the use of such risk-based approaches in international clinical trials.

9. It is with this in mind that the OECD Global Science Forum (GSF) worked to establish a common framework for the better governance of clinical trials. This framework introduces a risk-based oversight and management methodology for clinical trials. It combines a stratified approach that is based on the marketing authorisation status of the medical product and can be applied in a common manner across countries' regulatory frameworks, with a trial-specific approach that considers other issues such as the type of populations concerned by the trial, or the informed consent of the patients. The principles that were ultimately embodied in the Recommendation on the Governance of Clinical Trials [OECD/LEGAL/0397] (hereafter "the Recommendation") were developed by the Committee on Scientific and Technological Policy (CSTP), through the GSF – a subsidiary body thereof, following extensive consultations and intensive work by an expert group over six months. The Health Committee, also provided input for the development of the Recommendation.

10. The Recommendation was adopted by the OECD Council in December 2012 and seeks to facilitate international co-operation in clinical trials on medicinal products, particularly for trials initiated by academic institutions, and calls for an adaption of national regulations and procedures to incorporate a risk-based methodology for the oversight and management of clinical trials. Although this Recommendation was primarily driven by the need to facilitate co-operation among academic groups for clinical trials undertaken for non-profit purposes, Member and non-Member countries having adhered to the Recommendation (hereafter "Adherents")[8], were invited to consider extending the implementation of the Recommendation to the oversight and management of all clinical trials regardless of the objective of the trial.

11. 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 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.

12. In the Recommendation, the OECD Council instructed the CSTP to "monitor the implementation of this Recommendation, review 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".

13. The review was delayed to be fully integrated within the 2017 general CSTP action plan for reviewing its legal instruments [DSTI/STP(2017)23], developed following the OECD-wide standard-setting review.

[8] To date, the Recommendation has one non-Member Adherent: Brazil.

14. This report therefore contains an analysis of the current level of implementation of the Recommendation.

2. Methodology

15. A qualitative survey questionnaire was developed by the Secretariat with input from the members of the Governing Board of the Clinical Research Initiative for Global Health (CRIGH). CRIGH is an initiative which stemmed from the work of the GSF on Clinical Research to foster the implementation of its 2011 report on Facilitating International Co-operation in non-Commercial Clinical Trials. Several members of the Governing Board of CRIGH participated in the Expert Group that prepared the 2012 Recommendation.

16. The survey questionnaire was divided into three parts:

1. A set of questions to learn whether any risk-based methodology for the oversight and management of clinical trials was included into the clinical trial regulatory process, the formal process involved, what types of trials were included in the process, whether this process followed the Recommendation or other guidelines and any challenge that may have been encountered in that process;
2. More specific questions on the details of relevant risk-based methodologies (risk categories, relevant provisions for the whole regulatory process) and a qualitative analysis of this process;
3. Questions regarding the evaluation of the country's current process and any need for revision or suggestions regarding the implementation of the Recommendation.

17. The questionnaire was reviewed and approved by the GSF at the 39th meeting of the GSF in October 2018. It was then transformed into a check-box online questionnaire for facilitating responses and analysis. Open-ended questions where included to provide opportunities for additional feedback.

18. A link to the questionnaire was sent to all Adherents, as well as non-Adherents participating in meetings of the CSTP in view of their interest in the topic, for completion. Delegations were requested to forward this link to the relevant authorities, with the understanding that only one response per country would be provided.

19. The analysis of the questionnaire answers was conducted by the Secretariat with input from CRIGH experts, who provided qualitative information whenever needed. This analysis is based on responses obtained from 22 Adherents[9] and from Colombia[10] and Thailand (hereafter "Respondents").

3. Process

20. GSF delegates discussed the draft report at the 42nd Session of the GSF (23-24 April 2020), and had until 22 May 2020 to provide further comments. The draft was also submitted to the Health Committee for comments. A small number of precisions provided by Delegations were incorporated into the revised version sent to the CSTP for approval.

21. CSTP approved the draft report and its transmission to the OECD Council via written procedure on 31 July 2020, with a minor factual error corrected in paragraph 58 at Norway's request [DSTI/STP(2020)11].

[9] Australia, Belgium, Canada, Chile, Czech Republic, Denmark, Estonia, France, Germany, Ireland, Italy, Japan, Latvia, Lithuania, Norway, Poland, Portugal, Spain, Sweden, Switzerland, United Kingdom, United States.

[10] Colombia became a member of the OECD on April 2020 and is now Adherent of the Recommendation

22. The Council may invite the CSTP to take further follow-up actions. Thereafter, a link to this report will be included in the public webpage of the Recommendation on the online Compendium of OECD Legal Instruments.

4. Dissemination

23. Initial dissemination to relevant national health authorities was carried out by GSF and CSTP Delegations. In addition, considering the complexity of the issue and that such a global recommendation required a significant follow-up effort and strong commitment of the relevant partners at national / regional level, a follow-up group was established within the GSF to explore options for facilitating its implementation.

24. This effort led to the launch in 2017 of the Clinical Research Initiative for Global Health (CRIGH) as an international research consortium. CRIGH's mission is to serve as a support to international collaboration in clinical research, for the benefit of patients, healthcare professionals and health systems worldwide. CRIGH is based on the connection of national / regional organisations acting as clinical research infrastructures, delegated by national governments, and has actively supported the implementation of the Recommendation and the development of this report.

25. In addition to the above, and considering the complexity of the issue, the GSF also developed an explanatory memorandum to help assist Adherents understand the context and facilitate the implementation of the principles contained in the Recommendation.

5. Implementation

26. The Recommendation was intended to facilitate international co-operation in clinical trials on medicinal products, particularly for trials initiated by academic institutions. It called for an adaption of national regulations and procedures to incorporate a risk-based methodology for the oversight and management of clinical trials. Although this Recommendation was primarily driven by the need to facilitate co-operation among academic groups for clinical trials undertaken for non-profit purposes, Adherents were invited to consider extending the implementation of the Recommendation to the oversight and management of all clinical trials regardless of the objective of the trial.

27. 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 combine:

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

Implementation of a risk-based methodology for clinical trials

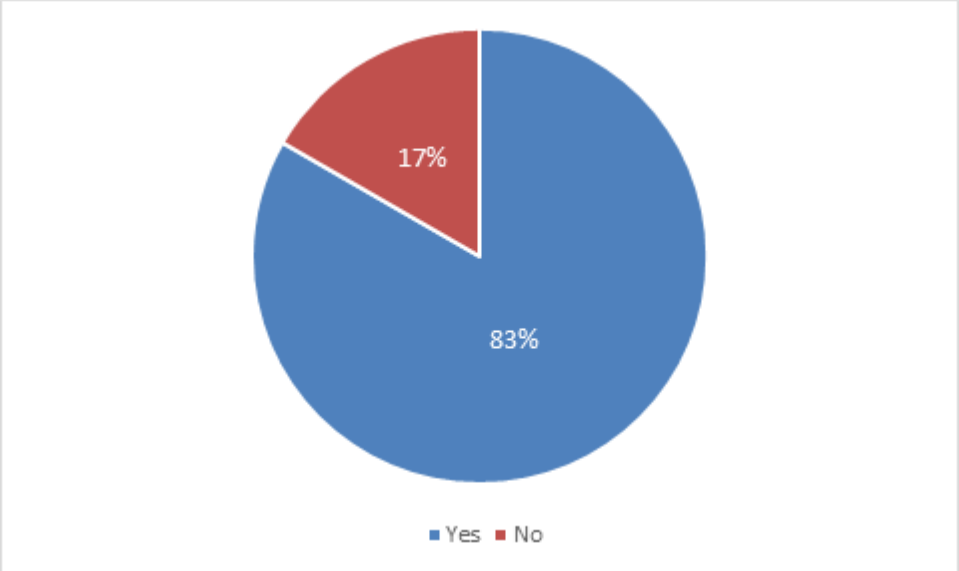
28. The primary focus of the monitoring report is whether Adherents implement a risk-based oversight and management methodology for clinical trials, combining a stratified and trial-specific approach, since this is the core of the principles set out in the Recommendation.

29. Among the Respondents, 83 % responded positively (20 out of 24, see Figure 1), to the question of whether any risk-based methodology for the oversight and management of clinical trials was included into their regulatory process, a high proportion. However, this high percentage should be analysed together with the more uneven feedback on how such an approach is actually integrated in the regulatory or legal process, how it is being

implemented and what such as risk-based methodology actually covers in different countries.

Figure 1. Respondents with a regulatory process that includes a risk-based methodology for the oversight and management of clinical trials

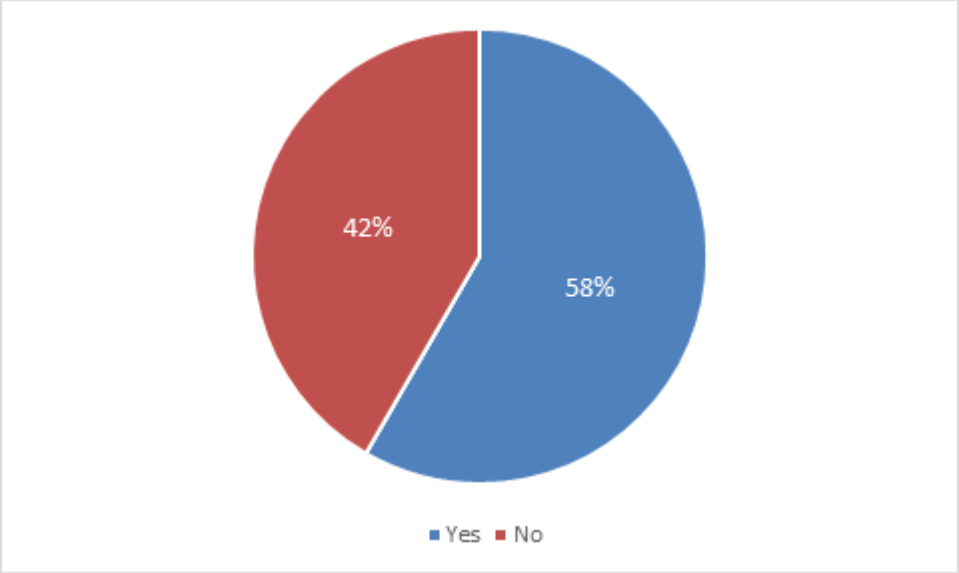
Q: Do your country's regulatory processes include a risk-based methodology for the oversight and management of clinical trials? (this excludes trials for veterinary products)



30. Risk-based methodologies are formally adopted into regulatory framework in only about 60% of the cases analysed (10 out of 24, see Figure 2). In the case of the other Respondents, risk-based methodologies are rather included into existing regulations as a more flexible mechanism, which may not be precisely defined. Such regulation or practice have often been introduced rather recently although provisions for risk-based methodologies were introduced much earlier in some Respondents, for example, in Australia and in the United States.

Figure 2. Respondents having a risk-based methodology formally adopted into their regulatory framework

Q: Was a risk-based methodology formally adopted as the regulatory framework?

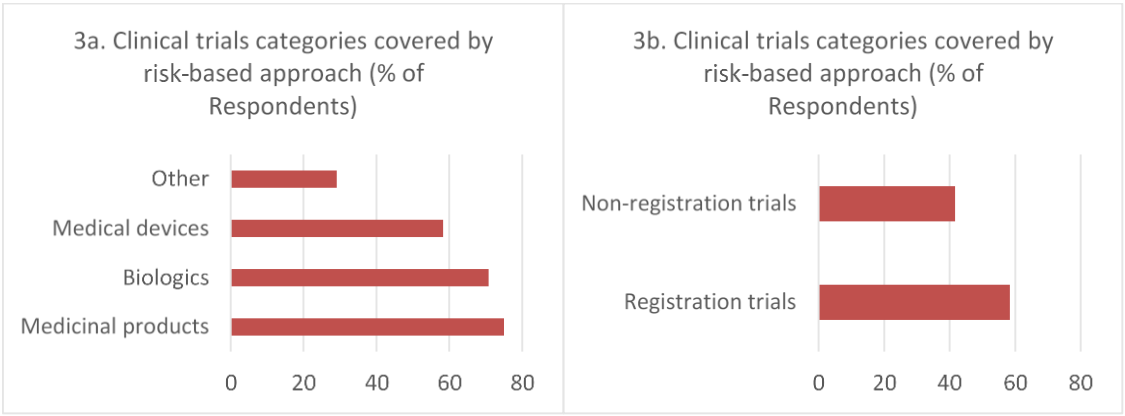


31. The types of clinical trials covered by risk-based methodologies vary greatly among Respondents (Figures 3a and 3b). This ranges from a very restricted number of fields (*i.e.* in Germany where this applies only to trials related to medical devices or in Estonia where only trials for medicinal products are concerned) to most or all clinical trials (such as in Australia or in the United States).

Figure 3. Types of clinical trials covered by a risk-based approach

Q: What types of trials are covered by risk-based regulation in your country? (several options)

Registration trials refers to clinical trials designed to secure regulatory approval; non-registration trials to those not conducted to obtain, maintain or expand regulatory approval

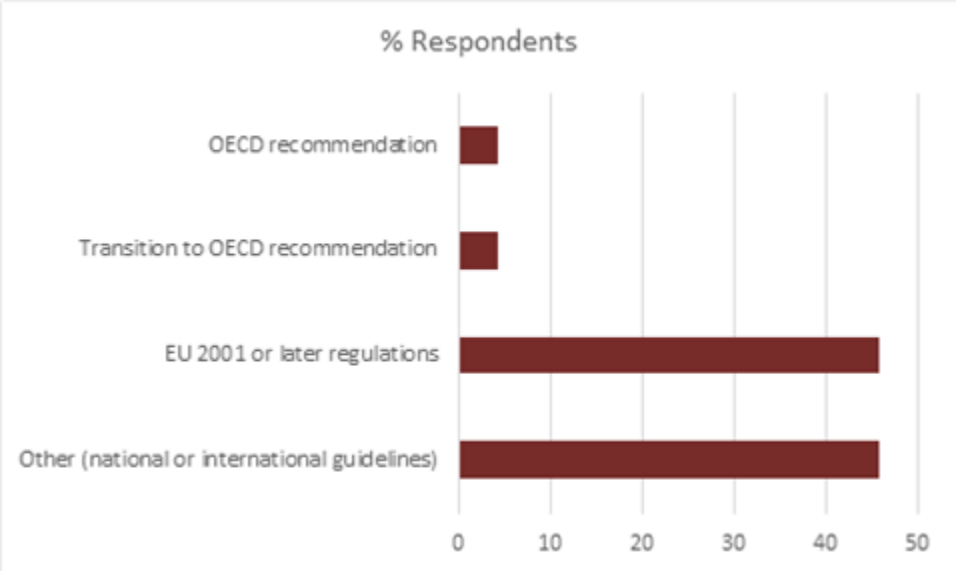


32. Regulatory processes are still mostly based on legal or regulatory texts that preceded the Recommendation. For about half of Respondents, regulation is defined by national laws or regulatory texts (see Figure 4). These regulations may also be influenced by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for

Human Use (ICH) in some countries. ICH is an international non-profit Association under Swiss law bringing together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration. The updated ICH-GCP guidelines include risk-based provisions for quality management (ICH GCP E6 (R2), 2015 3) although not according to precise risk categories as described in the Recommendation.

Figure 4. Type of text on which the regulatory process is based

Q: Is it based on the Recommendation as mentioned above or on other texts (if so please provide the reference)?



Note: Additional relevant question in the questionnaire: *Q*: *Were there any specific challenges linked to this implementation? (please describe).*

33. A number of Adherents have recently revised their regulations according to the OECD's Recommendation (or are planning to), such as Switzerland and Canada.

34. The situation is more complex in the European Union (EU) where a range of EU Regulations and Directives address the regulation of clinical trials. These regulations are generally compatible with the Recommendation, mandating approaches that would imply varying degrees of implementation of the Recommendation by EU Member States.

35. EU regulation of clinical trials for medicinal products was harmonised in 2001 by the adoption of Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, (hereafter the "Clinical Trials Directive"), which had to be implemented by EU Member States by 1 May 2004. In response to the clinical research community, this Directive recently undertook a revision process to improve the harmonisation and simplification of the administrative and regulatory aspects of clinical trials. The Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (hereafter "Regulation (EU) No 535/2014") now includes provision for low-intervention trials, which are partly aligned with the Recommendation (with two categories instead of three). However, this EU Regulation still awaits implementation. Therefore, EU Member States are still formally managing their clinical trials under the Clinical Trials Directive, which had no provision for risk-based

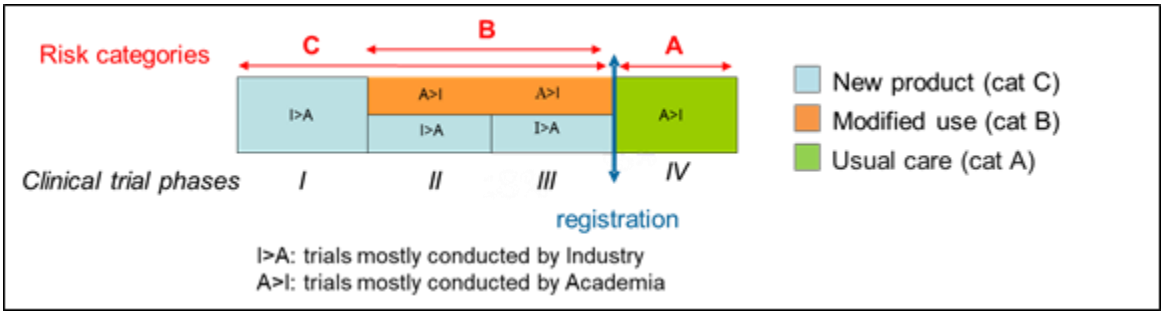
methodologies. Moving forward, implementation of Regulation (EU) No 535/2014 will bring EU Member States further into line with risk-based methodology provided for in the Recommendation.

36. Looking beyond the content of EU regulation, a number of EU Member States have introduced measures at the national level, some that are non-binding recommendations and others with more binding effect. For example, the French Legislation (Law No 2012-300 of 5 March 2012 on research involving the human person, (hereafter the "Jardé Law"), implemented in 2016 through Decree No 2016-1537 of 16 November 2016 on research involving the human person) includes, for clinical research other than clinical trials on medicinal products (which are covered by the Clinical Trials Directive and in the future by Regulation (EU) No 536/2014) the definition of a risk classification (research with minimal risk, with higher-than-minimal risk, and no-risk research) and of risk-based provisions.(on regulatory requirements, on monitoring, on the collection of informed consent). Other EU Member States however (such as Poland) still only apply the Clinical Trials Directive without any risk-based categories.

37. Regulation (EU) No 745/2017 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (hereafter "Regulation (EU) No 745/2017") also awaiting implementation, include provisions based on the risk associated with the category of devices. In particular, the marketing authorization (CE labelling in the EU) will be provided for 'high risk' devices (class III and some class IIb) based on evidence for efficacy and safety through clinical trials (called 'clinical investigation' in the EU wording). These instruments go further towards bringing EU Member States in line with the risk-based methodology provided for in the Recommendation.

38. A critical element in the implementation of a risk-based methodology for clinical trial is the definition of the risk categories. In the Recommendation, three risk categories were defined which were largely based on the marketing authorisation status of the product (Figure 5).

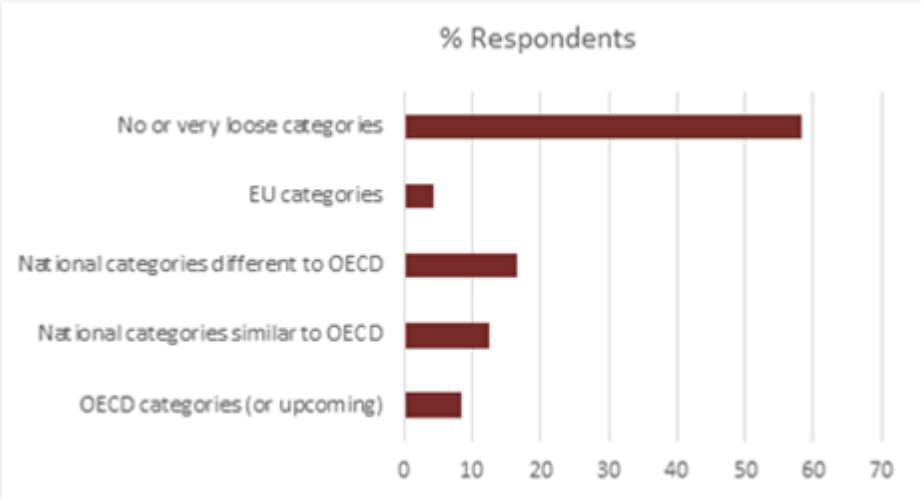
Figure 5. Risk categories defined in the Recommendation



39. Currently, only a minority of Respondents have clearly identified risk categories (Figure 6). In some countries such as Belgium, they are not really described and the current system is based rather as a continuum where studies are accepted when there is a perceived positive risk-benefit ratio.

Figure 6. Types of risk categories included in the regulatory processes

Q: Does your national regulation define risk categories according to the Recommendation (three categories based on marketing authorization status)? Or according to another regulation (please describe). What are these different risk categories? (please specify)



40. The situation is likely to evolve in the EU once the new regulations are implemented, an evolution that will provide scope for increased implementation of the approach set out in the Recommendation among EU Member States.

41. Looking beyond the EU, risk categories (when they exist) are specific to each Respondent and are usually different from those defined in the Recommendation, since most national regulations precede the Recommendation. This is unsurprising. Nevertheless, in several Respondents (Australia, United Kingdom, United States), the existing risk categories set up by national regulations are largely similar to those prescribed in the Recommendation and could be adapted with minimal changes to fully align with them. Switzerland has adopted the OECD risk categories with the revision of its regulation in 2014, and Canada is planning to do the same in coming years.

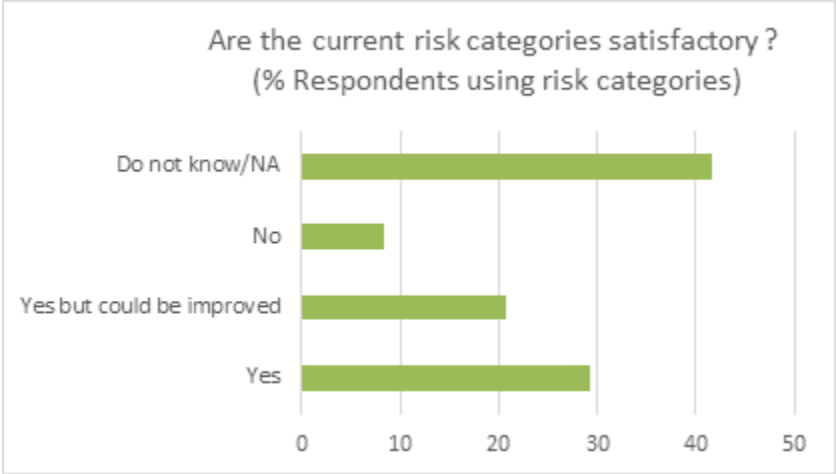
42. It is interesting to note that Respondents that have implemented risk categories based on the Recommendation report minimum challenges in that process. Switzerland, which has implemented risk categories based on the Recommendation, indicated "all concerned stakeholders were supportive of the new regulation in human research based on this Recommendation". Spain indicated that a possible issue for implementing new risk categories was the interpretation of "low-level intervention beside standard practice". In Canada, some challenges were identified with the legal interpretation of the current regulations, which is why support has been expressed by multiple stakeholders for moving in the direction of a clear risk-based approach such as defined by the Recommendation. France reported that it had not been possible to expand the Jardé Law to clinical trials on medicinal products, because, as an EU Member State, France had to follow the Clinical Trials Directive, which did not include risk-based provision. This will partly be fixed when the Regulation (EU) No 536/2014 is implemented, but the EU regulation also streamlines the use of a risk-based approach restricting the implementation of risk-based provisions to the risk categories defined in the Regulation as "low-intervention trials". The definition of "minimal risk" was also a source of debate in the Jardé Law. Japan had some challenges in their current system concerning non-commercial clinical research, and has now started to implement a Risk Based Approach into their investigator-initiated clinical trials, after the publication of ICH guideline E6(R2). Japan Ministry of Health, Labour and Welfare also

amended the GCP guidance of clinical trials for marketing authorisation of drugs to introduce a risk based approach into the clinical Quality Management System.

43. Although a majority of Respondents that use defined risk categories in their regulatory process report that those are satisfactory (Figure 7), a significant number also indicate that their current categories could/should be improved, or that they are not satisfactory at all, thus highlighting the relevance of the Recommendation. Furthermore, among those indicating that they are satisfactory, several Respondents nevertheless also indicated that further upcoming changes were expected from the new regulation to be implemented (in the EU) or that further feedback from the community was required.

Figure 7. Satisfaction over current risk categories

Q: Are these risk categories satisfactory within your national context? or in need of further development (please provide details)



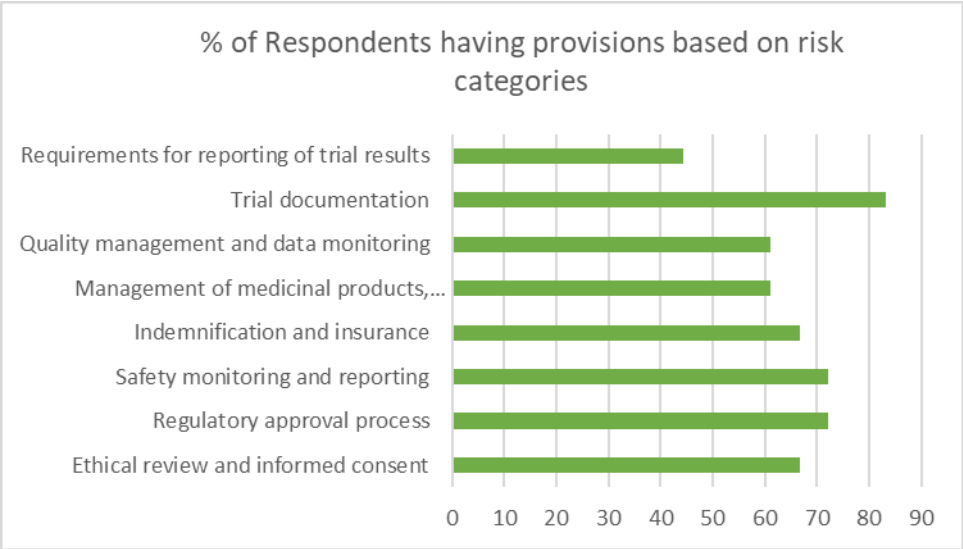
Implementation of a risk adaptation to the clinical trial process

44. The second major element of the Recommendation concerns the adaptation of the oversight and governance processes to the risk related to the various risk categories. That is to establish common principles to mitigate potential risks for each trial and adapt the procedures accordingly, optimising burden and costs while ensuring high quality data, integrity and rights of patients.

45. It was therefore important to investigate how Adherents had integrated a risk adaptation to their authorisation and regulatory processes. Survey results from Respondents (Figure 8) indicate that, when risk categories are defined in some manners (75% of the case surveyed), adequate provisions are made to mitigate risks alongside the various elements of the regulatory approval process in a significant majority of Respondents.

Figure 8. Provisions based on risk categories included in national regulations

Q: Does your national regulation include specific provisions based on the risk categories, or the risk assessment, related to (various options)



Note: Additional relevant question in the questionnaire: *Q: If there are requirements for reporting of trial results (transparency requirements), is reporting carried out at the individual or aggregate level and does this include return of information to the research participant?*

46. Unsurprisingly, most Adherents that have adopted risk categories have adapted the trial documentation requirements; typically this means that Investigational Medicinal Product (IMP) dossier are not required for low-risk trials since the said product is used in the trial according to usual care.

47. Transparency requirements for reporting trial results appear less often adapted to the risk, probably because regulatory agencies do not wish to adapt their established procedures. However, a number of Respondents have nevertheless adapted their requirements or practices. In Canada, the requirement to report trial results will be included in the revised regulations. In the European Union, the aggregated results are published in the European Clinical Trials Database at the end of the clinical trial. In Portugal, aggregated results are in addition also made public at the end of the clinical trial at the National Registry for Clinical Studies. France reported that, beside the mandatory reporting of aggregated results, individual patient data sharing was the object of a national recommendation (open science policy), enforced by some journal editors, but that the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) did raise significant obstacles to its implementation.

48. Additional requirements have also been set up in some Respondent countries. In Canada, the current policy supports the removing of some labelling and record retention requirements for low risk drugs used in clinical trials. In Chile, local regulations have introduced restrictions in certain areas of research, such as that included in Article 28 of Law 20584, which requires that a participant in a trial be in full mental and cognitive capacity to provide informed consent. This has hampered trials in the areas where patients have mental or cognitive deficits. Also, the requirement of a sponsor to provide free, lifelong treatment for participants of a trial, whatever the risk, has had a negative impact. Thus, most of the clinical research in Chile is in the Phase III/IV stages, with foreign corporations/CROs

constituting the majority of sponsors. These discrepancies highlight the need for better harmonisation.

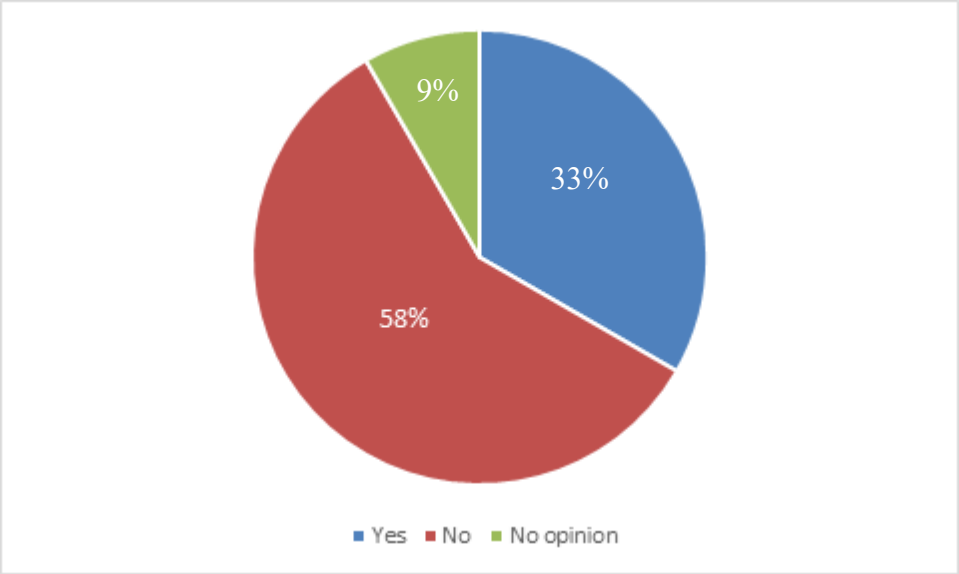
6. Continued relevance of the Recommendation

49. Although this Recommendation was only adopted at the end of 2012, national regulations of clinical trials are still in the process of being revised in many Adherents and this monitoring exercise was an opportunity to gather feedback on its relevance in current and future regulatory contexts.

50. Overall, a significant majority of Respondents did not see the need to modify the current Recommendation (Figure 9). Nevertheless, some Respondents suggested that it could in the future be adapted to take into account some particular concerns.

Figure 9. Need for revising the Recommendation

Q: Do your relevant authorities consider that there is a need for revision(s) (modification, deletion, or addition) to any parts of the Recommendation? (Figure); If yes, what should that include?



Note: Additional relevant questions in the questionnaire:
Q: Are there any technical or policy changes that have taken place or are planned and which might inform a future review of the Recommendation?
Q: Have your national regulations been evaluated or is it planned and if yes, are there evaluation reports available?

51. For example, it was suggested that advanced innovative therapies (e.g. 3-D printing of implants or tissues, etc.) could be taken into account in a future revision. Similarly, cell and gene therapy as well as genomics were identified as playing an increasing role in medical therapy, and that information was required to control these methodologies with the same standards. France underlined that individual patient data sharing, and secondary use of data, was an emerging topic over the past few years, which could be integrated in a future revision. It was also suggested that indemnification and insurance could be more clearly related to the risk categories, to avoid situations such as described by Chile above, whereby administrative and insurance factors may prevent low-risk trials to be undertaken by public research organisations. Several EU Member States also indicated that obtaining a clear view of the state of play regarding implementation of the Recommendation would not be practical until the new EU regulations are fully implemented, at which time a fuller analysis of the

compatibility and complementarity of EU regulation with the Recommendation would be possible, as well as the identification of any remaining issues.

52. It was interesting to note that few Respondents had actually conducted an assessment of their current regulatory process, although the introduction of the new EU regulations provided an opportunity to re-evaluate ongoing processes in many EU Member States.

7. Summary and conclusions

53. The main users of this Recommendation are the national or regional clinical research regulatory authorities. These are very heterogeneous in their nature, organisation and responsibilities. This was reflected in some Respondents' feedback, which in some cases could not cover all aspects of the Recommendation. Furthermore, despite the efforts of national Delegations and of interested stakeholders such as CRIGH, it was noted that some regulatory authorities had only a limited knowledge of the full content of the Recommendation. A coordinated effort between the relevant OECD Committees (CSTP and Health Committee) and international organisations and non-profit associations such as CRIGH, ICH and WHO may be needed to improve dissemination of the Recommendation as well as to fully monitor its implementation and impact.

54. The Recommendation was found to be implemented unevenly. This was linked to its novelty, partial dissemination, and to the extreme diversity of existing national regulatory processes which are difficult to adapt, at least rapidly. Nevertheless, the situation is improving as many Adherents have realised the necessity to adapt their current regulation to emerging needs, in which context the Recommendation serves as a recognised international reference. In the EU, the implementation of the new EU Regulations which have been developed in close cooperation with the OECD and are compatible with the Recommendation should bring an increasing number of Adherents in line with its provisions and thereby contribute to its increased implementation.

55. The main lesson learned from this monitoring exercise is the growing awareness regarding the need for clinical research regulation to support a risk-based approach, as provided for in the Recommendation. Although Respondents still have different interpretations of risk-based regulatory processes, a very high percentage have started to adopt this approach. This should accelerate implementation of the Recommendation and the validated standardised framework it prescribes. Indeed, Respondents that have recently or are currently in the process of modifying their regulations to incorporate a risk-based approach have used or are planning to use the Recommendation.

56. Another important and positive element is that, when Respondents have set up a risk-based approach, they have usually adapted their regulatory procedures to take into account the consequences of risk categories on the various elements of the regulatory approval process, as provided for in the Recommendation. It is worth nothing that, as many Adherents have already adopted a risk-bases approach, amending their existing national regulatory processes to fully implement the Recommendation would not require major changes in their system.

57. While significant progress has thus been made, this monitoring exercise also revealed is a lack of standardisation of regulatory process between Respondents, even when they have adopted coherent risk-based approaches. Even in the EU, where common regulation could be expected to lead to harmonisation, significant differences in interpretation of the various elements and terms remain. 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 (when patient numbers are small) or during emergency crisis (to obtain results for a large number of tested

treatments very quickly). This is one of the key issues that the Recommendation seeks to address. Thus, although a majority of Respondents consider their existing regulatory processes as satisfactory, an assessment that may be entirely reasonable when considering clinical research carried out within a national context, the development of international clinical research requires the adoption of common standards and procedures.

58. Finally, while implementation remains somewhat uneven, several Respondents provided information on changes in their regulatory frameworks that are planned or already being undertaken that may lead to fuller implementation of the content of the Recommendation. For example, Norway is preparing a National Action Plan on Clinical Trials. Furthermore, national indicators have been developed to monitor the number of clinical trials and the number of patients participating in clinical trials. Such initiatives will contribute to a better registration and transparency of clinical trials conducted in Norway. In Colombia, stakeholders of the clinical research process have recently proposed a review of the regulatory framework, including the application of risk management regulations in this area. Canada's planned regulatory changes will also look at advanced innovative therapy, although Canada indicated that it was too early to make specific recommendations yet. As such, even in cases where more could be done to improve implementation, ongoing or planned actions may address these areas and bring further Adherents' in line with the provisions of the Recommendation.

Continued relevance

59. The majority of Respondents did not see the need for any change in the current Recommendation, and no remarks were made regarding the substance of the text, i.e. the risk categories and risk adaptation process. Indeed, whenever suggestions were made regarding possible adaptation of the Recommendation, they were more forward-looking, proposing minor additions or clarifications for clinical trials on innovative therapies that may become important in coming years and that should be taken into account by regulators and hence in the Recommendation if and when they become more widespread.

60. Indeed, many Adherents indicated that the relevance of the Recommendation was increasing in a context where they are being invited by clinical research stakeholders to amend their existing regulatory process. Indeed, evidence from Respondents that have recently modified their regulatory process or are planning to do so suggest the high relevance of the Recommendation to current needs and expectations. Further relevance is also related to the increase in funding for non-commercial trials aiming at optimising the use and cost-effectiveness of authorised treatments, meeting the expectations of health authorities and health technology assessment.

61. In the EU context, on the other hand, a number of EU Member States were more cautious in assessing their capacity to integrate the Recommendation within their national regulatory system, indicating that they would be better able to analyse this once they have fully implemented the new EU regulations.

Next steps

62. In conclusion, while some key elements of the Recommendation are increasingly being implemented by Adherents, there remains further work to do. For this reason, Adherents – particularly those planning to adapt their existing regulatory frameworks – should focus on taking further steps to implement the provisions of the Recommendation in the coming years. One area on which Adherents' focus should be particularly concentrated is the development of common international standards and procedures. In addition, EU Member States could take the Recommendation into account in the context of implementing new EU regulations.

63. Furthermore, it is proposed that Adherents, individually as well as through the CSTP and with the support of the Secretariat, work with relevant national and international organisations to facilitate broader dissemination of the Recommendation among relevant stakeholders.

64. In view of the additional work to be done, it is proposed that the CSTP continue to monitor the implementation of the Recommendation and report again to the Council in five years' time.