

OECD Global Science Forum

Facilitating International Cooperation in Non-Commercial Clinical Trials

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Facilitating International Co-operation in Non-Commercial Clinical Trials

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Executive Summary

Rationale and Background Clinical research involves testing new discoveries by carrying out carefully controlled investigations on patients – known as clinical trials. This includes testing not only new medicines, but also new therapies (*e.g.* radiation), devices, diagnostic techniques (*e.g.* imaging) and surgical procedures, as well as optimising existing medicinal products and procedures to promote better health and welfare. Many of these trials are non-commercial, usually driven by pressing public health needs and scientific opportunities, which do not offer a strong business case to private companies. They increasingly involve international studies and collaborations to deal with rare diseases, pathologies of developing countries, etc. Stringent national regulations have been introduced over time to ensure patient safety and research quality. However, these regulatory mechanisms remain very diverse, a heterogeneity that can become a serious impediment to conducting international multi-centre trials, particularly for academic researchers who cannot rely on well-developed administrative support mechanisms.

To address this issue, the OECD Global Science Forum launched, at the initiative of the German and Spanish Delegations, a “*Working Group to Facilitate International Co-operation in Non-Commercial Clinical Trials*”. This policy report and its annexed survey analysis identify the hurdles encountered by the clinical research community in setting up international clinical trials, and propose a series of policy recommendations aimed at overcoming the main difficulties.

Findings

- **Excessive administrative complexity limits the opportunity to conduct international clinical trials.** The current administrative complexity is such that many well-conceived clinical trials that are aimed at addressing important public health problems can either never be conducted or are so delayed that their impact is dramatically reduced. A series of obstacles have been identified, among which three constitute probably the most urgent challenges to be overcome by clinical research teams wishing to undertake international clinical trials:
 - Knowing about and understanding the existing national laws and regulations, which currently differ widely among countries;
 - Filling in the submission dossiers and defining the assessment procedures required by all the national competent authorities involved in international trials, as there is currently no mutual recognition of national authorisations;
 - Responding to the various requirements of the numerous ethics committees involved in multi-centre studies, as national single opinions are not yet widely implemented.
- **Adopting a risk-adapted approach to the management of clinical trials is welcome but challenging.** Two main models (with broad variations) of regulatory frameworks currently coexist for clinical research: one of them distinguishes between the registration of new health products and other (non-registration studies) categories of clinical research, while the other, centred on the participants, makes no such distinction. However, both models have been built to deal mostly with traditional

commercial trials for new medicines, and are often less suited to address academic trials. The idea of a new regulatory framework has therefore emerged, with different requirements based on the actual risk associated with the study. Such a framework could help to simplify and speed up the procedures, especially for low-risk clinical trials.

Such a new regulatory framework would, however, necessitate a consensus agreement 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 seems to be a broad consensus to adopt a risk-based approach to clinical-trial regulation, no mechanism yet exists that would help align the regulatory requirements for clinical trials worldwide, and that would help develop and validate the risk-assessment tools and risk-adapted monitoring procedures needed for its use in multinational clinical trials.

- **International clinical trials are impeded by heterogeneous clinical staff training and infrastructure support.** Launching and managing complex clinical trials, particularly at the international level, often remains a challenge for academic researchers from both developed and developing countries. In many cases, the education, training and infrastructures required remain inconsistent; this may affect the capacity of some clinical structures to participate efficiently in multi-centre trials, and it may even affect the robustness of the studies. In addition, clinical research may be affected by a decreasing willingness of patients to be involved in clinical trials because patients' opinions are often poorly taken into account, clinical studies may lack transparency and administrative requirements for patients may be too burdensome.

Recommendations

The recommendations address three main challenges:

- A. The excessive administrative complexity of clinical-trial processes;
- B. The desirability of introducing a risk-based approach to the management of clinical trials;
- C. The need to improve the education and training support as well as the infrastructure framework in clinical research, and the involvement of patients.

A.1 Create a common web-based repository of information about national laws and regulations for performing clinical trials. This repository should list the key information (preferably in English) on how to start, conduct and report a clinical trial, with identification of key contacts and links to the Internet sites of national competent authorities.

A.2 Launch an international co-ordination mechanism among competent authorities to initiate a harmonisation process of legal and administrative requirements for multinational trials. Such an initiative would work towards the harmonisation of the content of the submission dossiers to competent authorities and to Ethics Committees (ECs), propose a harmonisation and a proportionality of the rules for conducting clinical trials, and

recommend the adoption of the principles of Good Clinical Practice (GCP) for all international interventional studies.

A.3 Establish a set of common principles for the work of Ethics

Committees/Institutional Review Boards (IRBs) to achieve a single opinion per country for international clinical trials. This should involve a clarification of the role of ECs/IRBs and the implementation of good practices.

B.1 Introduce risk categories in national legislations and/or regulations, based on the marketing-authorisation status of the health product. Practical details (number and standard definitions of these categories, implementation mechanisms, etc.) would be debated at the international level under OECD auspices before being recommended for adoption by interested governments.

B.2 Develop and validate at the global level a set of tools and guidelines on risk assessment, as well as a set of risk-adapted monitoring procedures to be used and applied for every protocol. Such tools should include two components: guidelines and decision trees supporting the definition and assessment of risk (to the patient and to the data...), and subsequent procedures and strategies to mitigate these risks (including monitoring procedures, etc.).

C.1 Develop a concept of *Global Core Competencies* for clinical research trials. These *Global Core Competencies* should be developed as a compendium of required knowledge and skills for investigators and other members of the clinical research team, adapted to their different responsibilities and roles. Standardised as well as mutually and internationally recognised *accredited qualifications* in patient-oriented clinical research should also be defined.

C.2 Establish national/regional/global networks for co-operation in clinical science. Such networks will facilitate international multi-centre clinical research, as well as provide guidelines and examples of good practices for national or local support infrastructures.

C.3 Increase patient involvement in clinical trial processes. The roles of patients in clinical trials should be strengthened by means of mandatory participation of their representative in Ethics Committees; a consultative and participative role in the planning, design, conduct, dissemination and implementation of results from clinical science; simplified informed consent documents; and more accessible information for patients, families and the general public.

1. Rationale, background and working group process

Rationale Clinical research has evolved in recent years and increasingly involves global multi-site collaborative undertakings. International co-ordination of clinical trials has become necessary for evaluating a broad number of therapeutic interventions that have a very significant public health impact¹. While many clinical trials are conducted by the pharmaceutical industry on new medicinal products, non-commercial clinical trials [clinical studies initiated and driven by academic researchers for non-commercial purposes] form a substantial and critical element of medical research. Their independent approach includes the assessment and evaluation of the therapeutic effects, safety and socio-economic implications of both established and novel treatments within the real conditions of the health systems. Non-commercial clinical research therefore contributes to the evaluation of various treatment strategies and options as a basis for developing rational therapeutic guidelines and governmental policies. The market-driven pharmaceutical industry does not pursue research and development for a number of diseases because of the small number of patients involved (as is the case with orphan diseases such as cystic fibrosis) and the insufficient profitability of the treatments (*e.g.* paediatric therapies, treatments for pathologies in developing countries), or because the objective is simply to improve existing procedures and prescriptions (finding the optimal drug combination or timing, for instance). Furthermore, many clinical research studies are not drug-related, but instead involve various medical practices (*e.g.* radiation therapies, new medical devices, diagnostic techniques such as imaging, and surgical procedures).

It is of utmost importance to ensure the welfare, safety and rights of the patients participating in research, and the reliability of the scientific data that is generated. The legislative and regulatory framework is one of the major determinants of the implementation of clinical research. Different national regulations have been introduced over time to ensure patient safety and research quality. However, this diversity can at times be an impediment.

To facilitate trans-national medical research, initiatives such as the ICH-process² have been undertaken to harmonise existing rules in several regions, but they are focused mostly on clinical trials performed by industry on medicinal products. The European regulation on the clinical research environment for medicinal products was harmonised in 2001 by the implementation of Directive 2001/20/EC, the “Clinical Trials Directive” (CTD); however, following concerns expressed by the clinical research community, this Directive is now undergoing a revision process to improve the harmonisation and simplification of the process to conduct clinical trials,

¹ Trimble EL, *et al.* (2009), Improving Cancer Outcomes through International Collaboration in Academic Cancer Treatment Trials, *Journal of Clinical Oncology* 2009; 27:5109-14.

² 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.

Although such initiatives have significantly improved patient safety and quality, a number of challenges in the conduct of clinical trials remain at the 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.

In its recent work on clinical research (www.esf.org/fileadmin/links/EMRC/FL_IDCT.pdf), the European Medical Research Councils (EMRC) at the European Science Foundation (ESF) identified a series of major impediments to conducting Investigator-Driven Clinical Trials (IDCTs) in Europe; the findings echoed a recent analysis by the US National Institute of Health on international collaboration on clinical trials. Three major issues are emerging:

- **Persisting differences in administrative processes.** Differences in the interpretation of existing regulations and other processes have led to even higher levels of complexity – especially in multinational clinical trials. Today, the sponsor of a clinical trial needs to have a very detailed knowledge of every country’s requirements for clinical trial authorisations – from both competent authorities and ethics committees. The sponsor has to integrate different national requirements to the protocol resulting from parallel submission in multinational trials. 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 non-commercial clinical trials are hampered by the regulatory framework that adopted a “one-size-fits-all” national approach. In Europe, for instance, the same 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 the objective of the trial. As a result, the requirements for low-risk trials, using already licensed drugs for similar indications, for example – which are often almost indistinguishable from standard care – can be prohibitively onerous and time-consuming for academic institutions. One of the questions, which evolved especially in the context of non-commercial clinical trials, is whether there might be a rationale for discriminating different categories of clinical trials, using a risk-based approach.
- **Uneven national and regional support for education, training and infrastructures for academic clinical trials.** In many cases, the personnel involved in clinical trials are not being sufficiently well trained to cope with a new multidisciplinary environment, and there is no clear career track identified for clinicians. Training is highly variable and lacks a minimum set of common requirements. Similarly, infrastructure and funding mechanisms required for academic clinical trials remain inconsistent, with substantial national and regional variation. This can undermine the scientific validity of trials whose enrolment is not representative of the population, and limits the extent to which results may be generalised and applied to those who may receive the tested interventions or diagnostics.

The Working Group objective was to propose practical recommendations to governments and interested institutions for reducing the various impediments that persist in clinical research, particularly for international academy-driven clinical trials.

This final policy report contains the Working Group's findings and recommendations.

Background As a number of challenges in the conduct of clinical trials (and especially non-commercial clinical trials) remain at the national and international levels, the Global Science Forum of the OECD approved the creation of a Working Group to Facilitate International Cooperation in Non-Commercial Clinical Trials, at the initiative of the Delegations of Germany and Spain. A preliminary proposal for a new activity was introduced by the Delegation of Germany at the 21st meeting of the Global Science Forum in Kraków on 5-6 October 2009. Following extensive work by a scoping group, a revised proposal was then proposed jointly by the Delegations of Germany and Spain and adopted at the 22nd GSF meeting in Vienna on April 8-9, 2010.

Over 35 experts from 20 countries and international organisations, nominated by GSF delegations and invited by the Working Group members, composed the Working Group (Annex 1).

Working Group Process In its first phase, this activity consisted in developing a survey framework to obtain information on existing regulatory processes and hurdles, training and funding mechanisms worldwide, and existing risk-based policies. A survey process and an interview questionnaire were elaborated during the first meeting of the Working Group, which took place in Madrid in May 2010. Over 70 people from all over the world were interviewed; they included regulatory experts, clinical investigators, administrative officers, ethics committee members and sponsor representatives, as well as representatives of major international networks, pharmaceutical or relevant industries, and major patient advocacy groups. A consultant, Dr. Christine Kubiak (executive manager of the European Clinical Research Infrastructures Network, or ECRIN), carried out this survey, thanks to the generous support of the Delegation of Germany. The survey's results are shown in Annex 2 of this final report.

In parallel to the survey work, three subgroups (Annex 1, for members) were created to prepare draft recommendations for discussion on regulatory framework harmonisation; education, training practices and infrastructure support; and practical aspects of the risk-based approach. Preliminary proposals were discussed extensively during the second Working Group meeting, which took place at NIH headquarters in Washington in November 2010. A third and final meeting, which was extended to include the broader participation of stakeholders and experts (Annex 1), took place in Berlin on 12-13 May 2011. At this meeting, participants debated the relevance of the various proposals and recommendations, and whether these or additional new measures were required, with a particular focus on their practical dimension and the implementation process.

2. Findings

2.1 Administrative challenges in conducting international clinical trials

Although many clinical trials are still performed in a single country, over the years there has been a trend to perform large-scale clinical trials across borders. International collaboration brings many advantages for all types of clinical trials. Patient 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 possibly encompass patients of different ethnicities.

On the other hand, the complexity of performing a study increases significantly with international clinical trials. This relates in particular to the legal framework. In larger pharmaceutical companies, regulatory affairs departments manage this complexity. Furthermore, the companies often have subsidiaries in the different countries where a trial is being performed, giving them access to local information and expertise.

Contract research organisations (CROs) often help sponsors of clinical trials to perform the study. The pharmaceutical industry often uses its financial resources to benefit from the services of CROs, whereas academic sponsors in most cases are performing trials on tight budgets and cannot afford outsourcing to a CRO.

Because of a lack of expertise, infrastructure and resources, academic sponsors of clinical trials in many instances have great difficulties dealing with the requirements of performing a study in different countries.

2.1.1 Ethical and legal framework for performing clinical trials

When performing a CT, a sponsor must ensure the following: the scientific rigour of the protocol, respect for the ethical principles for conducting research on humans, the protection of the research participants and the validity of the data generated. In the end, any research on humans is justified only if it is able to answer a clinically or scientifically relevant question. If a trial is inconclusive because of a flawed protocol or the data cannot be used because key ethical principles were violated, research participants have volunteered for no benefit. Ethics and science in human research are closely linked and cannot be separated.

The essential ethical principles to be respected when conducting research on humans have been described in several international codes or declarations; of these, the Declaration of Helsinki of the World Medical Association is the most broadly accepted.

Furthermore, the ethical, operational and quality requirements for planning, conducting, analysing and reporting clinical trials are commonly referred to as “Good Clinical Practice” (GCP). To ensure that results from clinical trials with medicinal products can be used to support authorisation of medicines in all major markets, the principles of GCP have been harmonised among Japan, the United States and the European Union through the International

Conference on Harmonisation (ICH) and implemented through the GCP tripartite harmonised ICH guideline E6³.

Although this guideline recommends that the principles of GCP be applied to all types of clinical trials, the guideline formally addresses only CTs on pharmaceuticals. The legal framework for other types of clinical trials is much more diverse.

In the European Union, a legislative framework for interventional clinical trials on investigational medicinal products was introduced with the Clinical Trials Directive. This Directive does not distinguish trials by type of sponsor.

In contrast, in the United States and Japan, the regulatory framework for clinical trials differs between trials conducted with the aim of requesting a marketing authorisation (such trials are conducted mostly by commercial sponsors) and other types of clinical trials (conducted mostly by academic sponsors). Trials under an investigational drug application (IND) in the US or “Chicken” trials in Japan have to be authorised by the competent authority and must be approved by local institutional review boards. Trials outside this framework need approval only from IRBs at sites where they will be conducted.

In other countries, such as South Africa, principles of GCP drive clinical trial conduct; the national South African GCP Guidelines are in accordance with the Declaration of Helsinki and the GCP ICH Guidelines. All clinical trials of non-registered medicinal substances and new indications of registered medicinal substances must be reviewed by the statutory body, the Medicines Control Council. This is legislated under section 90 of the National Health Act. No 61 of 2003. It does not apply to non-medicinal products, although the approving ethics committee would anticipate that non-medicinal clinical trials conform to international guidelines despite the absence of legislative imperative.

2.1.2 Challenges in performing multi-centre international clinical trials

It is well recognised that multinational clinical trials are difficult to set up and perform, particularly for academic sponsors. The results of the consultant survey (Annex 2), conducted as part of this activity of the Working Group, show that this is due mainly to the lack of knowledge and application of legislations, as well as to the lack of harmonisation of national legislations and administrative processes. Eight major issues can be identified:

a) Knowing and applying legislations that differ among countries

One of the major challenges for performing international clinical trials is the diversity among countries in terms of the laws, regulations and guidelines governing clinical trials. Issues arise primarily because sponsors and investigators need to be aware of and comply with a multitude of rules that are often divergent.

³ EU: Adopted by CPMP, July 96, issued as CPMP/ICH/135/95/Step5, Explanatory Note and Comments to the above, issued as CPMP/768/97; Japan - MHLW: Adopted March 97, PAB Notification No.430, MHLW Ordinance No.28; USA -FDA: published in the Federal Register, Vol. 62, No. 90, 9 May 1997, pages 25691-25709E7.

Today, interventional clinical trials on medicinal products have to be reported to and, in some cases, authorised by the competent authority in each country where the trial is planned to take place. The requirements for the submission of dossiers to get the trial authorised may differ among countries, leading to considerable administrative burden. The fact that competent authorities from different countries evaluate a single trial leads to lots of work and opens the door to different national interpretations and requirements – regarding, for example, the scientific validity of the trial protocol. Some regions, like the EU, are now proposing a common application dossier and co-ordinated assessment by the different national competent authorities concerned by a single clinical trial, but this is not yet the case at the international level.

b) Ethics review may be complicated

The 1975 revision of the Declaration of Helsinki established that an experimental protocol needs to be reviewed by an “independent committee”. These ethics committees (ECs) or institutional review boards (IRBs) represent the interests of society, including the trial participants, and are composed of individuals with different backgrounds (ethics, law, medicine) as well as lay people.

For a given clinical trial, numerous ECs/IRBs at a number of centres may need to be consulted, typically at every site, where patients for the clinical trial are recruited. Even in the European Union, where a single EC opinion per Member State is mandatory, the local arrangements (*e.g.* qualification of the investigators at a given site) are often looked at by a local EC/IRB. The different ECs/IRBs, whether nationally or internationally, may come to a divergent assessment of the clinical trial under review.

It is typical that, when consulting ECs or IRBs, sponsors need to make changes to the protocol for the clinical trial. These changes come on top of changes requested or queries raised by the competent authority for those trials, where notification/authorisation is required. The iterative process of refining the protocol and other arrangements for performing a clinical trial in some cases is made difficult because the various requests may not be compatible and may make the conduct of a trial impossible.

Given the fact that the science and ethics are closely related, the situation may arise that ECs/IRBs may come to an assessment of a clinical trial that diverges from the assessment of the competent authority(ies), thus raising further problems for the conduct of a clinical trial.

c) Lack of expertise/resources at academic centres; difficulties for funding

As mentioned above, performing a clinical trial is a resource-intensive endeavour requiring specialised expertise in addition to the medical/scientific qualifications of academic physicians. For academic clinical trials, resources are often lacking at several levels. Investigators may have little “protected time” from clinical duties to perform research, including clinical research. The number of support staff (such as study nurses) may be inadequate.

Performing a clinical trial may require a dedicated infrastructure to deal with the administrative and legal requirements in running a trial, such as an infrastructure for packaging the investigational medicinal product for a double-blind trial, for monitoring the

trial or for reporting adverse events. Throughout the world, this type of infrastructure has been created in (conjunction with) academic medical centres. However, it may not be accessible to all sponsors of academic clinical trials, and existing infrastructures may have limited capacity, if any at all, to deal with international clinical trials.

Typically, academic clinical trials depend on external grants. The peer review during these funding application processes is a good check on the relevance and quality of the study. Unfortunately, individual awards are often rather small, with the result that funding of a study must be obtained from several sources. Also, with notable exceptions, many funding agencies do not allow grants to be spent outside their region or country – or, if they do, they place additional burdens on the grantee. This may require parallel submission to funding agencies in different countries or regions, each of which will have its own time scale for awarding the funding and its own rules.

d) Lack of standard definition of roles and responsibilities of investigators and sponsors

This is a special aspect of the differing legal requirements for the conduct of a clinical trial, and the challenge is to know about the rules in different countries. Survey respondents raised this point because the sponsor has such a central position in a clinical trial. Academic sponsors of clinical trials, in particular, are unsure of the responsibilities they are taking on when they launch a multinational clinical trial. They also wonder about which aspects of the responsibilities stemming from conducting a clinical trial they can delegate. Sponsors in Europe are particularly concerned, as the legislation specifically requires a single sponsor for each trial. Academic sponsors also struggle to orchestrate the funding for multinational clinical trials, which often originates from many different sources.

e) Insurance

The different health and indemnity insurance requirements can also stifle international collaborations. Sometimes it is difficult for international sponsors to be aware of all the varying insurance requirements in the different jurisdictions where the trial will take place. In addition, purchasing the necessary insurance cover may be a challenge. Clinical-trial insurance is a rather narrow market, with a limited number of clients and only a few companies offering this type of insurance. Considering the small number of claims that are reported, many sponsors of clinical trials have the impression that premiums are too high.

f) Standard of care

For many multinational clinical trials, this may not be an issue, but for others it can become a major hurdle. It is of particular concern in trials conducted in resource-poor settings, where the medical practice may differ significantly from the standard applied in the planned clinical trial. This can cast doubt on the results of the trial. In addition, the vulnerability of potential trial participants may be exacerbated because access to quality care by participating in the study can be an undue inducement. The population from which the participants are planned to be recruited may be unfamiliar with the concept of clinical trials, and this can raise questions about the validity of the informed consent. Furthermore, in resource-poor settings, clinical trials must carefully consider how to address issues such as continuing treatment after the study ends and providing access to the standard developed in the trial for the population from which the study participants were recruited.

g) Adverse Drug Reactions (ADR) reporting rules are different

A lower priority, according to the survey, is that the requirements for recording and reporting adverse events that occur during a clinical trial vary among different types of clinical trials and among countries.

Also, when reporting adverse events, sponsors use classifications, codes and dictionaries in databases to store, process and analyse the data, as well as to identify safety signals. While either national organisations (such as the US Federal Adverse Events Task Force) or international ones – such as ICH and the Council for International Organisations for Medical Sciences CIOMS) – have made tremendous efforts for further harmonisation, different classification systems and dictionaries are still used in different institutions and different countries, and sometimes in different medical conditions. These discrepancies make it complicated to report adverse events, and difficult to detect signals regarding the (lack of) safety of an intervention.

h) Drug importation requirements/compliance with GMP

According to the survey, this aspect is also a lower priority, but it can be a serious impediment to conducting multinational clinical trials.

Medicinal products used in a clinical trial need to have been produced under good manufacturing practices (GMP). There is no mutual recognition between the United States and Europe, as well as between other regions, on compliance with GMP rules (although this exists between the EU and a few other countries, like Australia). As the application of such rules in different countries may differ, this can raise large hurdles for the conduct of a multinational clinical trial. The hurdles are all the more cumbersome for clinical trials on marketed products, where the “production process” may refer to repackaging to be able to conduct a blinded study. It can be mentioned that with regard to inspections for the manufacture of approved drugs, competent authorities from different countries and regions are working together. This could provide a basis for co-operation extended to other areas, such as provision of investigational medicinal products.

2.1.3 Consequences of the administrative hurdles

The most serious consequence of these impediments is that a well-conceived clinical trial that was aimed at addressing an important public health problem is never conducted.

It often occurs that sites in a given country or in several countries cannot participate in a multinational trial. As a consequence, the recruitment of the required number of patients may be jeopardised. Even if the difficulty of recruiting a sufficient number of patients can be overcome, the applicability of the results may still be limited because of the bias in selecting countries for participation in the trial. In addition, populations that are particularly affected by a given disease may be excluded from participating in clinical trials addressing this condition.

Even for trials where the hurdles can be overcome and the sites in all countries can finally participate, time delays may arise, retarding the results of a trial accordingly. This is all the

more an issue as medical science advances and questions addressed in a clinical trial often are relevant only in a certain time window.

The hurdles in conducting multinational trials and the large resources in time and money needed to overcome them also limit the number of clinical trials that can be conducted. This is a real issue because even in conditions where treatment options are clearly limited, only a small percentage of patients are enrolled in clinical trials. The progress of medical science and improvements in public health are unduly delayed.

2.2 Risk-adaptation of clinical trials

Clinical-trial supervision is intended to protect the participants' rights and minimise participants' risks in any given study, as well as to ensure the quality of data and the robustness of analyses (scientific and ethical soundness of the study). According to the country and to the nature of the trial, supervision is based either on a specific legislation, on rules originating from the competent authorities or merely on ethical guidelines. Two main models (with broad variations for individual situations) of regulatory frameworks currently coexist for clinical research across the world's regions:

- *A model centred on the use of data*, with different requirements and regulations for clinical trials whose objective is the registration of a health product (IND trials in the United States, “Chicken” trials in Japan, or commercial trials) vs. the other categories of clinical research. In this model, the data collected by non-registration studies cannot be used for registration purposes;
- *A model centred on the participant* that makes no distinction between registration (commercial) or non-registration objectives of the study, ensuring the same level of protection of the participants in both cases. In this model, data from non-commercial trials can later be used for registration purposes, but in turn the requirements represent a major bottleneck for academic clinical research, which deals mostly with lower-risk studies using already marketed products.

Most non-European countries have developed regulatory frameworks that make a distinction between registration or non-registration studies. While in theory this should allow for increased flexibility, a number of issues remain within the different systems. In some cases, the boundaries and definitions between the mechanisms are unclear and can lead to confusion. Alternatively, the existing rules for non-commercial trials are so loosely framed that they are not really suited for health treatment/procedure trials.

Europe opted for the second model: the 2001/20/EC Directive does not make any distinction between commercial and non-commercial trials. Although the text of the Directive contains a certain degree of flexibility, it was transposed into national legislations that are not only poorly harmonised, but also in most cases more stringent and less flexible than the Directive. This resulted in difficulties for academic clinical research because a large majority of the academic trials are phase IV (comparing marketed interventions in their licensed indications), or phase II-III (exploring the efficacy of already marketed drugs in new indications / populations / conditions).

To overcome this difficulty, the 2005/28/EC Directive considered the possibility of “specific modalities for non-commercial trials” that would have made the EU legislation closer to model 1; after public consultation, however, the corresponding guidance document was never accepted. The academic community, in turn, promoted the idea of risk-based legislation, with different requirements based on the risk associated with the study, and not on its commercial or non-commercial objective. This in turn raises the major issue of how to design and implement a risk-based legislation, how to define the risk, who should be in charge of defining and validating the risk, and which processes should be affected.

Moving towards a risk-based approach may contribute to the harmonisation of requirements for multinational trials. There is a growing demand to explore ways to promote the alignment of the regulatory framework in European and non-European countries, based on risk categories. For instance, in the Japanese and US systems, the clear boundary between phase IV and other trials leads to an explicit risk adaptation. In addition, the FDA makes an implicit difference between trials on drugs already marketed vs. those never marketed. A boundary also exists in Australia, although less clearly defined, between low- and high-risk trials. As indicated above, although the current European Directive does not make any distinction between clinical trials, a new interpretation of the Directive (the 3-categories UK pilot initiative) could allow for risk-based provisions making distinctions between the requirements for different risk categories.

Based upon the consultant survey (Annex 2) and these initiatives, a consensus framework for risk-adapted approaches to the management of clinical trials is starting to emerge.

2.2.1 What is risk in clinical trials?

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. These two major components can be further detailed as follows:

- hazard to participants
 - hazard to participants’ rights
 - informed consent
 - personal data protection
 - hazard to participants’ safety
 - safety of health product / treatment intervention
 - protocol-related diagnostic / follow-up procedures
 - population/context-related
- hazard to trial results
 - credibility of data
 - robustness of study design and analysis

2.2.2 How can risk be assessed?

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.

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”, or SERR)⁴, 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 include:

- an approach (“stratified approach” in this document) based on the definition of discrete risk categories⁵⁻⁶⁻⁷, although this captures only part of the risk items (mostly the hazard related to the health product’s safety).
- an approach (“personalised approach” in this document) based on a case-per-case assessment of each individual protocol⁸, using guidance and decision trees covering all the aspects of risks (hazard to participants, and hazard to results).

The relevant concept for clinical trials is the “additional” or “incremental” risk, 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 should be taken into account for a broad variety of processes, including for clinical- trial insurance and indemnity.

Given the complexity of risk assessment in clinical trials, appropriate training modules for investigators, clinical research professionals, ethics committee members, competent authorities and health industry staff are yet to be developed to ensure both the reliability of the assessment and the harmonisation of opinions.

2.2.3 What is the risk for an individual protocol?

This issue is being debated over a number of different fora, both within and outside Europe. For instance, the United Kingdom initiated in 2011 a pilot reform of the supervision of clinical trials⁹ to include some risk-adaptation, using three major risk categories based on the marketing-authorisation status and the conditions for use in the trial of the medicinal product.

⁴ Rid A, *et al.*, Evaluating the risks of clinical research. JAMA 2010, 304:1472-9.

⁵ Brosteanu O., *et al.*, Risk analysis and risk adapted on-site monitoring in noncommercial clinical trials, Clin Trials 2009; 6; 585

⁶ 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.

⁷ www.drcc.aphp.fr

⁸ www.ct-toolkit.ac.uk

⁹ www.mhra.gov.uk/home/groups/l-ctu/documents/websitesresources/con111784.pdf

Simultaneously, the European Medicines Agency (EMA), together with the EU national competent authorities, released in August 2011 a consultation¹⁰ on risk-based quality management in clinical trials, with a proposal on a series of items for risk identification, coupled to a series of measures for risk mitigation. At the same time, the US Food and Drug Administration (FDA) drafted for consultation a guidance document on risk-based approach to monitoring,¹¹ reflecting the discussions within the Clinical Trial Transformation Initiative (CTTI, supported by the FDA Critical Path programme). This initiative promotes the concept of quality by design: the protocol should clearly identify procedures and data that are critical to the reliability of the study findings, and the monitoring plan should be designed to focus on these critical aspects. This is embedded in a broader initiative by the Department of Health and Human Services and the FDA¹² to rejuvenate the regulation governing research with human subjects in the US, which now includes a reference to the risk-based approach to regulation¹³.

From all these recent initiatives, it appears that there are two complementary approaches that could be used in parallel to define the risk associated with a given clinical trial: a ***stratified approach***, defining a discrete number of categories for legislation purposes; and a ***personalised approach***, taking into account the whole spectrum of risk items for a given trial, based on decision trees. Each individual trial supervision process could be adapted based on the stratification and on the personalised risk assessment (particularly the monitoring strategy).

a) The “stratified” approach: risk-adapted legislation using a classification based on the marketing authorisation status of the health product.

This consists in defining categories of clinical studies associated with different levels of risk. Only a restricted number of discrete categories can be defined, focusing on a single dimension of the risk definition – e.g. the hazard to participants related to drug safety¹⁴ (this approach is therefore non-valid for clinical studies that do not deal with health products but instead focus on, for example, surgical procedures, radiotherapy, etc.). Such stratification, which has inspired the current UK pilot initiative, for instance, could distinguish between:

- “Category A”: Clinical trials using already marketed medicines under the licensed indication;
- “Category B”: Clinical trials using already marketed medicinal products, exploring their use in new indications, new populations (“repurposing trials”);
- “Category C”: Clinical trials exploring safety and efficacy of never-marketed medicinal products.

¹⁰ www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500110059.pdf

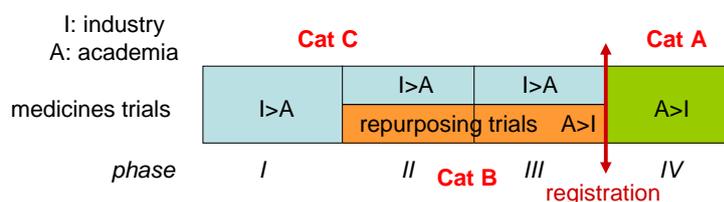
¹¹ www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf

¹² Federal Register, Vol. 76, No. 143, 26 July 2011, Proposed Rules, pp. 44512-44531

¹³ Emanuel EJ, Menikoff J. Reforming the regulations governing research with human subjects. *N Engl J Med.* 2011, 365:1145-50

¹⁴ www.ecri.org/fileadmin/user_upload/public_documents/News/Activities/Report%20Roadmap%20Workshop%20on%20Risk-%20based%20regulation%20Barcelona%2018%20Jan%202010-1.pdf

Box 1. The “stratified” approach: risk-adapted legislation using a classification based on the marketing-authorisation status of the health product



A similar approach may be used for medical devices; however, “performance” is evaluated in the pre-registration phase in Europe – not “efficacy”, as is the case in the US. This will have an impact on the risk category of post-registration trials for high-risk devices in Europe, compared with the US.

Other possible options – for example, using only two categories, marketed (category A) vs. non-marketed (category B and C) – may also be envisaged, as they may be more compatible with regulatory traditions in some EU countries. They might also be easier to describe in some regulatory texts and could be compatible with some adapted rules in each category according to other characteristics of the trial. The main advantage of distinguishing between categories A and B/C is to allow a better alignment of the requirements for international clinical trials, as category A roughly corresponds to the “non-commercial” (non-IND, non-Chiken) trials outside Europe. In addition, this would facilitate the independent assessment by academic institutions of health products and treatment strategies, which is a critical activity for the optimisation of health-care strategies and for cost-containment. Making an additional distinction between category B and category C allows to be taken into account the fact that information is already available on the efficacy and safety of the health product (although for a different disease indication or population). Compared with category C, category B would therefore be associated with a lower risk and lower 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.

Stratification of clinical trials based on such categories could result in adaptations of various clinical-trial supervision processes, which are influenced by the marketing-authorisation status of the health product:

- Authorisation by the competent authority (no authorisation, or just notification, for category A studies);
- Ethical review (with the possible use of expedited review for low-risk studies¹⁵);
- Adverse event reporting;

¹⁵ Wolzt M, *et al.*, Protocols in expedited review: tackling the workload of ethics committees. *Int Care Med* 2009, 35:613-5.

- Insurance/indemnity (that could be covered by the public health system for low-risk studies);
- Monitoring practicalities;
- Labelling requirements and study documents should also be adapted.

In turn, the monitoring strategy cannot be driven only by the status of the health product. Ensuring data quality and robustness of analyses requires an in-depth assessment of the individual study protocol, as proposed in the personalised approach.

b) The “personalised” approach to risk assessment and risk mitigation of every single clinical study.

Such an approach consists in assessing, on a case-per-case basis, the risk associated with an individual protocol. This could be supported by a decision tree or a guidance document, and takes into account the various dimensions of the risk as previously defined: hazard to the participants (rights, safety) and hazard to the results (data, design and analysis). It also considers the experience and training at the investigation site, as well as, the robustness of procedures, as determinants for data credibility. Moreover, this approach is not restricted to health products only, but is also valid for clinical research involving medical devices, diagnostics, etc. As mentioned earlier, the emerging concept of quality-by-design expands this approach, stating that the study should be designed to maximise the robustness of data collection and analysis, the protocol should identify the critical data and procedures, and the monitoring plan should focus on these critical points.

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. In turn, the specific risk of a trial determines the adaptation in the trial supervision processes, such as insurance/indemnity; this risk impacts above all the monitoring of data quality and of the robustness of results. Monitoring can be adapted to the risk (as stated in ICH E6 guideline); however, the scientific community lacks validated strategies for risk-adapted monitoring in multinational trials.

2.3 Education, training, infrastructures and patient involvement

Support for and facilitation of the education, training and infrastructures required for academic clinical trials are key elements of the success of clinical research.

According to Good Clinical Practice (GCP), the training of clinical investigators is indeed a mandatory requirement, but this is hardly regulated, and the content of the training is usually not specified. In addition, there is rarely mention of training requirements for the other staff and stakeholders involved in clinical trials. Training activities may comprise a variety of approaches, such as on-the-job training or short web-based online courses – in many cases provided from private sources such as Contract Research Organisations and pharmaceutical companies – as well as courses at University level. However, their content remains in many cases inconsistent, with substantial national and regional variation, and there is also a lack of training options in many places. Similarly, general curricula for future professionals involved in clinical trials are highly variable and often contain only very minimal training on

clinical trial requirements. Furthermore, the complexity and specificities of those requirements are rarely recognised in the career structure of health researchers, hence often acting as additional hurdles.

The complexity of setting up and managing clinical trials, particularly when multi-centred, and the administrative burden involved also weigh heavily on academic clinicians. National or local support structures are therefore often necessary to allow for ambitious or complex clinical trials.

Finally, it is also important to recognise the increasing role of patients, and even of the general public, in clinical trials. Patients are not just objects of study, but also contributors and partners in clinical trials, and patient associations are keen to play an increasing role in clinical research definition and practice. In parallel, the public is asking for better transparency and information on such research. Finding a balanced role for these new actors is a challenge that the professional community has to properly address.

2.3.1 Education and training frameworks in clinical science

The field of education and training related to clinical trials is characterised by a high degree of variation in existing activities and programmes – and, to a large extent, a lack of standardised content with reference to the educational needs of the clinical staff. However, several examples of good practice – from Japan and Germany, for instance – include a defined list of essential issues for training clinical investigators and other professionals involved in clinical trials. In France, a guidance document was launched for the training of investigators ([www.afssaps.fr/Activites/Essais-cliniques/Formation-des-investigateurs/\(offset\)/2](http://www.afssaps.fr/Activites/Essais-cliniques/Formation-des-investigateurs/(offset)/2)); in the United States, numerous universities offer one or two-year graduate programmes in clinical trials for doctors and nurses. In India, the Indian Council for Medical Research has formulated the Good Clinical Practice Guidelines and the Guidelines for Biomedical Research on Human Participants. These are among a number of valuable examples that represent an important basis for the further development of framework and content of education and training within clinical research.

There is also a variety in practice with reference to certification and accreditation in relation to training in clinical research. However, in many instances, certificates are provided only from GCP courses (for example, in China, all staff members involved in clinical research are required to hold an accredited GCP certificate issued by the China State Food and Drug Administration). In Japan, some hospitals require investigator certificates, which can be obtained after taking education programmes provided by the hospitals. At the international level, though, there is a lack of established accreditation systems with a mutual recognition mechanism to verify knowledge and skills of training related to clinical trials.

As a prerequisite for an educational framework in clinical science, it is also worth bearing in mind the broadening diversity of the professionals who are involved in and support the planning and performance of clinical trials; this diversity characterises the current international development of clinical research. Clinical trials now often involve large teams of medical doctors, nurses, pharmacists, bioengineers, data managers and biostatisticians, as well as other professionals. This reflects the increased complexity and risk levels of the various trials. Another critical aspect of the field is the situation in a number of countries and

regions where educational and training programmes are scarcely developed, even though clinical trials need to be conducted in these regions for many neglected diseases.

Progress in the development of educational frameworks for clinical science must thus take into account the diversity of situations with regard to the availability and content of training, in addition to the multi-faceted needs for training of different staff members and professionals in managing increasingly complex clinical trials.

2.3.2 Infrastructure supports

Infrastructures for clinical research (health units, information and support platforms and networks) are very diverse and may be structured on a local, national, regional or international basis. Efficient planning and performance of clinical trials rely on the interplay among clinical research teams and units, hospitals and other parts of the health care system, patients and public, ethics committees, regulatory bodies and funding institutions at different levels. Weaknesses in any one of these network components may seriously hamper the efficiency or even the accomplishment of clinical trials. In addition, an important element of the clinical research infrastructure is the situation pertaining to the clinical researchers themselves – their working conditions and career paths, the latter often poorly defined or funded. To address this issue, a number of initiatives have been launched to support infrastructure development in different parts of the world:

- In Korea, a national project supported by the Ministry of Public Health Welfare (Korea National Enterprise for Clinical Trials, KoNECT) was established in 2007 to develop better infrastructure for clinical trials. KoNECT has identified 15 Regional Clinical Centres and supports these throughout three different phases: 1) providing hardware facilities, equipment and human resources; 2) developing specialisation for each centre; and 3) building international recognition. In Japan, the government has designated 20 core institutions to promote clinical trials, while in Hong Kong, the infrastructure for clinical-trial units has been strengthened in medical universities and tertiary teaching hospitals.
- In Europe, the European Clinical Research Infrastructures Network (ECRIN) has been established as a not-for-profit infrastructure to support multinational clinical research projects. The Innovative Medicines Initiative (IMI) Joint Undertaking is a different organisation, being a large-scale public-private partnership between the European Union and the pharmaceutical industry association EFPIA to promote pharmaceutical innovation, while EMTRAIN aims at establishing a sustainable, pan-European platform for education and training covering the whole life-cycle of medicine research.
- In the US, the NIH, both through its National Center for Advancing Translational Sciences and through individual NIH institutes, supports much of the infrastructure for academic clinical trials at both the national and institutional/university hospital level. In addition, local institutions/university hospitals devote some of their own budgets – often supplemented by funds raised through charitable campaigns – to help support the infrastructure costs for academic clinical trials, including the costs of local ethics committees and clinical-trial offices. Mechanisms for NIH support

include both support for ongoing clinical-trial networks as well as grants and contracts for specific trials.

- In Africa, most countries have only limited capacity in terms of both infrastructure and human resources to conduct high-quality clinical trials. A number of national governments, through bilateral or multilateral relationships, and philanthropic agencies are now engaged in creating such capacity, but there are few African research centres with adequate infrastructure and a critical mass of scientists with the requisite clinical-trial expertise. The capacity of clinical-trial support teams, in particular, is often limited, with few trained clinical research associates, clinical trial assistants, data managers, medical advisors, internal auditors, trial pharmacists, regulatory staff, data-safety monitoring boards (DSMBs) etc.

In parallel to these support infrastructures, some international initiatives focused on specific therapeutic areas are being set up. In Latin America, a network of National Cancer Institutes (RIC) is developing co-ordinated actions considering different aspects of cancer research. This network now comprises the NCIs from Mexico, Colombia, Peru, Brazil, Uruguay, Panama, Cuba, Paraguay and Argentina. Similarly, the global academic gynaecological cancer community has developed a strong intergroup – the Gynaecologic Cancer Intergroup – to exchange information about current clinical trials and develop joint clinical trials. The current membership includes 18 clinical-trial groups from Asia, Australia-New Zealand, Europe and North America.

Considering the complexity of international clinical trials, further development of regional and global networks would have considerable value.

2.3.3 Patient involvement

The role of patients in clinical science is largely limited to their participation as “study subjects”. However, the success of clinical trials is strongly dependent on the trust that can be established between the patients/public and the clinical research environments. This confidence is a challenging issue and a critical factor for the willingness of patients to take part in clinical trials. To address this issue, information to the patients must be improved and the transparency of the process increased; in addition, the patients themselves should have an enhanced influence on clinical science.

One of the major hurdles to patients’ participation in clinical trials is the mandatory informed-consent forms, which are all too often difficult to understand, do not contain the necessary information about the clinical study for decision making and are also in many cases far too long.

Information to the public in general, aimed at increasing the transparency of clinical research, is slowly improving; it could benefit from initiatives such as the European database for clinical trials (EUDRACT), which contains detailed information about clinical trials and is now open to the general public. However, this covers only technical aspects of clinical trials, and more focused action – such as regular dialogue meetings set up in some hospitals for patients and their families regarding ongoing and future clinical trials – has had very positive impacts.

The influence of patients on the clinical research itself remains limited, despite the fact that patients may contribute importantly to the value and quality of specific clinical trials – for example, by helping to define relevant parameters to monitor throughout a clinical study, which have significance for the patient’s quality of life. Initiatives like the EUPATI-project (European Patients Academy on Therapeutic Innovation), which aims to educate patient advocates and the lay public about therapeutic innovation, deserve to be analysed in more detail.

3. Conclusions and policy recommendations

This report presents the main challenges faced by those who design and carry out international clinical trials, and it describes ways of overcoming these difficulties so as to benefit health-related research. The recommendations are focused primarily on academic research without commercial sponsors. However, the constraints also confronting industry sponsors make these groups likely to support substantially fewer clinical trials in the near future. Interested governments and institutions may therefore also consider whether some of the proposed recommendations may be applied more generally.

The recommendations address three main challenges:

- A. The excessive administrative complexity of clinical-trial processes;
- B. The desirability of introducing a risk-based approach to the management of CTs;
- C. The need to improve the education and training support and the infrastructure framework in clinical research, as well as the involvement of patients.

3.1 Developing efficient processes to ensure appropriate regulation of clinical trials

Based upon the global survey (Annex 2) and the analysis of the Working Group, a series of administrative challenges were identified in conducting multi-centre international clinical trials. These are linked primarily to the complexity of regulatory and legislative requirements, through which academic sponsors are rarely equipped to navigate, and to the lack of harmonisation of the national laws and administrative processes.

Three areas were more specifically identified as requiring urgent action:

- Providing clear and reliable information on the existing national laws and regulations, which differ widely between countries;
- Simplifying and clarifying the submission dossiers and the assessment procedures for clinical trials;
- Reducing the duplication of efforts in ethical reviews.

Recommendations

A.1 Create a common web-based repository of information about national laws and regulations for performing clinical trials

Such a repository should be hosted by a recognised international organisation and/or frequently used clinical trial (CT) registers.

Information should be provided in a harmonised format (common template) that should be reasonably short and simple. The repository should list the key information (preferably in English) on how to start, conduct and report a CT (such as flowcharts), with identification of key contacts and links to the Internet sites of national competent authorities. The exact balance between basic information linked to national web sites and processed information presented in the web-based platform will depend on available resources.

National competent authorities should commit to provide and update this information, with the understanding that funding would be available to cover the additional resources needed.

Existing resources – such as the one run by the WHO for the pre-qualification of drugs and vaccines, or the upcoming European Medicines Agency (EMA) “identity card” that will provide provisions for the different steps of CTs – may be used as possible models for the recommended repository.

A.2 Launch an international co-ordination mechanism among competent authorities to initiate a harmonisation process of legal and administrative requirements for multinational trials

The objectives of this enhanced co-operation process would be:

- To consider the harmonisation of the content of the submission dossier to competent authorities and to Ethics Committees/Institutional Review Boards (ECs/IRBs), with common principles of assessment. This could be discussed via a working group of the International Conference of Harmonisation (ICH) or set up by national competent authorities. Such a harmonisation could then lead to a single dossier mechanism and a co-ordinated assessment through a step-by-step process;
- To propose a harmonisation and a proportionality of the rules for conducting clinical trials, with specific provisions for different types of trials (using a risk-based approach);
- To recommend the adoption of the principles of Good Clinical Practice (GCP), such as those of the ICH, for all international interventional studies of medicinal products;
- In parallel, to initiate a high-level co-operation among major funders of biomedical research to co-ordinate their efforts in promoting international clinical research and work on the implementation of the OECD recommendations (with a focus on public health needs).

A.3 Establish a set of common principles for the work of Ethics Committees/ Institutional Review Boards to achieve a single opinion per country for international clinical trials

The role, practical operating procedure and quality standards of ethics committees are largely described in the operational guidelines for ethics committees published by the WHO (the soon-to-be released second edition of this document incorporates 10 standards for the review of health-related research, which cover some of the issues described in this report). However, international collaboration in clinical trials necessitates some additional elements that should include:

- A clarification of the role of ECs/IRBs (particularly for a common dossier); for international non-commercial clinical trials, a single opinion per country is desirable for the overall scientific and ethical aspects. The leading committee in charge of the single opinion should consult local committees or sites for assessment of local issues/aspects.
- ECs/IRBs should work under Good Clinical Practice rules; this should include recommendations for EC/IRB composition and training, and for standard operating procedures and archiving; it should also include concepts of certification of ECs and audit of their work.

The build-up of expertise in resource-poor settings will be necessary to achieve this objective. Partnerships of institutions should be established when needed to support international clinical trials involving developing countries.

3.2 Risk-based approach to clinical-trial supervision

One of the questions which emerged during the review of non-commercial clinical trials is whether there might be a rationale for discriminating different categories of clinical trials based upon the actual risk of the study, which could entail the potential benefit of simplifying and speeding up as well as reducing the administrative/regulatory requirements for low-risk studies.

Although the clinical research community strongly supports adopting a risk-adapted approach to the management of clinical trials, such a mechanism raises a number of major issues: how to define the risk (who should be in charge of defining the risk, what are these risks...), what could be the possible risk categories, who should validate it and which processes should be risk-adapted.

The critical challenge is to propose a mechanism that will help align the regulatory requirements for a single clinical trial worldwide, and to develop a series of risk-assessment tools and risk-adapted monitoring procedures that will receive global validation for use in multinational clinical trials.

Two main issues were therefore identified as needing specific action:

- Promoting a risk-adapted legislation using a classification based on the marketing-authorisation status of the health product; and
- Developing a common strategy for a personalised approach to risk assessment and risk mitigation of every clinical study.

Recommendations

B.1 Introduce risk categories in national legislations and/or regulations, based on the marketing-authorisation status of the health product

These categories would be based upon the marketing status of the product, for instance:

- A. Health product used under an already licensed indication (risk similar to usual care)
- B. New indication/population for a marketed product
- C. New health product

i) The number (B and C categories could also be merged) and exact standard definitions of these categories and the range/type of clinical trials covered by this new mechanism would be debated at the international level under OECD auspices before being recommended for adoption by interested governments in accordance with their own national regulatory frameworks.

ii) The discussion should also cover the mechanism for assignment to the risk categories. For instance, the sponsor/investigator submitting the dossier would first propose a risk category for the trial, and the IRB/EC would validate the risk category, whereas the competent authorities would (when applicable, *i.e.* when authorisation or notification is requested) be able to re-qualify the risk level.

iii) The various processes impacted by the risk categories would need to be defined. For studies with authorised products, faster and simplified regulatory procedures would be set up, which could concern approval, adverse-event reporting, insurance/indemnity, inspection, labelling, provision for Investigational Medical Products, etc.

B.2 Develop and validate at the global level a set of tools and guidelines on risk assessment, as well as a set of risk-adapted monitoring procedures to be used and applied for every protocol

Such tools should include two components:

- Guidelines and decision trees supporting the definition and assessment of risk (to the patient, to the data...);
- Subsequent procedures and strategies to mitigate these risks (including monitoring procedures, etc.).

Multiple tools, based on distinct concepts and strategies, could be made available to the scientific community; however, these tools must be recognised and validated worldwide to allow their use in multinational trials.

The development and validation of such tools would require a broad collaboration by an international panel of stakeholders from both developed and developing countries (academy-based and industry sponsors, investigators, regulators, ethics committee members, patients' representatives), under the umbrella of an appropriate international organisation, in order to reach consensus on a few selected tools and procedures commonly agreed worldwide. To ensure consensus, this panel should include the already established regional or national initiatives (United States FDA and CTI, European Commission, European Medicines Agency, United Kingdom MHRA/DH/MRC, Optimon, Adamon, etc.).

3.3 Education, training, infrastructures and patients' involvement

Investigator-driven clinical research plays a major role in promoting public health, but launching and managing complex clinical trials, particularly at the international level, is often a challenge for academy-based groups. In many cases, education, career structures, training and the infrastructure required remain inconsistent, with substantial national and regional variation. This impedes the capacity of public research teams to initiate necessary but complex clinical studies in both developed and developing countries. It may also undermine the scientific validity of trials when enrolment is not representative enough of the population (for lack of properly trained or equipped clinical teams), or may limit the extent to which results may be generalised and applicable to those who may receive the tested interventions or diagnostics.

Three main areas of actions were identified:

- Improve training and career development;
- Support infrastructure development;
- Develop patients' role and involvement.

Recommendations

C.1 Develop a concept of *Global Core Competencies* for clinical research trials

These *Global Core Competencies* in clinical research should be developed as a compendium of required knowledge and skills for investigators and other members in the Clinical Research Team adapted to their different responsibilities and roles. Connected to this concept, standardised, mutually and internationally recognised *accredited qualifications* in patient-oriented clinical research should be defined.

All members of ethics committees, as well as members of regulatory bodies and sponsors, should also receive education/training in the principles of clinical research in accordance with the development of *Global Core Competencies*. These competencies and training programmes should be developed and implemented in collaboration with the relevant international agencies, and they should also be open to members of the general public.

A Working Group, convened under the auspices of an appropriate international organisation (ideally the WHO), should be initiated with representation from international health organisations, scientific societies and other relevant international bodies, clinical research

experts, and representatives from ethics committees and consumer organisations in order to follow up and translate these recommendations into action.

C.2 Establish national/regional/global networks for co-operation in clinical science

National institutions and non-governmental (charitable) organisations should promote the development of clinical research infrastructures with adequate staff and support functions organised in networks of research units and investigators. Such networks will facilitate international multi-centre clinical research as well as provide guidelines and examples of good practices for national or local support infrastructure. They should foster relationships between the whole chain of personnel involved in clinical trials, including patients' representatives, and propose a catalogue of resources and tools for academy-based clinical investigators. In addition, they may also work on useful frameworks for the careers of clinical research personnel (including clinical research physicians, study co-ordinators, nurses, pharmacists, biostatisticians and data managers).

A Working Group could be initiated to develop a framework for a global network structure covering the different therapeutic areas. Existing clinical networks and scientific societies could take the lead in such an effort.

C.3 Increase patient involvement in clinical-trial processes

More direct involvement of patients in the design and monitoring of clinical trials – as well as their contribution to improve the quality, safety and relevance of clinical research – is of critical significance for the success and impact of clinical science as a whole.

The roles of patients in clinical trials should be strengthened by means of:

- Mandatory participation of a representative of patients' opinion in ethics committees (as such, they would be involved in the decision regarding future risk categories of clinical trials).
- Consultative and participative role in the planning, design, conduct, dissemination and implementation of results from clinical science, in part mediated through the activities of the global networks as well as their regional and local network members and through other relevant channels.
- Simplified informed-consent documents, containing the vital information for decision making, using shorter and pedagogically sound explanations.
- Accessible information, for patients, families and the general public. This should include educational websites, ad hoc documents and open dialogue sessions with clinical staff at the hospital/clinical unit level, and transparent access to clinical registers and information databases about planned, ongoing and completed clinical trials by regulatory authorities.

Glossary

Terminology	Definition
Adverse Event (AE)	<p>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)</p> <p>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)</p>
Adverse Reaction (AR)	<p>Any untoward and unintended responses to an investigational medicinal product related to any dose administered. (Directive 2001/20/EC)</p> <p>ADVERSE REACTION: (Adverse Event.) An unwanted effect caused by the administration of drugs. Onset may be sudden or develop over time. (Source: clinicaltrials.gov)</p>
Advocacy and support groups	<p>Organisations and groups that actively support participants and their families with valuable resources, including self-empowerment and survival tools. (Source: clinicaltrials.gov)</p>
Audit	<p>A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted and data recorded, analysed and accurately reported according to the protocol, sponsors' standard operating procedures (SOPs) and good clinical practice (GCP). (ICH 6 GCP)</p>
Clinical Trial (CT)	<p>Any investigation on 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)</p> <p>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</p>

Terminology	Definition
	the drug or treatment has been licensed and marketed. (Source: clinicaltrials.gov)
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 be valid only 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)
Clinical trial authorisation application (CTAA)	A valid request that, before commencing any clinical trial, the sponsor has to submit for authorisation to the competent authority of the Member State in which the sponsor plans to conduct the clinical trial. (Directive 2001/20/EC article 9)
Competent Authority (CA)	Regulatory body. Based on the ICH, its tasks include reviewing the submitted clinical trial applications and clinical data, as well as conducting inspections.
Diagnostic trial	Refers to trials that are conducted to find better tests or procedures for diagnosing a particular disease or condition. Diagnostic trials usually include people who have signs or symptoms of the disease or condition being studied. (Source: clinicaltrial.gov)
Ethics Committee (EC)	<p>An independent body in a Member State, consisting of health care professionals and non-medical members, whose responsibility is to protect the rights, safety and well-being 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, as well as on the methods and documents to be used to inform trial subjects and obtain their informed consent. (Directive 2001/20/EC)</p> <p>The Regulations require a single ethical opinion for multi-centre trials; the Directive 2001/20/EC calls it “the concerned ethics committee”.</p>
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 incorporating addenda on the Essential Documents and on the Investigator’s Brochure, which had been agreed upon earlier through the ICH process.

Terminology	Definition
Good Epidemiological Practice (GEP)	A guideline written by the International Epidemiological Association for proper conduct in epidemiological research.
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)
Informed Consent Form (ICF)	<p>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)</p> <p>Informed consent: Person’s voluntary agreement, based upon adequate knowledge and understanding, to participate in human-subjects research or undergo a medical procedure.</p> <p>In giving informed consent, people may not waive legal rights or release or appear to release an investigator or sponsor from liability for negligence. (Source: NIH Glossary)</p>
Institutional Review Board (IRB)	<p>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.</p> <p>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)</p> <p>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 Institutional Review Board has the authority to approve, require modifications in or disapprove all research activities that fall within its jurisdiction. (Source: NIH Glossary)</p>

Terminology	Definition
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)
Monitor	A person entrusted with overseeing the progress of a clinical study, and of ensuring that it is conducted, recorded and reported in accordance with the protocol, SOPs, GCP and the applicable regulatory requirements. (ICH-GCP 1996)
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)
Participant Information Sheet (PIS)	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 wishes 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)
Phases	<p>PHASE I TRIALS: Initial studies to determine the metabolism and pharmacologic actions of drugs in humans and the side effects associated with increasing doses, and to gain early evidence of effectiveness; may include healthy participants and/or patients.</p> <p>PHASE II TRIALS: Controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks.</p>

Terminology	Definition
	<p>PHASE III TRIALS: Expanded controlled and uncontrolled trials after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather additional information to evaluate the overall benefit-risk relationship of the drug and provide an adequate basis for physician labelling.</p> <p>PHASE IV TRIALS: Post-marketing studies to delineate additional information including the drug's risks, benefits and optimal use. (Source: clinicaltrials.gov).</p>
Pharmacovigilance (PhV)	Pharmacovigilance is the process and science of monitoring the safety of medicines and taking action to reduce the risks and increase the benefits of medicines. It is a key public health function. (European Commission-Public health)
Processing of personal data (“processing”)	Any operation or set of operations which is performed upon personal data, whether or not by automatic means, such as collection, recording, organisation, storage, adaptation or alteration, retrieval, consultation, use, disclosure by transmission, dissemination or otherwise making available, alignment or combination, blocking, erasure or destruction. (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)
Sponsor	<p>An individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial. (Directive 2001/20/EC)</p> <p>Sponsor means a person who initiates a clinical investigation, but who does not actually conduct the investigation, <i>i.e.</i> 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</p>

Terminology	Definition
	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 (<i>e.g.</i> 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)
Standards of care	Treatment regimen or medical management based on state of the art participant care. (Source: clinicaltrials.gov)
Standard Operating Procedure (SOP)	Detailed, written instructions to achieve uniformity of the performance of a specific function. (ICH Harmonised Tripartite Guideline: Guideline For Good Clinical Practice E6)
Subject (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 participant is also used.
Substantial amendment(s)	<p>Amendments to the trial where they are likely to have a significant impact on (one or more of the criteria are met):</p> <ul style="list-style-type: none"> • The safety or physical or mental integrity of the subjects; • The scientific value of the trial; • The conduct or management of the trial; or • The quality or safety of any IMP used in the trial.

**Annex 1. Members of the Working Group and Subgroups, Berlin workshop participants
(12-13 May 2011)**

Argentina	Eduardo Cazap ²	International Union for Cancer Control
Australia	Warwick Anderson* James Best* ^{3#} Cleola Anderiesz ²	National Health and Medical Research Council (NHMRC) Cancer Australia
Belgium	Frank Hulstaert [#]	KCE – Centre Fédéral d'Expertise des soins de santé
Canada	Peter Monette* [#] Gavin C.E. Stuart ^{2#}	Health Canada University of British Columbia
China	Anthony Chan ² Jun Ren ²	Chinese University of Hong Kong Beijing Cancer Hospital
Denmark	Liselotte Højgaard* [#] Anne Mette Holm [#]	Rigshospitalet, Copenhagen Danish Medicines Agency
European Commission	Elmar Nimmegern* ^{1#} (co-chair subgroup 1)	Research DG, Directorate Health
ESF	Stephane Berghmans* Kirsten Steinhausen* ^{2#}	European Medical Research Council
Finland	Mikael Knip*	University of Helsinki
France	Jacques Demotes* ^{3#} (chair subgroup 3) Pierre-Henri Bertoye ^{3#} Valérie Journot ^{3#} François Lemaire ^{3#} Mihaela Matei [#] Anne Raison ³	INSERM/European Clinical Research Infrastructures Network AFSSAPS INSERM APHP APHP AFSSAPS
Germany	Insa Bruns* ^{3#} Ulrich Dietz [#] Ingebord Geisler [#] Alexander Grundmann* [#] Steffen Luntz [#]	KKS network Federal Ministry of Health Federal Ministry of Health BMBF KKS network

	Herbert Maier-Lenz* [#] Kenan Maric [#] Ulf Müller-Ladner [#] Ute Rehwald* [#] (co-chair WG) Gabriele Schwarz [#] Daniela Von Bubnoff [#] Stephanie Wolff [#]	KKS network Federal Ministry of Health Justus-Liebig University BMBF German Federal Institute for Drugs and Medical Devices BMBF KKS network
India	Elisabeth Vallikad ²	St. John Medical College
Israel	Talia Agmon [#]	Ministry of Health
Italy	Filippo Belardelli* Patrizia Popoli* [#] Flavia Pricci* Stefano Vella ²	Istituto Superiore di Sanità, Roma
Japan	Takayuki Abe [#] Keisuke Kouyama [#] Eriko Aotani ² Mamoru Narukawa* Noriko Morishita* Takeyuki Sato ^{3*} Shigeki Shiiba* Kenichi Tamiya* ^{3#} Nobuko Ushirozawa ³ Hiroshi Nagano [#]	Keio University Keio University Kitasato University Kitasato University Ministry of Health, Labour and Welfare (MHLW) MHLW then PMDA MHLW MHLW MHLW then National Hospital Organisation Chairman of the GSF; National Graduate Institute for Policy Studies
Korea	Byung-Ho Nam* ^{2#}	National Cancer Center
New Zealand	Ian Reid* ³	University of Auckland
Norway	Gunnar Kvalheim* ^{2#} Øyvind Melien* ^{2#} (chair subgroup 2)	Oslo University Hospital Norwegian Directorate of Health
Poland	Andrzej Gorski*	Medical University of Warsaw
Portugal	Eduardo Carvalho Campos [#]	Ethics Commission for Clinical Trials

	Maria Emilia Monteiro [#] Fátima Vaz ^{2#}	National Ethics Committee for Clinical. Research (CEIC) Portuguese Institute of Oncology, Lisbon
South Africa	Nandi Siegfried ^{*1,2,3#} Lyn Horn ³	Medical Research Council Stellenbosh University
Spain	Joaquín Casariego [*] (co-chair WG)	CAIBER, Carlos III National Institute of Health
Switzerland	Andri Christen ^{3#} Martin Goetz ³ Brigitte Meier ^{3#} Françoise Jaquet ^{*#}	Federal Office of Public Health Federal Office of Public Health Federal Office of Public Health Swissmedic
United Kingdom	Catherin Elliot ^{*1,3#} Sarah Meredith ^{*3} Martyn Ward ^{3#}	Medical Research Council (MRC) Medical Research Council (MRC) Medicines and Healthcare Products Regulatory Agency
United States	Leslie Ball ^{*3} Wilson Bryan ³ Cynthia Kleppinger ^{*1,3} Kathy L. Kopnisky [*] David Lepay [*] Michelle Limoli ^{*1} Susan Shurin ^{*3#} Mary Smolskis ^{*#} Jorge Tavel ^{*1} Edward Trimble ^{*2#} Celia Witten ³	Food and Drug Administration (FDA) FDA FDA National Institute of Health (NIH) FDA FDA NIH NIH NIH NIH NIH NIH FDA
OECD	Christine Kubiak ^{*#} (consultant) Frédéric Sgard ^{*#}	
Clinical Trials Facilitation Group	Chantal Bélorgey ^{*1#} (co-chair subgroup 1)	AFSSAPS (France)
European and Developing	Michael Makanga ²	

Countries Clinical Trials Partnership (EDCTP)		
European Forum for Good Clinical Practice (EFGCP)	Petra Knupfer [#]	
European Federation of the Pharmaceutical Industries and Association (EFPIA)	Christine-Lise Julou	
European Medicines Agency (EMA)	Fergus Sweeney ^{*1,3} Maria Isaac ²	
European Medicines Research Training Network (EMTRAIN)	Michael Woltz ² Gouya Ghazaleh ^{2#}	
European Organisation for Research and Treatment of Cancer (EORTC)	Christine de Balincourt ^{*3#}	
European Science Foundation (ESF)	Stephane Berghmans ^{*#} Kirsten Steinhausen ^{*2#}	European Medical Research Council European Medical Research Council
Novartis Pharma A.G.	Detlev Niese ¹	
World Health Organisation (WHO)	Davina Gherzi ^{*2#} Christine Halleux [*] Soumya Swaminathan [#]	

* indicates members of the Working Group

^{1, 2 or 3} indicates member of Subgroup 1, 2 or 3

[#] indicates participants to the Berlin meeting

Annex 2. Global Survey Results

Christine Kubiak

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1. Introduction

Clinical research is a critical activity for science and for developing knowledge on diseases and their treatments.

Clinical research involves testing new discoveries in the clinic by carrying out carefully controlled investigations on patients- known as clinical trials. This not only includes testing new medicines but also new therapies (*e.g.* radiation), devices, diagnostic techniques (*i.e.* imaging) or surgical procedures, as well as optimising existing medicinal products and procedures to secure better health and welfare/high-quality medical care.

There are two major sources for funding clinical research: industry and non-profit organisations including government funders and foundations. Industry develops diagnostic and therapeutic drugs and devices with a major goal of product development. These mechanisms have extensive economic and public health impacts. Non-commercial clinical trials – clinical studies initiated and driven by academic investigators for non-commercial purposes – are usually driven by pressing public health needs and scientific opportunities which do not offer a strong business case to private companies.

Over the years, international collaborations have increased and, although this makes access to patients easier, patient recruitment faster and the results of the trials more rapidly available and more generally applicable, it also increases the difficulty in conducting clinical trials. The complexity is mainly linked to the diversity of regulatory and ethical requirements, guidelines and schedules, or the divergent interpretations at national level, the specific legal requirements for contracts and the lack of harmonisation of the administrative requirements and timelines.

Non-profit organisations can hardly face the difficulties involved in dealing with the different requirements, due to a lack of expertise, infrastructures and resources.

To evaluate at the global level the challenges in conducting international clinical trials and how to overcome them, the Global Science Forum of the OECD (Organisation for Economic Co-operation and Development) has approved the creation of a Working Group on non-profit international clinical trials, at the initiative of the Delegations of Germany and Spain, with the following objectives:

- evaluate the persisting differences in regulatory processes;
- analyse the existing national and regional support for education, training and infrastructures required for academic clinical trials;
- analyse the funding mechanisms for infrastructures and clinical projects;
- analyse the feasibility of a risk-based approach and what could be the definitions of new international risk-based categories for multinational clinical trials; and
- propose practical recommendations to governments and interested institutions to reduce the various impediments which persist in clinical research, particularly for international academic-driven clinical trials.

To facilitate the elaboration of future policy recommendations, a global survey of the existing situation was undertaken, to take stock of the current difficulties and potential remedies as perceived by the different stakeholders involved in international clinical trials themselves.

2. Methodology

The survey process and objectives were elaborated by the Working Group at its first meeting in Madrid.

A questionnaire was developed addressing a series of key issues:

- Current national regulatory process and framework for clinical research
- Existing hurdles in conducting multinational non-commercial clinical research and in particular what impedes the conduct of multinational clinical trials, what are the issues, do services exist to support investigators and what should be recommended to improve the situation
- Existing national and regional support for education, training and infrastructures required for academic clinical trials
- Existing funding mechanisms for infrastructures and clinical projects
- Feasibility of a risk-based approach and what could be the definitions of new international risk-based categories for multinational clinical trials.

A list of important questions was determined for each topic in order to collect information, feedback and recommendations from different stakeholders.

Interviews were conducted with experts nominated by the working group. These experts were required to have knowledge of and experience in multinational clinical trials, to represent the different world regions, and to represent all the stakeholders involved, *i.e.* regulatory experts, clinical investigators, ethics committees representatives, sponsor representatives, representatives from major international networks, administrative officers, representatives from major patients advocacy groups, and representatives from the pharmaceutical or other relevant industries. Each expert was free to answer questions on one, several or all topics depending on his expertise and experience.

The interviews were based on the general survey framework that was developed, and were conducted by a unique consultant, hired by the GSF secretariat. The consultant has extensive experience in clinical research, both at the industry and academic level, and was involved in several initiatives on the evaluation of the European Directive 2001/20/EC¹⁶⁻¹⁷. She was also in charge of the development and analysis of the survey performed by the European Clinical Research Infrastructures Network on regulatory requirements¹⁸.

¹⁶ ICREL- Impact on Clinical research of European legislation (report): www.efgcp.be/ICREL/

¹⁷ Frewer LJ, Coles D, Champion K, Demotes-Mainard J, Goetbuget N, Ihrig K, Klingmann I, Kubiak C, Lejeune SA, McDonald F, Apperley J. Has the European Clinical Trials Directive been a success? *BMJ* 340:c1862 (2010).

¹⁸ Kubiak C, de Andres-Trelles F, Kuchinke W, Huemer KH, Thirstrup S, Whitfield K, Libersa C, Barraud B, Grählert X, Dreier G, Grychtol R, Temesvari Z, Blasko G, Kardos G, O'Brien T, Cooney M, Gaynor S, Schieppati A, Sanz N, Hernandez R, Asker-Hagelberg C, Johansson H, Bourne S, Byrne J, Asghar A, Husson JM, Gluud C,

A total of 115 experts representing the different stakeholders and different geographical areas were proposed by the members of the working group or by the consultant. All of the experts were contacted and asked whether they were interested in participating in the initiative and answering the survey, either in face-to-face meetings or via teleconference.

A total of 70 experts representing 55 stakeholders (complete list – Appendix 8.1, p. 69) were interested in the initiative and accepted to share their views and expertise in the field, and to be interviewed by the consultant (68 experts) or to complete the questionnaire (2 experts).

The collection of information was carried out between August 2010 and March 2011.

Another eight people responded favourably to the request, but it was not possible to organise the interviews due to lack of availability or because of technical issues.

The average time for the interview was approximately 90 minutes for the face-to-face interviews and one hour for the telephone interviews.

Eighty per cent of the interviewees asked to see the framework interview to prepare their interview, and in most cases the framework was used and followed during the interviews, while allowing for a completely open discussion.

Although the objective of the survey was not to provide extensive information, the group tried to involve experts who represent all types of stakeholders and all geographical areas. This objective was not completely achieved, as some areas such as South America, Asia and Africa, and some stakeholders such as regulatory bodies, ethics committees, academic sponsors and patients' organisations, are less represented (Table 1).

Table 1. Type of experts interviewed

	Europe	Japan	US/ Canada	NZ/ Australia	South Africa	South America	China	India	Other
Regulatory bodies/ policy makers	5	2	3						
Ethics committees	2		1		1				
Investigators	8	4	7	2	3	2	1	1	
Support structure (CTU, CRCs...)	(8)	(4)	10	(1)	(3)	(1)			
Academic sponsor	1		(2)						
Industrial sponsor	1	2	(1)						
Funding organisation					1		1		1
Patients organisations		1	1						

Demotes-Mainard J. Common definition for categories of clinical research: a prerequisite for a survey on regulatory requirements by the European Clinical Research Infrastructures Network (ECRIN). *Trials*. 10:95 (2009)

Regarding experience in clinical research:

- All of the experts interviewed have experience in multinational clinical research. Two-thirds have collaboration at the global level (including several continents) and one-third has experience with surrounding countries or within the same region.
- Around 60% of the people interviewed performed mainly non-commercial trials (even with commercial funding), 20% mainly commercial trials and 20% both types of trials.
- All phases (Phase I to Phase IV) and all type of studies (studies on medicinal products/studies on medical devices/diagnostic studies/other therapeutic studies/nutritional clinical studies/other interventional studies/epidemiological studies) were performed by the experts interviewed with a majority of Phase III studies involving medicinal products.

3. National regulatory framework

It is of utmost importance to ensure the welfare, safety and rights of the patients participating in research, and the reliability of the scientific data that is generated. The legislative and regulatory framework is one of the major determinants in the implementation of clinical research. Different national regulations have been introduced over time to ensure patient safety and methodological quality.

The objective of this section of the survey was to collect information on:

- regulatory and ethical requirements for the different categories of research
- competent authorities, their role, timelines, procedures
- ethics committees, their type (local, regional, national), their role, timelines, procedures
- definition of the sponsor - is there a specific definition for non-commercial sponsor? is co-sponsorship allowed?
- specificities for non-commercial trials (requirements, waivers, etc.)
- definition of Investigational Medicinal Product (IMP)
- insurance requirements
- adverse events reporting (definition, requirements)
- specificities for some categories of clinical research such as medical devices, diagnostic studies, epidemiology, surgery trials, phenotype/genotype, non-interventional studies, standard of care
- specificities for compassionate use/studies, biopharmaceuticals, biotherapy, stem cells, animal derived products
- requirements for specific populations such as healthy volunteers, vulnerable populations and critically ill patients, or in emergency situations

In terms of **regulatory framework**, two main models exist in the different countries surveyed:

- One model is based on the objective of the study, and makes a distinction between studies with a registration purpose and studies without a registration purpose, with regulations and requirements that are different for each category.
- Another model, which focused on the protection of the participants, was developed in Europe, without distinction between registration or non-registration purpose, or between commercial or non-commercial studies, and with no difference in regulations and requirements.

United States

The registration studies (Investigational New Drug applications -IND) for treatment, diagnostic or preventive products follow the FDA regulations.

Non-IND (Non-Investigational New Drug applications) studies are not regulated by law. All the categories of clinical research without health products follow the non-IND guidance.

In addition, all the studies funded through an NIH grant need to follow a policy that protects human subjects and is called the “Common Rule”. This policy requires that an IRB reviews and approves the trial protocol.

All categories of research should undergo an ethical review.

Canada

Clinical trials for a new drug, biologic, medical device, natural health product or an already marketed drug, biologic, medical device or natural health product intended for a different indication or dose, need to be authorised by Health Canada, the national competent authority before recruiting potential subjects. These trials must also be ICH-GCP compliant and approved by a research ethics board. In addition, academic trials must follow the *Tri-Council Policy Statement: Ethical conduct for research involving humans*.

Japan

There is a distinction between clinical trials intended for application for marketing authorisation (“chiken”) falling under the Pharmaceutical Affairs Law (PAL) and following the GCP, and the studies without registration purpose that are covered by ethical guidelines for clinical trials. Only data derived from clinical trials performed under PAL regulation can be used for marketing authorisation, and there is different enforcement by law.

“Chiken” trials are supervised by the Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceutical and Medical Devices Agency (PMDA), and other trials are supervised by ethics committees.

The PAL law, which governs “Chiken” trials includes punitive provisions. “Chiken” trials can be industry-sponsored but also investigator-sponsored with the same requirements.

The clinical trials other than “Chicken” are covered by specific ethical guidelines:

- Ethical guidelines for other clinical trial (other than those with a registration purpose)
- Ethical guidelines for epidemiological research
- Guidelines for gene therapy clinical trials
- Guidelines for stem cell clinical trials

These guidelines contain the essence of GCP, but they are not binding, they do not contain provisions for monitoring and audits, and there is no punitive provision under the applicable guidelines.

New Zealand

Trials on non-licensed medicines are supervised by the standing committee on therapeutic trials (SCOTT), which is a committee of the Health Research Council. The committee evaluates clinical studies to assess whether or not the proposed clinical trial of a medicine will provide clinically and scientifically useful information, particularly in relation to the safety and efficacy of the agent, assess the ability of the investigators to conduct the trial and attempts to improve trial design and the quality of clinical pharmacological research.

All the other categories of clinical research, including trials with licensed drugs (even if the sponsor has a commercial objective), non-drug trials and other categories of clinical research including epidemiology do not need the approval of SCOTT, but still need to undergo the ethical review process.

South Africa

The Medicines Control Council (MCC) is the statutory body that regulates the performance of clinical trials and the registration of medicines and medical devices. The MCC is responsible for ensuring that all clinical trials of both non-registered medicines and new indications of registered medicines comply with the necessary requirements for safety, quality and efficacy.

The other categories of clinical research are supervised by ethics committees.

Australia

In Australia, the Human Ethics Research Committee (HREC) with the therapeutic group is the regulatory body and there are two notification schemes: one called the “trial notification scheme” (CTN) for which an acknowledgement is enough to start the trial, and the “trial exemption scheme” (CTX) for which a full review and approval is needed to start the trial.

There is no clearly defined boundary between both schemes; the decision is left to the HREC, based on the data already available on the product, including previous marketing authorisation in other indications, or previous authorisation of the clinical trial in other countries.

Under the CTX scheme, a sponsor submits a package of data to the TGA (Therapeutic Goods Administration) for evaluation and comment. The TGA examines these data in order to assess the safety of the product, paying particular attention to its overseas status, proposed usage guidelines, pharmaceutical data sheets, details of medical device construction and

principles of operation, and pre-clinical and clinical data. The TGA then decides whether or not it has any objection to the proposed usage guidelines for that product. If no objection is raised, the researcher then submits the data to the ethics committee associated with the institution or organisation where the trial is to be conducted. This committee then considers the data, together with any comments provided by the TGA, assuming responsibility for assessing, and where appropriate, approving the proposal.

India

All the researchers need IRB approval (clearance). For clinical trials with medicinal products (new drugs or new indication or new dosage) there is a need to comply with the Revised Schedule “Y” of the Drug and Cosmetic Act and to obtain DCGI (Drug Controller General India) written approval.

Phase IV studies only need IRB approval

Minor amendments only have to be submitted to an ethics committee (EC) but major ones also require DCGI clearance, although there is no clear definition of what is a major or a minor amendment.

China

SFDA is responsible for approval of CT (if the drug comes from a foreign country). If the drug has already been tested in China, the application can be processed by local authorities.

An IRB review is necessary for all clinical researchers.

Europe

The approach is different from the other countries as the Directive 2001/20/EC focuses on interventional clinical trials for medicinal products and does not make any difference between trials for registration purpose and non-registration purpose.

The other categories of clinical research such as medical devices, surgery trials, diagnostic studies, other therapeutic studies, epidemiology, are not covered by the Directive, and are therefore subject to very divergent legislation between European countries.

Fixed timelines for competent authority approval are specified in some of the regulations/guidelines such as in Europe, the United States, Japan, Canada, New Zealand and Peru, whereas there are no fixed timelines in the regulation of South Africa or Australia.

For **ethical reviews**, there are again two main approaches:

- One approach is being developed in Europe following the implementation of the EU Directive 2001/20/EC, with a single ethical opinion requested. This single opinion has been implemented in different ways in the different European countries, with either a true single opinion with only one EC giving the opinion for all sites within

the country, or with a lead EC that will provide the single opinion but will take the advice from the different local or regional ECs where the study will be performed¹⁹.

- In the other countries such as Australia, the United States, Japan, New Zealand and South Africa, each institution or research organisation has its own Institutional Review Board and multi-site trials need IRB approvals for each site.

Each EC or IRB gives its own opinion and there is no consolidation of the different opinions making approval for multicentric clinical trials more difficult. However, in some countries a more centralised approach was developed as described below.

United States

The National Cancer Institute (NCI) formed the Central Institutional Review Board (CIRB) with the objective of conducting a single review for multisite phase III oncology trials. The process is a voluntary one, and institutions interested in using the CIRB must meet some basic requirements and sign an authorisation agreement. The local IRB conducts a facilitated review, meaning that only the chairperson or a small subcommittee review the recommendations that are posted with the protocol, correspondence on the CIRB website and give the approval. Minor alterations are permitted to tailor the informed consent document for the local context. If the local IRB accepts the facilitated review, the CIRB assumes full responsibility for handling continuous reviews, amendments, and serious adverse event reports.

New Zealand

Regional health and disability ethics committees evaluate research that is to be carried out in their region. A multi-region ethics committee undertakes the assessment if the trial is conducted in more than one ethics committee region or nationally.

The Health Research Council Ethics Committee has produced referral guidelines to clarify when an institutional ethics committee should refer a study to the appropriate health and disability ethics committee. Health and disability ethics committees are accredited by the Health Research Council (HRC).

Canada

Canada does not have a single national research ethics board for multi-site clinical trials. There are provincially based central ethics boards in some provinces (for example, Newfoundland and Labrador), for health research, and for some cancer trials (Ontario).

South Africa

The National Health Research Ethics Council (NHREC) is a statutory body responsible for the national oversight of research ethics committees and processes. The NHREC provides common guidelines for ECs and plans an accreditation process.

¹⁹ The EFGCP Report on The Procedure for the Ethical Review of Protocols for Clinical Research Projects in Europe: <http://www.efgcp.be/EFGCPReports.asp?L1=5&L2=1>

Their missions are the following:

- determine guidelines for the functioning of health research ethics committees
- register and audit health research ethics committees
- set norms and standards for conducting research on humans and animals including norms and standards for conducting clinical trials
- adjudicate complaints about the functioning of health research ethics committees and hear any complaint by a researcher who believes that he or she has been discriminated against by a health research ethics committee
- refer to the relevant statutory health professional council matters involving the violation or potential violation of an ethical or professional rule by a health care provider
- institute such disciplinary action as may be prescribed against any person found to be in violation of any norms and standards, or guidelines, set for the conducting of research in terms of this Act; and
- advise the national department and provincial departments on any ethical issues concerning research.

For ethical reviews, fixed timelines are defined in the EU Directive and in New Zealand regulation but not in the United States, Japan or South Africa.

The respective roles of CA and ECs are defined by laws, regulation or guidelines but not in such a detailed way as to avoid overlaps, and many stakeholders pointed out the lack of communication between both types of institution.

For most of the stakeholders interviewed, the definition of a **sponsor** is specified in the regulation and is the ICH one, *i.e.* “An individual, company, institution, or organisation which takes responsibility for the initiation, management, and/or financing of a clinical trial”.

In Japan, the sponsor is mandatory for registration trials and can be commercial or academic, but for the non-registration trials, the term used is principal investigator or researcher.

In New Zealand, the term “applicant” is used.

On the other hand, the term **non-commercial sponsor** is not clearly defined in regulations or guidelines and usually refers to what is not driven by industry.

Co-sponsorship (defined as the real sharing of responsibilities and not as task delegation) is allowed in Japan.

The national rules regarding the support of non-commercial trials are highly variable, leading from no difference between commercial and non-commercial trials (for example, in Japan, when an investigator is performing a “chicken” trial with exactly the same rules as commercial trials) to provision for non-commercial sponsors such as waivers or reduction of fees for regulatory submission or national support in terms of insurance.

Although **amendments** are defined in most of the regulations, the definitions and the requirements are highly variable, resulting in the following different attitudes:

- submission of any modification and approval needed
- submission of substantial amendment and approval needed
- immediate notification of major amendments
- delayed notification (during a periodic reporting) for minor amendments
- notification for all amendments

This results in many unnecessary submissions, and harmonisation would be welcome.

The inclusion of a new trial site in the country is considered as an amendment in most of the cases but not as a substantial one if it does not affect the total number of subjects involved in the study. When a new trial site is opened in a new country, some ECs/IRB request a notification but in most cases no information is required.

Liability insurance in clinical trials refers to the insurance or indemnity covering the liability of the sponsor and the investigator in respect of claims made against them by the participants in the trials and the insurance covering the participants for injury and damage.

In all of the countries surveyed, except in the United States, insurance is requested to conduct clinical trials; however, the requirements are very different in terms of who is covered or needs to be covered, the maximum provision for damages, and the type of insurance required. Some countries impose “no fault” insurance, intended to provide compensation to clinical trial subjects, without proof of fault, in the event of their suffering an injury (including illness or disease) that is directly attributable to their involvement in the trial.

In Europe, each country has its own rules and the requirements are very difficult to understand for foreign sponsors; this is considered a major hurdle for multinational clinical trials.

The **Investigational Medicinal Product** is usually defined in the regulation or in guidelines, but there is no common agreed definition in the different areas.

For **adverse event reporting**, clear definitions exist in the different regulations or guidelines as well as clear rules of reporting.

Additional requirements for specific categories of research such as medical devices, diagnostic studies, genotype/phenotype studies, standard of care studies, compassionate use studies, biopharmaceuticals, biotherapy, stem cells, animal derived products or for specific population (healthy volunteers, vulnerable population, critically ill patients or emergency situation) are mentioned in the regulations or guidelines.

- Information regarding clinical research on medical devices is covered by regulation in most of the countries surveyed.

- When covered by national regulations, no specific requirements are needed for clinical research on diagnostic studies, surgery trials, phenotype/genotype studies, or standard care studies.
- For specific categories such as biopharmaceutical, biotherapy, stem cells and animal derived products, some additional requirements such as submission to specific committees (such as a “gene committee”), are requested in most of the countries. In addition, for example in Europe, timelines for competent authorities and ethics committees can be extended.
- Provisions for vulnerable population are included in most of the regulations or ethical guidelines.
- Specific provisions are also included in some regulations for 1st in man studies.

4. Analysis of existing hurdles in conducting non-commercial multinational clinical trials

The objective of this section of the survey was to identify the major hurdles faced when performing non-commercial multinational clinical trials, and to classify them from “not difficult to overcome” to “very difficult to overcome”.

All the stakeholders agreed that the diversity of national regulations for clinical trials impedes the conduct of multinational trials. The regulatory framework itself, as a normative basis, is not subject to major criticism, but the differences in transposition and interpretation in national regulation as well as the differences in the requirements and operations by the regulatory bodies or other governance bodies, and the lack of a clear definition for sponsor (and especially sponsor responsibilities), investigational medicinal product, insurance or indemnification, are considered as major obstacles to multinational clinical research.

4.1 Main hurdles identified by the different stakeholders

In this paragraph, the hurdles identified are already listed according to the rate of difficulty encountered by the different experts, from the “most difficult to overcome” to the “least or not difficult to overcome”.

Of course this evaluation is subjective and is highly dependent on the type of clinical trials performed, the countries involved, the experience of the investigator/sponsor and the existing support in conducting clinical trials. However, the difficulties identified and faced by the different stakeholders and reported during the interviews were found to be highly similar for most interviewees, although the way to overcome them, and the consequences on the clinical trials may be different.

4.1.1 Procedures for authorisation (CA and EC)

CAs and ECs are bodies having the power to regulate and to ensure that clinical trials are performed according to applicable regulatory and ethical requirements.

In the ICH GCP guideline the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections. These bodies are sometimes referred to as competent authorities.

ECs or IRB are independent bodies comprising medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial. The legal status, composition, function, operations and regulatory requirements pertaining to ECs or IRB may differ among countries, but should allow them to act in agreement with GCP.

The main hurdles identified for the procedures for authorisation are:

- Lack of available and centralised knowledge on regulations, requirements and timeframe in other countries;
- Lack of infrastructures and resources to support investigator driven clinical trials (IDCT) and help with the different regulations and requirements;
- Lack of harmonisation and, especially in Europe, heterogeneous interpretation of the directive and various implementations in national regulations;
- Diversity of the requirements and formats regarding clinical trial applications;
- For stakeholders involved in clinical trials with developing countries, lack of regulation and lack of capacity to review the applications.

However, progress is ongoing in this area with the development of regulatory frameworks; under the initiatives of sponsors or funding agencies, there has been some improvement noticed in the organisation and practice of the regulatory bodies:

- Language issues with the need for local support and translation;
- Identical framework for industry and academic clinical trials despite having different objectives;
- Local approval (from local authorities or governance bodies at the local level) that cost time and resources.

This mainly creates operational burden and the ways to overcome the hurdle depend on the sponsor. The commercial sponsors have a different education, extensive experience and more resources available to face those issues in the different countries, which is not the case for academic sponsors.

In addition to the previous issues, some specific hurdles were identified for ethical review and ethics committees' procedures:

- Wide variances (even within one country) in terms of expertise, procedures, frequency of meetings and resources;
- Unnecessary operational burden and increase in time needed for approvals, created by the multisite approval and the differences in requirements by each single EC or IRB, although the multiple submissions and reviews have not proven to be of any benefit for the protection of the participants;
- Lack of co-ordination and communication between ECs reviewing the same protocol;

- Lack of harmonisation in the review process, although some countries have developed programmes to train their ECs to work in the same way;
- Lack of quality control within the EC;
- Absence of fixed timelines.

4.1.2 Insurance

As described above, provisions need to be made for insurance or indemnities to cover the liability of the investigator and sponsor and the compensation for participants injured in a clinical trial. The main hurdles identified in relation with insurance are:

- Lack of information on national requirements, on level of coverage required, and on whether the insurance provider needs to be a local company;
- Lack of harmonisation in terms of risk evaluation (and especially in the case of combination of drugs) and costs;
- Lack of global coverage to cover multinational clinical trials;
- Monopoly of private organisations;
- Absence of support to deal with insurance issues;
- Exorbitant fees;
- Difficulty in insuring some trials;
- Lack of information in case a claim is made.

4.1.3 Sponsor responsibilities

According to ICH and the European Directive 2001/20/EC, the sponsor is an individual, company, institution, or organisation that takes responsibility for the initiation, management, and/or financing of a clinical trial. Although this definition seems to be agreed at a global level, the interpretation may differ from one country to another, leading to difficulties in setting up and managing multinational clinical trials and especially:

- Difficulty in knowing what is required in other countries;
- Heterogeneous definition of sponsor and legal representative and how sponsors can delegate their responsibilities, and clarification of final liability;
- The need for a single sponsor in Europe without the possibility to share the liability and responsibility.

4.1.4 Standard of care

“Standard of care”, which refers to physicians' usual practices, is well characterised in all of the countries reviewed. This is not considered as a major hurdle except in the following aspects:

- In Japan, non-registered drugs cannot be used in non-commercial studies, and many products are not developed in Japan. Global trials with Japan are difficult to perform as the standards and doses are different.

- For stakeholders working with developing countries, the differences in standard of care may impact the set up of some trials when there is a big gap between the standard of care in the country and the practice developed in clinical trials. In resource-limited countries, many participants can be considered as vulnerable because they have a low education level, they lack familiarity with modern scientific concepts and experience in providing informed consent. It also raises the issue of follow up of patients after the study, the responsibility of the sponsor to make the study of benefit to the local population and make the population aware of the results;
- This difference in standard of care may impact the confidence in results obtained.

4.1.5 Funding, costs and fees

The funding of non-profit clinical research comes from different sources (paragraph 5) and has to cover all the costs linked to set up, run and manage the clinical trial (treatments to be used, the research staff to run and manage the trial and collect the data, the staff and computer technology to collect data, analyse the results, the administrative costs and fees, insurance, the cost of additional exams, treatments, procedures for participants taking part in the trial, the infrastructures providing support to the investigation or to the sponsor).

In multinational clinical trials, the obstacles linked to the cost and funding were the following:

- the high cost to perform CT especially outside the country with no real or insufficient sources to fund multinational clinical trials;
- difficulty to take into account the real costs of clinical trials (including proper monitoring, quality management, project management, fees for regulatory submission, etc);
- difficulties in obtaining funding (with many different rules and requirements and no harmonisation between funding agencies) and then difficulties in co-ordination and distribution of money to different partners in different countries, difficulties in co-ordinating and managing various sources of funding;
- lack of waivers for fees in some countries (application fees, for example);
- overly rigid grant or funding systems that are not adapted to the reality of clinical trials, and are very dependent on recruitment and on delays to obtain regulatory authorisations;
- lack of dedicated funding to support research in the interest of the population;
- difficulty in using funds outside the country where they were obtained (only for some European countries);
- currency fluctuation that may impair the continuation of clinical trials;
- higher costs in some countries that may bias the inclusion of those countries in multinational clinical trials.

4.1.6 Adverse event reporting

During clinical development, all important clinical safety information needs to be collected and reported. The definition of AE as well as the appropriate mechanisms to handle the reporting are described in ICH guidelines²⁰ and in national regulations. The main hurdle when performing multinational clinical trials are:

- lack of resources to review at the regulatory level;
- lack of experience, education and lack of infrastructures to support IDCT;
- difficulty to ensure, in foreign countries, that the appropriate reporting system is in place for proper reporting (sometimes need to use CRO as monitoring adverse events may be an issue).

However, safety reporting is not considered as a major hurdle, although standardisation of requirements would facilitate multinational clinical research.

4.1.7 Informed consent

Informed consent is a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

Although the translation, the length of some information and consent forms and the different national requirements and specificities are considered as difficulties, this was not identified as a main hurdle by the stakeholders regardless of their expertise or location.

One particular issue raised is the procedure to use when children reach majority.

4.1.8 Other hurdles identified

- Language diversity;
- Lack of infrastructure to support IDCT;
- Lack of training and education of investigators, lack of trained trialists;
- Drug supply and especially the need to provide the IMP for the study participants;
- Bureaucracy that requires significant resources without any benefit to the patients;
- Lack of transparency in clinical research and dissemination of results;
- Use of the pretext of Good Clinical Practice to impose unnecessary procedures;
- Sample management and circulation of samples;
- Absence of mutual recognition and acceptance of standards from other countries even if requirements are met;
- Lack of co-ordination, sharing tools between organisations;

²⁰ ICH Topic E2A Clinical Safety Data Management: definitions and standards for expedited reporting (CPMP/ICH/377/95)

- Specific requirements in terms of IT;
- Lack of harmonisation of the definition (not the same meaning for some endpoints for example);
- Biobanking, tissue, samples transportation.

4.2 Specific feedback from patients organisations/advocacy groups

Although only two patients' advocacy groups were interviewed, and although they have a broader objective than just clinical research, their feedback on clinical research is interesting and in line with the comments collected from other stakeholders.

The US group interviewed focuses on patient support, education, fund raising and policy. In particular, they provide government representatives with information on the benefits of medical research. They are also in charge of training lay people and develop training material and information on how research works, what is the value of research, and how it can provide innovation to the patients. They can also train the clinical staff to better explain the study and obtain informed consent. Patients or patients' advocacy groups are involved in steering committees taking decisions on the research to be performed and sometimes patients' advocacy groups become funders of research. Patients' advocates are also involved in discussions on regulatory processes.

According to the Japanese group, there is a lack of information on clinical research for lay people and there is a negative perception of clinical research in the general public, even in the oncology area where communication is more developed.

In addition, the patients' associations are not always involved in IRB as this is not mandatory.

The patients' rights are very fragmented in the law.

Although approaches to train people may be different from one country to another, and from one disease to another, exchanging with foreign groups and identifying and sharing communication and best practices would benefit the whole community.

Patients can provide some feedback on what is acceptable from their point of view and help the medical community to adapt the protocol (balance between sufficient science and acceptable constraints).

4.3 How does this affect clinical trials and what are the infrastructures that can support non-commercial clinical trials?

The hurdles identified have a direct impact on the implementation and management of multinational clinical trials, especially:

- Increase the delays in regulatory approval, time to implement the clinical trial and to start recruitment, and also the time necessary to carry out a study. This is considered as detrimental to patients and participants in clinical trials. It can drastically impact the methodology of the study and especially the sample size calculation in case of

major objection coming very late from one country while the trial has already started in other countries.

- Make CT and especially multinational CTs more and more difficult to set up. This may, in some cases, result in the decision to restrict the studies to a well known surrounding environment at the expense of the scientific quality of the trial.
- Increase of manpower needed and of the costs.
- Decrease of multinational co-operation due to the difficulties.
- Risk of bias in the selection of countries participating in global clinical trials, with the selection of only those countries with regulatory approvals compatible with other countries, resulting in a loss of credibility and opportunity for some countries.
- Cancellation of sites or countries if issues are too difficult to solve.

For all the stakeholders, the burden is more dependent on the type of study than on a specific country.

For industry, the impact is the same but to a lesser extent as the funding and resources are higher than for academic institutions.

Regarding **infrastructures** that exist to support non-commercial clinical research, the objective of the interviews was not to collect information on the national situation but more to collect the direct experience of the stakeholders, what kind of support was available for their studies and what support was considered to be missing.

The answers were highly dependent on the stakeholders and their experience, but for all of them, the infrastructures to support investigator-driven clinical trials need to be strengthened.

When national/local support exists, they are considered to be quite well adapted to provide support to national (even multicentre) studies but less adapted to support multinational clinical studies.

Some of these support infrastructures were part of the panel. The support infrastructures interviewed in the different countries have qualified and professional staff with expertise in all aspects of clinical trial development. In most of the cases, the infrastructure is not dedicated to purely academic research but is also involved in industry-sponsored clinical trials. But for most multinational clinical trials and collaborations, they have to rely on local staff.

The following support infrastructures were described:

- In Germany, the network of KKS is very well organised to provide support to IDCT and multinational clinical studies with for example the creation of a Pharmacovigilance centre able to provide support in multinational studies;
- In Japan, the Ministry of Health, Labour and Welfare established 40 centres for clinical research and specifically two centres with the objective of supporting global clinical research and multinational collaboration;

- In New Zealand, different CTUs or support structures exist, but not under a co-ordinated initiative;
- The Clinical Trial Research Unit in Auckland is ISO9001 certified and can provide the whole range of support to clinical research from the methodology to the follow-up, monitoring and writing of reports;
- In the United Kingdom, CTUs can provide support to all aspects of clinical trials but not all have expertise in multinational studies;
- In France, a nationwide network exists, with the creation in most university hospitals, since 1992, of Clinical Investigation Centers (CIC), which provide support to investigation, particularly in experimental medicine and early phase studies. In parallel, the Ministry of Health created in the early 90s, including university hospitals, structures designed to sponsor and co-ordinate clinical research at the local and later, in 2006, at the interregional level. A co-ordination of institutional sponsors was also created to federate all the institutions with a clinical research activity.
- In the United States, a network of medical research institutions is located throughout the country and funded by NIH to support clinical research with also a clear training objective. They share common practice;
- In Australia, there is no co-ordination in terms of infrastructure development. Co-operative groups that are well organised and promote international co-operation are able to develop such useful infrastructures but are individual initiatives;
- In South Africa, some of the institutions and especially the South African Medical Research Council, can provide support to and are conducting clinical trials but there is a need to strengthen at a national level the development of such infrastructure to support investigator driven clinical trials;
- In Canada, infrastructure is supported by charities and various levels of governments. Some provinces have clinical trial networks but this is not consistent across the country. In the view of one respondent, it is very difficult to convince government and local authorities of the economical benefit of clinical trials;
- In India, some clinical trial units exist in large hospitals such as the Centre for Chronic Disease Control, which was developed in New Delhi. In these units they are starting to develop data management and statistical support as there is an increasing demand from the community. In the CTU in New Delhi they are more or less working as a CRO applying for their own research, but also support other institutions through consulting;
- In China, in some large hospitals, there are infrastructures with professionals who support both the pharmaceutical industry and academia. But at the moment all the clinical research is driven by the pharmaceutical industry, and this raises the issue of the independence of academic groups.

As a general comment, in many countries, well developed and structured collaborative groups have developed their own disease-specific structures to support clinical research. This is

working very well but is only dedicated to a specific disease area and community, and does not allow for the support of all types of clinical research, and of investigators and sponsors working in different therapeutic areas, and there is no mutualisation of resources or sharing of practices and tools.

For most of those infrastructures, the funding is not sustainable, and raises the issue of keeping experienced staff within the infrastructure. In addition there is usually no co-ordinated effort in the development of the infrastructures at the national level.

4.4 Recommendations

- Regarding the procedures for authorisation or approval (CA/EC), the recommendations are to:
 - Streamline the CA and EC procedures, to streamline the collaboration of regulatory agencies, to harmonise the application schemes with a common CTA dossier for competent authorities and ethics committees, and spread more widely the idea of a single CTAA for multinational clinical trials with only one authorisation process. An idea would be to have one single application portal (one application to fill in and post and to be collected by the different regulatory bodies). Another idea would be to take the example of the ICH process for harmonisation and think of an organisation that could lead this harmonisation process;
 - Have a clear and identical definition of responsibilities between competent authorities and ethics committees;
 - Develop a common set of regulations or global standards and allow mutual recognition of IRB decisions;
 - Harmonise and simplify the rules to start and conduct clinical trials
- For the infrastructures, the suggestions are to:
 - Develop infrastructures with sustainable funding and develop the capacity to perform clinical research at the multinational level;
 - Strengthen the infrastructures at the national level. One idea could be to make the use of infrastructure with high quality standards mandatory. Improve global networking to facilitate international research;
 - Provide regulatory and scientific advice and support for non-commercial sponsors, such as practical support for regulatory submissions through an easy-to-follow flow chart. Centralise information and make it available on a website for all of the researchers (the international compilation of human research protections is an example of this kind of support listing over 1 000 laws, regulations, and guidelines on human subjects protections in over 100 countries and from several international organisations²¹) with a forum for academic investigators to share their issues.

²¹ www.hhs.gov/ohrp/international/intlcompilation/intlcompilation.html (access in May 2011)

- Provide a definition of terms and compare the definition in the different countries.
- Provide a database of experts from the different countries and information on national ethical norms;
- Provide incentive for collaborative and multinational projects.
- For training, two main recommendations were suggested:
 - Develop training, education and knowledge on clinical research. Develop a «culture» of clinical research and make the career in clinical research more attractive;
 - Develop a professional network of experienced people in the different countries able to provide guidance.
- For funding, which is considered a major hurdle, the proposals to improve the situation are:
 - Recognise the real cost of clinical research (including regulatory costs and quality costs) and make funding available at multinational level;
 - Generalise the waiver of fees for academic research and allow some revision of budget when there are very big currency fluctuations;
 - Develop funding systems that avoid conflict of interest with the same people distributing and using the funds.
- Additional suggestions were proposed to facilitate multinational clinical research:
 - Develop a data base with a common classification system to know which research is performed and where the bottlenecks are;
 - Increase transparency and publicly available information; increase the dissemination of study results and especially ensure that the local population is properly informed. Develop registries;
 - Avoid over-interpretation of GCP and the implementation of guidelines as rules;
 - Develop a risk-based approach;
 - Would be worth involving funding bodies in the negotiation with MAH when they are asked to provide their medicinal product to investigator-driven clinical trials;
 - Develop global insurance and a harmonised approach for litigation and think of institutional insurance;
 - Build an international working group on indemnification to harmonise the requirements;
 - Streamline the safety process with a unique point of submission and a central data base;
 - Use standard of care in the context of the community where the trial is implemented and not on what is recommended elsewhere.

5. Funding mechanisms

5.1 Infrastructures and clinical trials

These infrastructures are different from one country to another but are structures (clinical trial units, clinical research units/centres, clinical investigation centres) with professional staff able to provide adequate support for clinical research. The support can be full support for all aspects of clinical trials including trial management or can be limited to some aspects of the clinical trial such as data collection, biostatistics, or monitoring.

The information collected only reflects the situation of specific infrastructures or projects from the experts involved in the survey and does not necessarily describe the national situation of funding mechanisms, and is more an estimation than precise figures.

In addition, in most of the cases, it was very difficult to identify specific funding for the infrastructures since they may be financed through project funds.

In some countries, government funds were available to set up the infrastructure but diminished or stopped after few years; such was the case for the KKS in Germany that were funded by the Ministry of Research for the first four years.

Table 2. Funding sources of infrastructures

	Ministries	Funding agencies	Regional/local funds	Universities	Hospitals	Charities	Industry	PPP
France	Health Research		X	X	X	X	X	X
Germany	Research (first years)			X				Other sources
Japan	Health, Labour and Welfare			X (very small amount)	X (very small amount)			
Norway	Health					X	With strict rules of implication in IDCT	X
Peru		Federal agency						
South Africa	Health (very few)							
United Kingdom	Health	Medical Research Council (MRC)		X	X	X		
United States		X		X	X			

Table 3. Funding sources of clinical trials

Country	Funding source
Argentina	Ministry of Health Ministry of Research (but mainly for basic research) Funding agencies Universities (very little involvement)
Belgium	FP7 calls Charities (external) Universities Hospitals
Canada	Governmental funds The Canadian Institutes of Health Research Industry Charities and patients organisations
France	Ministry of Health Universities Hospitals Charities/patients organisations Industry Public-private partnership European funds
Germany	Ministry of Research (national programmes) National/regional funds Universities Charities Industry
Japan	Ministry of Health, Labour and Welfare Ministry of Education Charities (but only very few existing in Japan) Universities Industry
New Zealand	National funding agencies Charities Ministry of Health Universities (very few)
Norway	Ministry of Health (National Research Council) National Committee of Quality in Health Care Charities Public-private partnership
South Africa	External funds
United Kingdom	Medical Research Council Ministry of Health Charities Funding agencies European funds (FP7) Public-private partnership
United States	National funding agencies Charities Universities

In all cases, the funding of projects is linked to competitive calls, specific timelines, milestones or reports on the progress of the project and is made by sequential instalments.

In most of the countries, the support of commercial sponsors for non-commercial clinical trials is in principle possible but raises the issue of the independence of clinical research and may be limited to in-kind contributions from commercial sponsors, for example, by providing the investigational medicinal product and placebo. In countries where the level of public funding is low, the support from commercial sponsors is usually not limited.

5.2 Recommendations

Funding is probably the most important factor to consider for non-commercial clinical trials; although the level of funding is considered as insufficient by most stakeholders and therefore the primary focus for recommendation, the following areas of improvement were proposed as recommendations to encourage and promote non-commercial multinational clinical trials:

- International collaboration of funding agencies should be encouraged in order to develop a real possibility to fund multinational clinical trials without the issue of distributing the money in the different countries;
- The real costs of high quality non-commercial research should be taken into account and this should be discussed at the international level with the involvement of the different funding agencies;
- The level of funding is a challenge but the main question remains how to better allocate and better use the funds, with a need to perform cost efficient high quality academic clinical trials with a high public interest;
- Streamline and harmonise the funding procedures;
- Improve the public-private partnership and develop a more transparent relationship with industry;
- Allow more flexibility in the implementation of government grants.

6. Training

6.1 Training of staff conducting clinical trials

According to GCP principles, which describe the ethical and scientific standards for designing, conducting, and reporting clinical trials involving the participation of human subjects, “the investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies) and should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties”.

In all countries surveyed, investigators need to be appropriately trained as specified above, but this is not regulated by law, and the content of the training is not specified. In addition, there is no mention of requirements for other staff involved in clinical research.

In some cases (for example, Canada, the United States), the medical curricula can include formal education in the regulatory issues and conduct of clinical trials.

6.2 Requirements and certificate or official recognition

In all the countries surveyed, training of investigators and staff involved in clinical research is available either through face-to-face training, tutorials, and e-learning and includes:

- GCP training;
- In the United States and for US funded projects: training on protection on human research participants;
- In South Africa, initial GCP training is followed by a refresher course every three years;
- Training on studies specificities, therapeutic area;
- Specific training such as data management, pharmacovigilance, co-ordination of studies for specific staff.

Demonstration of skills can be requested by the sponsors, ethics committees, hospitals, funders or research governance bodies, institutions, or auditors.

Ethics committees and IRBs have the responsibility to check the suitability of investigators and staff participating in a given clinical trial. Some ethics committees in Europe have issued a catalogue with training and experience required to be part of clinical trial as an investigator. In Germany for example, ethics committees request a two-day training of investigators and co-ordinating investigators should have in addition at least two years of experience in clinical research. They are also considering adding a refresher course after two years.

But even in the countries where such a catalogue exists, there is no harmonisation at the national level and no common requirements across the ECs.

Sponsors (mainly commercial, but also institutional), infrastructures and support organisations have their training rules and request mandatory training that goes beyond the basic GCP training for their own staff and for the investigators and staff they work with.

Although most of the training organisations (private or public organisations) provide a certificate of achievement or completion, there is no official certification or national recognition.

6.3 Infrastructure and support that exists for training

- In all of the countries surveyed there are no structured or coherent public offers for training of staff conducting clinical trials.
- There is a lack of resources and funding for academic institutions.

- Training can be provided by:
 - support organisations (such as Clinical Trials Units in the United Kingdom, KKS in Germany, R&D offices, Clinical Research Centres in South Africa and New Zealand, core institutions designated by MHLW in Japan);
 - competent authorities;
 - non-profit organisations (examples: EORTC, Vienna School of Clinical research, e-learning organisations funded by members states [EDCTP]). Other examples include the GCP web-based training that is mandatory for all participants working on NCIC-Clinical Trials Group (Canada) trials²²;
 - universities;
 - hospitals;
 - private organisations (either face-to-face training or e-learning).

No co-ordinated initiatives were collected, except the one developed by the KKS network with a working group dealing with a standardised content of the training programme and the evaluation of the programmes.

For many investigators, one of the main sources of training on clinical trials remains the pharmaceutical industry or CRO.

6.4 Training for ethics committee members

- In Europe, there is no obligation or definition on the training required for ethics committee members in the Directive.
- In the United Kingdom, there is an assessment of the competencies of the ethics committees and a national training facility provides training courses for ethics committee members.
- In Norway, a three-day training period is mandatory at the beginning of the mandate, but the updating of competencies is under each member's responsibility. In addition, regular meetings are organised to harmonise the practices.
- In South Africa, the National Health Research Ethics Council (NHREC) is a statutory body responsible for the national oversight of research ethics committees and processes. The NHREC provides common guidelines for ECs and plans an accreditation process helping the ECs to reach the same level of quality.
- In the United States, there is no formal training programme for members of local ethics committees, although training is widely available from scientific societies.
- In Japan, education of ethic committee members is required by the Ethical Guideline on Clinical Research and is provided by the institutions, but the content and training methods are not harmonised and vary from one institution to another.

²² www.ctg.queensu.ca/membership.html

6.5 Training for patients' associations or lay people

For patients' associations or lay people, the main source of information or training is provided by the disease specific groups or organisations and focus is on the disease, with a lack of information on clinical research, on how research works, on what is the value of research, or on how it can provide innovation to the patients.

There is usually no co-ordination between groups to share basic information on clinical research and provide tools to train the citizens and patients advocacy groups.

Patients' associations are not always involved in the IRBs.

6.6 Recommendations

- The training and education programmes should be developed at the European level or even more at an international level with a common syllabus. The IMI initiative could be a good approach²³ to develop a common framework.
- The knowledge should be included in the initial training.
- The development of a clinical trials "licence" was proposed by several interviewees. There is a need to really demonstrate that people (including all staff and not only the investigators) are correctly trained. The realisation of audits to evaluate training, to verify that people have acquired the knowledge and the ability to perform studies, could be considered.
- The "academic" infrastructures for training should be developed and the cost of training must be taken into account and either covered by the funding for the infrastructure or by the funding for the project.
- The training should not be limited to GCP but adapted to the specific needs of the study and continued during the whole duration of the project. A real clinical research culture needs to be developed. The objective of the training should be clearly specified and people need to understand their role in clinical research.
- Need to make clinical research more attractive and to promote career development.
- Develop some standard with minimal requirements valid everywhere.
- Train the entire team with different modules.
- Train the regulatory bodies including ECs and CA.
- Include training in funding, either for infrastructure or for projects.
- Core training for all countries in the world with the same basis everywhere (see core competencies proposed by the CTSA²⁴).

²³ Innovative Medicine Initiative: www.imi-europe.org/Pages/topic.aspx?Item=9&ListId=DA41E506-DF1A-46A3-A541-548CE8F0D9B5

²⁴ www.ctsaweb.org/index.cfm?fuseaction=home.showCoreComp

From the patients' perspective:

- Need to build comprehensive networks of centres to share basic information on clinical research and provide tools to train the citizens and patients advocacy on clinical research and their disease²⁵ ;
- Increase transparency on clinical research by developing registers on clinical trials including the results of clinical trials;
- Involve patients or patients' associations early in the discussions on clinical projects and in the decisions concerning the use of funds (as for example in Japan with the establishment of a national cancer control board where patients have rights and can vote on the decision and provide some recommendations on how to use the budget to make clinical trials more efficient).

7. Risk-based approach

As described above, whereas some countries have developed legislation making a distinction between registration/non-registration studies, Europe has chosen another option with the 2001/20/EC Directive, which was transposed into national legislation with no difference made between commercial and non-commercial trials. The same regulations that apply to higher risk clinical trials on medicinal products have been applied to all trials regardless of the risk involved. This results in making some trials, using already licensed drugs and comparable to usual care, prohibitively resource and time-consuming without any benefit for the safety of the participants or the quality of the data.

One of the questions, which evolved especially in the context of non-commercial clinical trials, is whether there might be a rationale for discriminating different categories of clinical trials, using a risk-based approach; and for example, following the recommendations resulting from EMRC/ESF analysis, minimising regulatory requirements for studies with a risk similar to usual care²⁶.

However, the major issue concerning this aspect is how to define the risk, who should be in charge of defining the risk, who should validate it, and which process should be affected.

The objective of this section was to evaluate where such risk-based approaches are already in place, and what could be the advantages and disadvantages of such an approach. This would need to be discussed and defined at a global level in order to facilitate the conduct of multinational clinical trials and better harmonise the legislative approach across the world.

²⁵ For example: www.healthtalkonline.org (formally DIPEX)

²⁶ EMRC/ESR Forward Look on Investigator-Driven Clinical trials: www.esf.org/fileadmin/links/EMRC/FL_IDCT.pdf

7.1 Are there different regulatory requirements/rules depending on risk associated with clinical studies

In Europe, for all stakeholders interviewed, no explicit risk-based approach is used in the different national regulations, with the exception of the new German regulation on medical devices that includes a minimal risk category²⁷.

However, a certain amount of risk adaptation is permitted with the current regulations, and in many national regulations studies other than clinical trials on medicinal products or medical devices have different rules and different requirements, although not always well defined.

In addition, risk adaptation is also applied by regulatory bodies for the evaluation of the applications, although not formalised, with:

- More stringent requirements and more comprehensive application requested for early phases, new products or advanced therapies, and more scrutiny for these protocols
- Assessment adapted to the type of clinical research
- Extent of monitoring different

In Japan, clinical trials with a registration objective follow the Pharmaceutical Affairs Law with minister's ordinance without any provision for a risk-based approach, whereas the other categories of clinical trials, stem cell clinical trials, gene therapy clinical trials and epidemiology studies follow ethical guidelines with the same principles but with minister's notification.

In the United States, there is the possibility to have expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

7.2 Definition of risk criteria

The risks identified are the risk for the patient safety, the risk for the validity of the data and the hazard to trials results.

According to the stakeholders interviewed, the degree of risk should be under the sponsor's responsibility but an independent review would be necessary to check whether there is agreement on the level of risk. This independent review could be performed by the CA or EC.

Mutual recognition would be in principle possible but there is a need to agree on a common set of criteria and this should be difficult to reach.

²⁷ Gesetz über Medizinprodukte - MPG (vom 7. August 2002, zuletzt geändert 24. July 2010)
<http://bundesrecht.juris.de/mpg/index.html>

In principle also, no difference between commercial/non-commercial studies or sponsors should be applied since there is a need to have scientifically good protocols, good quality data and to end up with good results; however, some interviewees feel that industry sponsors may be more accustomed and trained to evaluate clinical trial risk than academic sponsors.

7.3 Advantages, disadvantages and feasibility of such an approach

This question was considered as a very complicated one and very difficult to answer.

Although most of the stakeholders would support the idea of a risk-based approach that could help multinational non-commercial clinical research and can take into account the increase of the knowledge of a product during its development cycle, the following points were raised by the different stakeholders and need to be considered when discussing such an approach:

- How to define risk and common categories. To be beneficial, the process needs to be simple and not create additional burden, but this approach would need a common agreement and some consensus at a global level.
- Have guidance from regulators so that sponsors or investigators can justify their choice in term of risk linked to the study.
- It would be helpful to have a detailed scoring system, taking into account all kind of risks.
- Necessity to grasp the true risk for the patient and to guarantee the safety of the patient and the quality of data.
- If such an approach is implemented, there will be a need for explanation and to increase the support in terms of education/training at site level, in order to reinforce the quality and advocacy component.
- To start with such a process, an option could be to restrict it to certain aspects of the study (such as regulatory requirements).
- May be difficult to make categories but may be possible to define the risk trial per trial.
- Discuss whether it would be more appropriate to adapt the regulation, mentioning what can be lightened for low risk.
- Define a risk profile and mitigation of the risk identified, allow a certain degree of tolerance.
- Have a pilot phase to test the acceptability of criteria.
- Join efforts and use the work already done by other groups.
- Risk management is only one part of the GCP.
- Need to keep a proper framework to ensure quality.

The risk-based approach is already implicitly used in scientific and ethical evaluation. There is a need to take into account that the objectives of trials are different, depending on if it is a commercial trial or an academic trial. The risk can be linked not only to a product but also to an intervention and the kind of population (for example a blood sampling may be of high risk in some resource limited countries, so define the level of risk in comparison to the current practice within one kind of population).

A good question is to know if it can be of benefit to reduce the requirements and also what are the consequences, and for example, analyse whether this will impact the different processes and management of clinical trials.

We also need to keep in mind that the risk-based approach would not be a good approach if it exempts the sponsor or investigator from their responsibilities, and that even if the trial is considered as “low risk”, human rights may be impacted. The main principles of clinical research must not be forgotten, nor should the principle that to answer relevant medical questions we need to have good quality clinical trials.

8. Appendices

8.1 List of experts interviewed

Argentina

Cazap, Eduardo President, Latin American and Caribbean Society of Medical Oncology (SLACOM), Buenos Aires, Argentina

Australia

Anderiesz, Cleola Research, Clinical Trials and Data Cancer Australia, Canberra, Australia

Austria

Druml, Christiane Ethik-Kommission der Medizinischen Universität Wien und des Allgemeinen Krankenhauses der Stadt Wien, Austria

Belgium

Mathieu, Chantal Department of Experimental Medicine, Katholieke Universiteit Leuven, Belgium

Canada

Bacon, Monica Gynecologic Cancer Intergroup study of the NCIC Clinical Trials Group (NCIC CTG), Queen's University, Kingston, Canada

Hebert, Paul C. Canadian Institutes of Health Research, Canada

Meyer, Ralph M. NCIC CTG, Cancer Clinical Trials Division, Cancer Research Institute, Queen's University Kingston, Canada

Stuart, Gavin C.E. Faculty of Medicine, University of British Columbia Vancouver, Canada

China

Zhao, Dong Beijing institute of heart, lung & blood vessel diseases (BIHLBD), Beijing, China

France

Bazin, Brigitte National Agency for Research on AIDS and Viral Hepatitis (ANRS), France

Belorgey, Chantal French Health Products Safety Agency (Agence Française de Sécurité Sanitaire des Produits de Santé - AFSSAPS)

Germany

Bielack, Stephan	Klinikum Stuttgart- Zentrum für Kinder-und Jugendmedizin, Germany
Donatello	Klinikum Stuttgart- Zentrum für Kinder-und Jugendmedizin, Germany
Kirschner, Janbernd	Klinik Neuropädiatrie und Muskelerkrankungen, Freiburg, Germany
Luntz, Steffen P.	Coordination Centre for Clinical Trials (KKS), University of Heidelberg, Germany
Pohl, Annette	Clinical Trials Center, University Medical Center Freiburg, Germany
Sudhop, Thomas	Federal Institute for Drugs and Medical Devices, Germany

India

Prabhakaran, Dorairaj	Centre for Chronic Disease Control, New Delhi, India
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Japan

Aotani, Eriko	Clinical Trial Coordinating Center- Kitasato University, Japan
Dong, Ruiping	Bristol-Myers Squibb Company, Japan
Erb, Dennis M.	VP, Head of Japan Development- MSD K.K., Tokyo, Japan
Kurokawa, Kiyoshi	National Graduate Institute for Policy Studies, Japan
Narukawa, Mamoru	Division of Pharmaceutical Medicine, Kitasato University, Japan
Noritake, Ryoji	Health Policy Institute, Japan
Sato, Takeyuki	Ministry of Health, Labour and Welfare, Japan
Sato, Yuji	Centre for Clinical Research-Keio University School of Medicine, Japan
Shibata, Taro	National Cancer Center, Japan
Tamiya, Kenichi	Ministry of Health, Labour and Welfare, Japan
Ushirozawa, Nobuko	Ministry of Health, Labour and Welfare, Japan
Yamamoto, Seiichiro	National Cancer Center, Japan

New-Zealand

Bullen, Chris Clinical Trials Research Unit- The University of Auckland, New Zealand

Norway

Aamdal, Steinar Department of Clinical Cancer Research - The Norwegian Radium Hospital, Norway

Akselsen Assessment Norwegian Medicines Agency, Norway

Engelstad, Maiken Department of Specialist Health Care Services, Norway

Hølen, Jacob The National Committee for Medical and Health Research Ethics, Norway

Peru

Tovar, Shandher Instituto Nacional de Enfermedades Neoplasicas, Peru

South-Africa

Horn, Lyn Research Ethics and Administration, South Africa

Makanga, Michael European and Developing Countries Clinical Trials Partnership (EDCTP), South Africa

Mayosi, Bongani Department of Medicine, University of Cape Town, South Africa

Ramjee, Gita Medical Research Council, South Africa

Rustomjee, Roxana Medical Research Council, South Africa

Switzerland

Niese, Detlef Novartis Pharma A.G, Switzerland

The Netherlands

Mgone, Charles S. European and Developing Countries Clinical Trials Partnership (EDCTP), The Netherlands

United Kingdom

Armitage, Jane Clinical Trials Service Unit, Oxford, United Kingdom

Meredith, Sarah Clinical Operations Group MRC Clinical Trials Unit, United Kingdom

Mihaylov, Svet NIHR Clinical Research Network Coordinating Centre, United Kingdom

Pavitt, Sue Comprehensive Health Research Division, University of Leeds, United Kingdom

Ward, Martyn Medicines and Healthcare products Regulatory Agency, United Kingdom

United States

Ball, Leslie Center for Drug Evaluation and Research, Food and Drug Administration, US

Bartlett, Edward E. Office for Human Research Protections-Office of Public Health and Science, US

Bell, Tammie Office of International Programs, Food and Drug Administration, US

Bernard, Gordon R. Vanderbilt University Medical Center, Nashville, US

Bryan, Wilson W. Center for Biologics Evaluation and Research, Food and Drug Administration, US

Goldberg, Jacquelyne L Central IRB Initiative, National Cancer Institute/Cancer Therapy Evaluation Program- Rockville, US

Gordon, David National Heart, Lung, and Blood Institute, National Institute of Health, US

Hoots, Keith National Heart, Lung, and Blood Institute, National Institute of Health, US

Kaneshiro, Julie Office for Human Research Protections-Office of Public Health and Science, US

Kleppinger, Cynthia Center for Biologics Evaluation and Research, Food and Drug Administration, US

Kwiek, Jesse Infectious Diseases-Current Ohio State University, US

Lin, Melody H. Office of Public Health and Science, US

Lynch, David	Office of Sponsored Projects Administration-Mayo Clinic, US
Paulson, Kelly	Mayo Clinic Cancer Center's Clinical Research Office, US
Peddicord, Douglas	Association of Clinical Research Organizations (ACRO), US
Reaman, Gregory H.	Children's Oncology Group, US
Rosenblum, Daniel	National Center for Research Resources, National Institutes of Health, US
Smolskis, Mary C.	National Institute of Allergy and Infectious Diseases - National Institute of Health, US
Soreth, Janice M.	FDA Europe Office, Office of International Programs, US
Speers, Marjorie A.	Association for the Accreditation of Human Research Protection Programs, US
Tavel, Jorge A.	Division of Clinical Research- National Institutes of Health, US
Temple, Robert	Office of Drug Evaluation, Food and Drug Administration, US

8.2 List of abbreviations

CA: Competent Authority

CIRB: Central Institutional Review Board

CRA: Clinical Research Assistant

CRC: Clinical Research Centre

CRO: Clinical Research Organisation

CT: Clinical trial

CTAA: Clinical Trial Application Authorisation

CTSA: Clinical and Translational Science Awards (US)

CTU: Clinical Trial Unit

EC: Ethics Committee

EDCTP: The European and Developing Countries Clinical Trials Partnership

EORTC: European Organisation for Research and Treatment of Cancer

EU: European Union

FDA: Food and Drug Administration (US)

FP7: 7th Framework Programme

GCP: Good Clinical Practice

GSF: Global Science Forum

CTAC: Gene Technology Advisory Committee

DCGI: Drug Controller General India

ICH: International Conference on Harmonisation

IEC: Independent Ethics Committee

IDCT: Investigator Driven Clinical Trial

IMI: Innovative Medicine Initiative

IMP: Investigational Medicinal Product

IND: Investigational New Drug Applications

IRB: Institutional Review Board

IT: Information technology

KKS: Koordinierungszentrum für Klinische Studien (Co-ordination centre for clinical trials, Germany)

MAH: Marketing Authorisation Holder

MCC: Medicines Control Council (South Africa)

MHLW: Ministry of Health, Labour and Welfare (Japan)

MHRA: Medicines and Healthcare products Regulatory Agency (UK)

MRC: Medical Research Council (UK)

NCI: National Cancer Institute (US)

NCIC: National Cancer Institute of Canada

NHREC: National Health Research Ethics Council (South-Africa)

NIH: National Institute of Health (US)

OECD: Organisation for Economic Co-operation and Development

PAL: Pharmaceutical Affairs Law (Japan)

PMDA: Pharmaceutical and Medical Devices Agency (Japan)

PPP: Public-Private Partnership

SCOTT: Standing Committee on Therapeutic Trials (New Zealand)

SFDA: State Food and Drug Administration (China)

TGA: Therapeutic Goods Administration (regulatory agency for medical drugs and devices, Australia)

OECD Global Science Forum

Facilitating International Cooperation in Non-Commercial Clinical Trials

Clinical trials include testing new medicines, therapies, devices, diagnostic techniques, surgical procedures, as well as optimizing existing medicinal products and procedures to secure better health and welfare. Many of these trials are non-commercial, and are brought about by pressing public health needs and scientific opportunities rather than commercial interest to private companies.

Strict national regulations ensure patient safety and methodological quality of clinical trials, however, these mechanisms are very diverse. This heterogeneity has an adverse effect on the conduct of international multi-centre trials, particularly in academic structures which may not have adequate administrative support.

This working group policy report identifies the main challenges encountered by the clinical research community in setting up international clinical trials. It proposes a series of policy recommendations concerning difficulties in three main areas: the administrative complexity of clinical trials, the desirability of introducing a risk-based approach to clinical trial management, and the need to improve the education and training support as well as the infrastructure framework in clinical research.