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The European Medicines Agency Working Group on Clinical Trials conducted outside of the EU/EEA

Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU Regulatory Authorities

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1. Glossary

AR:	Assessment Report
COE:	Council of Europe
CHMP:	Committee for Medicinal Products for Human Use
CMD:	Coordination Group for Mutual Recognition and Decentralised Procedures
COMP:	Committee for Orphan Medicinal Products
CTFG:	Clinical Trial Facilitation Group
DCP:	Decentralised Procedure
EEA:	European Economic Area
EMA:	European Medicines Agency
EPAR:	European Public Assessment Report
GCP:	Good Clinical Practice
GCP IWG:	GCP Inspectors Working Group
HCP-WG:	Working Group with Healthcare Professionals' Organisations
ICH:	International Conference on Harmonization
IMP:	Investigational Medicinal Product
MAA:	Marketing Authorisation Application
MRP:	Mutual Recognition Procedure
MSs:	Member States
NGOs:	Non-governmental organisations
PCWP:	Working Party with Patients' and Consumers' Organizations
PDCO:	Paediatric Committee
SAG:	Scientific Advisory Group
WHO:	World Health Organization

2. Introduction

A marketing authorisation for a medicinal product for human use in Europe can be granted either *via* the centralised procedure, through the decentralised procedure, mutual recognition or at national level.

The EMA is responsible for the evaluation of applications for European marketing authorisation for medicinal products, through the centralised procedure.The decentralized procedure is to be used in order to obtain marketing authorization in more than one Member State where the medicinal product in question has not yet received a marketing authorization in any Member State at the time of application. The mutual recognition procedure is to be used in order to obtain marketing authorization in additional Member States where the medicinal product in question has received a marketing authorization in any other Member State at the time of application.

The scope of this Reflection Paper is to clarify the practical application of requirements for clinical trials conducted outside of the EU/EEA and submitted in Marketing Authorisation Applications to the EMA (through the centralised procedure) or to National competent Authorities (through decentralised, mutual recognition, or national procedures) . The Paper set up practical steps to be undertaken during the provision of guidance and advice in the medicine development phase and during the evaluation of Marketing Authorisation Applications.

In the context of this document the term "countries outside EU/EEA" means any countries that are not Member States (MSs) of the European Union (EU)/European Economic Area (EEA).
The final scope of the document is to strengthen the process (mainly in its earlier phases) to assure, at the time of MAA assessment, that clinical trials conducted in countries outside EU/EEA have been conducted in accordance with the principle of Good Clinical Practice (GCP) and equivalent ethical standards as those applied/requested in the EU.

Details for regulatory action/action plan to be implemented and/or to be translated in future guidance are described below. The Reflection Paper is a starting point in the context of a more extensive programme focussed on the acceptance, of clinical trials conducted in countries outside EU/EEA and submitted to the European Regulatory Authorities in MAAs. During the development of this paper a number of issues were identified which are not addressed in the present EU legislation. These have been communicated to the EU Commission for their consideration in the context of the future revision of the clinical trials legislation.

The scope of the Reflection Paper is endorsed by the Heads of Medicines Agencies and by the Coordination Group for Mutual Recognition and Decentralised Procedures (CMD-h) with regard to the Mutual Recognition Procedure (MRP) and Decentralised Procedure (DCP).

The best approach for achieving these objectives is to ensure that a robust framework exists for the oversight and conduct of clinical trials, no matter where in the world the clinical investigators' sites are located and patients recruited. An international network of Supervisory Bodies (Regulators and Ethics Committees) from all countries involved, working together to share best practices, experiences and information and working to standards agreed and recognized by all, can provide an effective platform for such a robust framework. The Reflection Paper highlights and emphasizes the need for cooperation between Supervisory Bodies involved in the supervision of clinical trials and the need to extend and link networks to support these activities in particular in countries where the ethics and regulatory systems/aspects are not fully developed/available. The EMA will seek to build and extend its relationship with regulators in all part of the world and with international organisations in order to work

to achieve this. Examples of activities already implemented, ongoing or to be implemented, in this context, are provided.

The revisions to the pharmaceutical legislation which came into place in 2005 increased emphasis on the ethical standards required of clinical trials conducted outside the European Economic Area (EEA) and included in MAAs submitted for Marketing Authorisation.

It is acknowledged that the number of patients recruited in countries outside of the EEA is substantial (http://www.ema.europa.eu/Inspections/GCPgeneral.html). Some clinical trials are conducted across several regions, including Europe, whereas many others are conducted solely outside of the EEA.

Regulation (EC) No EC/726/2004 states in recital 16:

> "*There is also a need to provide for the ethical requirements of Directive 2001/20/EC of 4 April 2001 of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use to apply to medicinal products authorised by the Community. In particular, with respect to clinical trials conducted outside the Community on medicinal products destined to be authorised within the Community, at the time of the evaluation of the application for authorisation, it should be verified that these trials were conducted in accordance with the principles of good clinical practice and the ethical requirements equivalent to the provisions of the said Directive*."

Paragraph §8 of the Preamble – Introduction and General Principles of Annex 1 to Directive 2001/83/EC states:

> "*All clinical trials, conducted within the European Community, must comply with the requirements of Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. To be taken into account during the assessment of an application, clinical trials, conducted outside the European Community, which relate to medicinal products intended to be used in the European Community, shall be designed, implemented and reported on what good clinical practice and ethical principles are concerned, on the basis of principles, which are equivalent to the provisions of Directive 2001/20/EC. They shall be carried out in accordance with the ethical principles that are reflected, for example, in the Declaration of Helsinki*."

The EMA Work Programme for 2008 (http://www.ema.europa.eu/pdfs/general/direct/emeawp/EMEA_Work_Programme_2008_full.pdf) set out a number of objectives relating to the acceptance, in MAAs submitted to the EMA, of clinical trials conducted in countries outside the EEA on medicinal products for human use. All clinical trials from phase I to phase IV (including BE/BA studies) are required to meet internationally agreed ethical and data quality standards or their equivalent. These objectives need to be built into the process of clinical development. They need to be addressed before and during the conduct of the clinical trials and not only by assessment and inspection at the time of MA evaluation, by which point the trials have been completed, in some cases several years earlier. Actions to meet this objective therefore need to encompass EMA processes having an impact on clinical trials commencing prior to early phase clinical development. These processes include development of guidelines, Scientific Advice, Orphan Product Designation and Paediatric Investigation Plans and continue through to the finalisation of the CHMP opinion on the MAA/Scientific Opinion/Article 58 application evaluation, and post-authorisation activities and inspections.

In December 2008 the EMA published a strategy paper "Acceptance of clinical trials conducted in third countries for evaluation in Marketing Authorisation Applications" (https://www.ema.europa.eu/en/documents/other/european-medicines-agency-strategy-paper-acceptance-clinical-trials-conducted-third-countries_en.pdf) outlining four areas for action. These are:

1. Clarify the practical application of ethical standards for clinical trials, in the context of European Medicines Agency activities.
2. Determine the practical steps undertaken during the provision of guidance and advice in the drug development phase.
3. Determine the practical steps to be undertaken during the Marketing Authorisation phase
4. International cooperation in the regulation of clinical trials, their review and inspection and capacity building in this area.

In 2009 the EMA established a Working Group on clinical trials on medicinal products for human use conducted outside EU/EEA.

The Working Group, includes representatives of Committee for Medicinal Products for Human Use (CHMP), of the Paediatric Committee (PDCO), of the Committee for Orphan Medicinal Products (COMP), of the Clinical Trial Facilitation Group (CTFG), of the GCP Inspector Working group (GCP-IWG),

Of the Working Group with Healthcare Professionals' Organisations (HCP-WG), of the

Working Party with Patients' and Consumers' Organisations (PCWP), of the Coordination Group for Mutual Recognition and Decentralized Procedures - Human (CMDh), of EMA and of the European Commission Pharmaceutical Unit

This working Group has been asked to develop practical proposals for tasks and procedures or guidance to address the four action areas set out above. The present document reflects the results of the activities of this Working Group.

3. International cooperation in the regulation of clinical trials, their review and inspection and capacity building in this area

International cooperation has been clearly identified as a key foundation in developing a robust international framework for the conduct of clinical trials. As more and more clinical trials on medicinal products marketed in the EU are performed in countries outside of the EU, enhanced international cooperation is seen as essential to ensure that, as far as possible, there is a common international approach to the oversight of clinical trials. In addition the clinical trials are conducted, increasingly in countries, where the ethics and regulatory systems are not fully developed and with which EU regulators have limited formal contacts or experience in the domain of clinical trials**.** Building contact with, and between, the National Regulatory Authorities and Ethics Committees in these countries, their regional networks and associations, and the establishment of an international network of clinical trial regulators should therefore be a fundamental objective.

The ultimate objective is to have a system for regulators of clinical trials i) with harmonized approach for clinical trial oversight, ii) with strengthened efficiency of the controls by exchange of information and implementation of synergies between countries. In this system, the following local instruments should be in place, wherever clinical trials are performed:

1. Regulations that permit trials of medicinal products only if the trial is authorised by the national regulatory authority and/or by the concerned Ethic Committee(s) in that country and that take actions against violations;
2. Ethics Committees that are truly independent, professionally sound and adequately resourced;
3. Clinical Trial information made public, by implementation of registers;
4. Systems of follow-up of clinical trials by the National Regulatory Authority and concerned Ethics Committe (s), with authority to suspend and or stop clinical trials when needed;
5. Systems of control of clinical trials before, during and after their conduct, through the use of GCP Inspection by the National Regulatory Authority;
6. Regulations that permit the marketing of medicinal products only if authorised and that take actions against non compliance;
7. Regulations that allow the possibility of refusal by National Regulatory Agencies of the marketing authorisation of medicinal products when safety and efficacy have not been shown through trials conducted in accordance with GCP and ethical requirements.

These instruments should be publicly available and transparent.

The scope of this section is to specifically reflect on how to enhance international cooperation in the regulation of clinical trials performed including countries outside the EEA. Such an approach will promote confidence among Ethics Committees and Regulatory Authorities, avoid unnecessary duplication and multiplication of on site inspections, and allow exchange of valuable information. This approach should be implemented in a consistent and explicit way. It is recognised that achieving this objective is a long-term goal; nonetheless in order to reach that goal it is necessary to identify and take steps, in a phased manner, towards its achievement. In order to set priorities and identify the possible steps to be taken in achieving the objective described, a number of concerns and opportunities have been considered.

3.1. Identification of priorities

It is recognised that with limited resources, there is a need to prioritise particular activities and/or interaction with particular regions/countries. A first step is to identify the countries where important or growing numbers of clinical trials are performed, followed by communication with the National Regulatory Authorities / international bodies and network the sharing of information on the regulatory systems in these countries.

The following criteria have been considered:

***Countries that recruit a significant or growing number of patients*.**

The European Medicines Agency has prepared statistics on the numerical distribution of patients participating in pivotal trials included in MAAs submitted to the Agency during the period January 2005 to December 2010, the distribution of patients is:

- Africa (this area provided 2.76% of the patient in total) : South Africa is the major contributor with 2.19% of the patients
- Middle East/Asia/Pacific (8.7% in total): India (1.6%), Israel (1.2%), Philippines (1.1%), Thailand (0.9%) and China (0.7%) followed in order by South Korea, Chinese Taipei, Japan, Turkey, Malaysia and Hong Kong contributing between 0.3 and 0.6%.

- Australia/New Zealand: this area provides 1.5%, mainly from Australia (1.3%).
- Central/South America (8.5 % in total): the major contributors is Brazil (2.5 %), followed by Argentina (2%), Mexico (1.3%), Costa Rica (0.5%) and Peru (0.5%).
- Commonwealth of Independent States (3.8 in total): Russia (2.8%) and Ukraine (0.8%)
- Eastern Europe-non EU (0.5 % in total) : Croatia (0.3%).
- North America (34.54% of the total, mainly from USA (29.98%))
- EU/EEA/EFTA (39.4% of the total)

Therefore some of these countries and others where there is an increase in the number of clinical trials or patient participation in trials should be considered as a priority. In addition some countries contributed less in terms of absolute/total number but are prioritised for assistance in development of their Regulatory activities and expertise. Since the EMA information is limited to centrally authorised products, collecting equivalent information from MSs and other regulatory partners, including WHO, and non-EU regulatory agencies, and from sponsor associations (in particular on ongoing trends) should also be considered. EMA will ensure that a process is developed to bring together the different sources of information to make these available for the International Network.

Type of Regulatory System in place

Those countries that have a limited regulatory system or one that is still under development (small or very new National Regulatory Authorities with a limited legal framework for the oversight of clinical trials) should also be considered as a priority as part of a wider contribution to capacity building across the global regulatory network and to enable countries to develop effective systems for development of medicines addressing their own health priorities. It will be useful to obtain high level information from all countries from which clinical trials are submitted to the EU or via WHO in order to identify these countries.

Countries where there is little information available and/or where information suggests that Ethics Committees may not be properly established should also be identified as priorities.

In order to evaluate the level of priority in the context of the aforementioned criteria, it is proposed that a high level "mapping" of information should be established in cooperation between EMA, MS, regulatory authorities and international organizations in relation to:

- the level of activity in the field of clinical trials, identifying subcategories of those clinical trials (e.g. Phase I including first in Human trials, Bioequivalence studies, phase II and III in specified therapeutic areas phase IV);
- the established and functional regulatory framework for clinical trial authorisation (national regulatory authorities and Ethics Committees), GCP inspections.
- the infrastructure for and levels of investigator support and training.

This 'mapping' should identify the strengths and weaknesses of the national systems, should identify whether capacity building or related development activities are ongoing and should help to select areas for possible cooperation: the selection of the areas for cooperation (i.e. GCP inspections, strengthening of Regulatory Systems or Ethics Committees (strengthened cooperation, capacity building and/or focussed, joint, training) will depend on the needs identified in the countries included in the priority list and should be oriented to avoid duplication with other initiatives in the same area of intervention. The

mapping should also identify the opportunities for cooperation with all countries including those where the systems are already developed, and authorities already exist and are functional (see section 3.2)

Regulatory action/action plan

1. *EU Regulatory Authorities will prioritise the countries outside EU/EEA with which it will focus its interaction based firstly on the numbers of trial subjects recruited there as part of clinical trials submitted to EU Regulatory Authorities and secondly on a review of the regulatory systems in place for the supervision of clinical trials in those countries, including countries where Bioequivalence trials are conducted.*

3.2. Identification of opportunities and partners

3.2.1. Identification of other initiatives

In order to look for synergies and avoid duplication of effort, any work performed by the EMA Working Groups should be complementary to the other numerous initiatives being carried out by international, European, regional and national organisations in this field.

Existing initiatives have not always been implemented with a clear picture of what has been done already, what the results have been and what is being done in the same geographical area, in the same field of study etc.. As a consequence, there may be little knowledge of:

- neglected areas of intervention;
- the necessity for complementary interventions that can be more effective;
- previous initiatives with favourable or unfavourable results;
- the risk of duplication of initiatives.

The group is aware of different initiatives at different levels carried out by different organisations. These initiatives can be categorised as follows:

3.2.2. Categories of initiatives and actions

- Assessment of National supervisory bodies (Regulatory Authorities and Ethics Committees)
- Strengthening National Supervisory bodies
  - national regulatory authority
  - ethics committee
  - other authorities

Examples of initiatives are provided in section 3.5.

- Strengthening the initiative of other Organizations
  - University education
  - Civil society organization
  - Investigator networks
  - Health care Systems

3.2.3. Establishment of contact with key initiatives

Relevant contact points for these different initiatives and countries of interest should be identified and good communication established in order to obtain:

- updated knowledge of the situation in each of the priority countries
- an evaluation on what has already been done to date;
- reciprocal knowledge of what is being done in this field;
- a continuous update on what is going to be done.

This will facilitate the identification of partnerships for joint, common or coordinated activities.

Regulatory action/action plan

1. *EMA will identify other initiatives that are being carried out in the area of clinical trials supervision, mapping of regulatory systems in place and capacity building.*
2. *EMA will identify contact points with the other initiatives in order to identify partnerships for joint, common or coordinated activities.*
3. *EMA will ensure that the mapping is established in cooperation with other partners*

3.3. Action plan

Three major directions are identified:

- Strengthening the efficiency of the controls (including GCP inspections) by Regulatory authorities
- Improving the capacity of National Supervisory bodies (Regulatory Authorities and Ethics Committees) to oversee clinical trials
- Motivating sponsors and Marketing Authorisation applicants to ensure adequate levels of control before and during the conduct of their own clinical trials.

The proposed action plan addresses them.

3.3.1. Core activities

The core set of actions consists in ensuring planned and coordinated contribution of GCP inspectors, marketing authorisation assessors and experts in the following areas of intervention depending on the needs identified in conjunction with the priority countries and based on the information obtained on the existence of other initiatives carried out by other organisations:

- Controls of clinical trials:
  - GCP inspection

    Increase the number of inspections in the priority countries and stakeholders of particular interest

    Encourage observed, joint inspections and complementary inspection programs with National Regulatory Authorities
  - Develop frameworks and priority topics for information exchange and follow up on inspections

- Regulatory authorities (evaluation and inspection sectors):
  - Assistance with the establishment and operation of National Regulatory Authority systems for review and oversight of clinical trials, and evaluation of the processes established
  - Training (courses, workshops, support in the preparation of guidelines/SOPs etc.)
  - Scientific / technical support
  - Protocol assistance/Scientific Advice
  - Support for Assessment of clinical trials. Seek the contribution of the Clinical Trial Facilitation Group and specialists in pharmaceutical/non-clinical/clinical evaluation in specific fields
  - Explore and establish frameworks for different types of information exchange and networking for Regulatory Authorities.
- Ethics committees (Ethics Committees):
  - Assistance with the establishment and operation of Ethics Committees, and evaluation of their processes
  - Training (courses, workshops, support in the preparation of guidelines/SOPs etc.)
  - National registries of Ethics Committees and documentation on their composition and activity should be established
  - Evaluation of clinical trials by Ethics Committees – the cooperation of EU *Ethics Committees* can be sought
  - Investigation of systems for accreditation or evaluation of Ethics Committees
  - Explore and establish frameworks for different types of information exchange and networking of Ethics Committees

This core set of actions should be refined in accordance with the results and will contribute to the update of the short term and long term activities, described hereunder.

3.3.2. Short Term activities:

In the following context, regional groups and associations of national regulatory authorities or ethics committee bodies will often facilitate activities and improve the efficiency and effectiveness of the activities involved.

- Establishing and maintaining high level information on:
  - the established regulatory frameworks for clinical trial authorisation (National Regulatory Authorities and Ethics Committees), GCP inspections, and investigator support and training in priority countries in order to identify and prioritise the areas for increased cooperation; this action can be done by assessment of the available systems, partly as a collaborative work with other established initiatives.
  - the level of activity in the field of clinical trials (numbers, types and purpose [national market/'export'] of clinical trials), in order to identify the interest of the country. This action requires identification of other sources of information (e.g. registries of clinical trials, National Regulatory Authorities etc).

- information on relevant activities underway by other regulatory authorities or international organisations/initiatives/partnerships.

- Establishing, sharing and maintaining a list of relevant contact points for the organisations, authorities and initiatives (international, regional, national etc.) involved in these areas including the priority countries
- Establishing links – formal and informal – with other projects and initiatives in relation to the priority countries:
  - Inventory of all organisations and initiatives (international, regional and national e.g. WHO mediated groups, ASEAN, African initiatives such as West African Health Organization (WAHO) and the Economic Community of West African States (ECOWAS etc.) and training and other capacity building initiatives already implemented and ongoing by these organisations.
  - Inventory of the models of initiatives implemented and their real efficacy
  - Information on relevant activities underway by other regulatory authorities and international partners.

3.3.3. Long Term activities:

The establishment of a "Service" or "Centre" that could enable sharing - through continuous links with the international organisations, the European Union MSs and institutions and those of countries outside EU/EEA, as well as NGOs (non-governmental organisations) - the following (and other) information for each country where a relevant number of clinical trials are conducted:

1. the laws and regulations governing this field;
2. Information on National Regulatory Authorities, Ethics Committees and GCP Inspectorates;
3. Information on GCP inspections and their outcome
4. Models of initiatives implemented and information on obstacles encountered and their real efficacy.

This could provide a useful support for implementing interventions that can be more targeted to the real needs, more selective, complementary and avoiding duplication. The interventions should be defined on the basis of the results of experiences already carried out with success, to contribute to the process of ensuring that research on medicinal products respects GCP and ethical requirements in accordance with the international human rights law.

In this way, such a "Service" would allow the participating partner countries and international organisations to be up to date on the latest developments in the field could be particularly useful in the following contexts:

1. when EMA and National Regulatory Agencies need to verify compliance to the principles of GCP for a certain clinical trial;
2. when EMA and other international, regional and national organisations or NGOs want to support a country through capacity building initiatives, such as training programmes for investigators or for members of Ethics Committees or GCP inspectors;
3. when a scientific institution or a pharmaceutical company wants to conduct a clinical trial;
4. when a qualified institution wants to provide advice on the preparation of regulations or procedures in this field.

3.4. Resource considerations

It is recognised that additional resources will be needed to address these objectives, both short and long-term. Liaison and communication with the actors identified below will help to establish possible funding and collaboration opportunities:

- EU Commission
- European Medicines Agency
- EU Member States
- Non EU National Regulatory Authority partners interested or concerned by such initiatives
- International and regional organisations:
  - Organisations responsible for funding projects
  - Organisations responsible for organizing the activities (without funding): to be categorized for areas of activity (e.g. training, legislation, GCP, etc.)
  - Organisations that fall under both categories

In this context it is recognised that WHO and some National Regulatory Authorities in particular have a range of activities ongoing that are of particular relevance and interest.

Regulatory action/action plan

1. *EMA and EU Regulatory Authorities will identify resource requirements and budget to support the contribution of the EU Regulators.*
2. *EMA and EU Regulatory Authorities will identify and work with other funding bodies in order to benefit from potential funds to support EMA or EU Member State experts contribution to capacity building exercises.*
3. *EMA and EU Regulatory Authorities will identify and work with other funding bodies in order to identify funds that may help delegates from concerned countries outside EU/EEA to participate and benefit from capacity building exercises.*

3.5. Example of initiatives

GCP Inspections:

- Increase the number of inspections in priority countries and stakeholders of particular interest

EU-CMDh Coordinated program between EU-MSs for inspecting bioequivalence trial facilities with high level of activity.

- Encourage observed and joint inspections with local authorities
- Increase the capacity for inspection information sharing
- The EMA and FDA lunched an initiative on GCP, with the following key objectives:
  1. To conduct Periodic Information Exchanges on GCP-Related Information
  2. To conduct collaborative GCP inspections

3. To share information on interpretation of GCP

Harmonization of practice

EMA, through its GCP IWG (Inspectors Working Group) organises every year a specific training for EU inspectors. Since 2007 it has included representation from WHO and non EU regulatory authorities (e.g. Australia, Bosnia and Herzegovina, Brazil, Canada, Costa Rica, China, Ghana, Kenya, Iceland, India, Indonesia, Israel, Jordan, Japan, Republic of Korea, Macedonia, Malawi, Montenegro, Mexico, Nigeria, Norway, Philippines, Russian Federation, Saudi Arabia, Singapore, Serbia, Singapore, South Africa, Switzerland, Taiwan, Thailand, Turkey, Ukraine, United States, Zambia) in order to contribute to increased communication and sharing of best practices and expertise among regulatory authorities from within the EU and from countries outside EU/EEA in relation to GCP inspection activities.

Regulatory authorities (evaluation and inspection sectors):

- Assessment of / assistance in implementing National Regulatory Authorities
  WHO, Immunization standards, strengthening national regulatory authorities,
- Training (courses, workshops, support in the preparation of guidelines/SOPs etc.)
- EDCTP training course on GCP, Gambia, 7-11 May 2007

Scientific / technical support:

- Protocol assistance/Scientific Advice
- Assessment of clinical trials and clinical data
- EMA works, in cooperation with the European Commission DG Development and with WHO on a project to help regulators from less well developed National Regulatory Authorities, to develop their expertise in the review of MAAs.

Ethics Committees:

- FERCAP initiative, http://www.fercap-sidcer.org/aboutus.php
- Assessment of / assistance in implementing Ethics Committes
- Training (courses, workshops, support in the preparation of guidelines/SOPs etc.)
- Evaluation of clinical trials.
- Investigation of systems for accreditation
- Information exchange

4. Clarification of the practical application of ethical standards for clinical trials on medicinal products for human use in the context of the activities of the European Regulatory Authorities

For the purpose of research, three ethical principles should be adhered to:

a) respect for persons,

b) beneficence/non-maleficence and

c) justice, where respect for persons includes the respect for autonomy and the protection of dependent and vulnerable persons, beneficence/non- maleficence is defined as the ethical obligation to maximize benefits and to avoid or minimize harms, and justice is a fair distribution of the burdens and benefits of research[1].

"The rights safety and wellbeing of the trials subjects are the most important consideration and should prevail over the interests of science and society". [2]

Clinical trials conducted in countries outside of the EU/EEA and used in MAAs in the EEA or in applications for a Scientific Opinion under article 58 of the Regulation (EC) No. 726/2004, must be conducted on the basis of principles equivalent to the ethical principles and principles of good clinical practice applied to clinical trials in the EEA[3].

Ethical principles have been established mainly by intergovernmental organisations such as the Council of Europe or WHO, or by professional bodies such as the World Medical Association, as well as in national or regional legislation or guidance. The latter often refer directly or indirectly to the internationally established principles.

Ethical principles governing the conduct of clinical trials are set out in the Charter of Fundamental Rights of the European Union (2000)[i] the Council of Europe's Convention on Human Rights and Biomedicine (1997)[ii] and its Additional Protocol on Biomedical Research (2005)[iii], the Universal Declaration of Human Rights (1948)[iv], the Convention for the protection of Human Rights and fundamental Freedoms (1950)[v], the United Nations' Convention on the Rights of the Child (1989)[vi], the Universal Declaration on Bioethics and Human Rights (UNESCO, 2005)[vii], the Universal Declaration on the Human Genome and Human Rights (UNESCO, 1997)[viii], the International Declaration on Human Genetic Data (UNESCO, 2003)[ix], the CIOMS-WHO International Ethical Guidelines for Biomedical Research Involving Human Subjects (Geneva 2002)[x], the Declaration of Helsinki of the World Medical Association (2008)[xi], Opinion 17 of the European Group on Ethics (2003)[xii] and the EU Ethical considerations for clinical trials on medicinal products conducted with the paediatric population (2008)[xiii]. Practical steps to implement ethical requirements are set out in the CPMP/ICH/135/95 guideline on Good Clinical Practice (1995) (ICH E6)[xiv] and ICH E11 Note for guidance on clinical investigation of medicinal products in the paediatric population (2001)[xv].

The European pharmaceutical legislation sets out the ethical requirements for the conduct of clinical trials in Directive 2001/20/EC[xvi], Directive 2005/28/EC[xvii] and Directive 2001/83/EC[xviii]. Provisions of the European Paediatric Regulation 1901/06/EC are equally taken into consideration[xix].

Provisions for the protection of personal data are laid down in Directive 1995/46/EC[xx],

The extent to which these various documents pertinent to clinical trials (both legal and ethical instruments) are taken into account in national or regional legislation within or outside EU is variable. They overlap in many areas, but some given greater precision on certain points whilst on others there are differences in approach. The aim of the present document is not to establish a new, additional, set of principles but rather to describe how the regulatory processes of the EMA and EU National Competent Authorities can take these into account in a practical way.

1 WHO (CIOMS) Guidelines 2
2 Paragraph 2.3 of ICH-E6
3 Paragraph 8 of the Preamble of Annex 1 to Directive 2001/83/EC

4.1. Ethics committee and national regulatory authority oversight

Research may only be undertaken if the research project has been approved by an EC (or other body authorised to review clinical research on human beings) with appropriate jurisdiction for the investigator sites and trial concerned, after independent examination of its scientific merit, including assessment of the importance of the aim of research, and multidisciplinary review of its ethical acceptability,[4] In many countries an application also has to be made to a Regulatory Authority, before a clinical trial may commence.

It is an important element of international cooperation that Regulatory Authorities support compliance with local requirements in each country as well as reinforcing international ethical and good clinical practice standards.

All the information which is necessary for the ethical assessment of the research project should be given in written form to the Ethics Committee. [5] The Ethics Committee, in preparing its opinion should consider amongst others the points set out in art. 3, 4, 5 and 6 of the Directive 2001/20/EC, the Appendix to the additional protocol on biomedical research (COE- Information to be given to the Ethics Committee), and chapters 2 and 3 of ICH E 6 and WHO (CIOMS) guidelines 2. The Ethics Committees hould be satisfied that no undue influence, including that of a financial nature (or limiting or increasing access to medical care), will be exerted on persons, to participate in research. In this respect, particular attention must be given to vulnerable or dependent persons.[6] EU legislation gives particular attention to protection of paediatric subjects[7].

The Ethics Committee shall give clearly stated reasons for its positive or negative conclusions. [8]

The declaration of Helsinki states that "No change to the protocol may be made without consideration and approval by the ethics committee".[9] EU Directive 2001/20/EC specifies that this should apply to substantial amendments.[10] Research projects should be re-examined if this is justified in the light of scientific developments or events arising in the course of the research. [11]

"The ethics committee must have the right to monitor ongoing studies"[12] "and to report to institutional or governmental authorities any serious or continuing non-compliance with ethical standards as they are reflected in protocols that they have approved or in the conduct of the studies".[13]

If the clinical trial is planned to be conducted in a country with limited Regulatory Authority or Ethics Committees framework and limited oversight of the clinical trial, the sponsor should put in place alternative solutions in order to ensure an adequate review of the clinical trial protocol. A possible option could be to consider complementing the ethics Committees review in that country by submitting the study protocol for ethical and scientific review to an Ethics Committee (s) that operates within an established regulatory framework with ethical standards equivalent to those applying in the EU (based in an EU or non EU Country). This would be particularly relevant where the study design (e.g. choice of comparator) or the vulnerability of the proposed patient population might give rise to additional

4 Art. 6 (2) and Art. 9 (2) of Directive 2001/20/EC, Art.9 and 10 Additional Protocol on biomedical research (COE), Paragraph 15 of Declaration of Helsinki, WHO (CIOMS) guidelines 2.
5 Art. 11 of Additional Protocol on biomedical research (COE).
6 Art.12 of Additional Protocol on biomedical research (COE).
7 Paragraph 8.2 of EU Ethical Considerations for clinical trials on medicinal products conducted with the paediatric population
8 Art. 6 (5) of Directive 2001/20/EC; Art.9 Additional Protocol on biomedical research (COE) Explanatory report paragraph 42.
9 Paragraph 15 of Declaration of Helsinki
10 Art. 10 (a) of Directive 2001/20/EC
11 Art. 24 of Additional Protocol on biomedical research (COE)
12 Paragraph 15 of Declaration of Helsinki
13 WHO (CIOMS) guideline 2

concerns. In this case the deliberations and conclusions of that committee(s) should be made available to the local Ethics Committee and regulatory authority, making clear to what extent the committee has considered the location and circumstances in which the trial is to be conducted. Such an approach does not substitute for the need to apply to, and follow the requirements of, a local Ethics Committee or to submit to the regulatory authority of the country where the trial is to be conducted.

It is the responsibility of the sponsor to ensure that an appropriate EC reviews the clinical trial

A clinical trial should not take place in a country in the absence of a review by an Ethics Committees in that country. If such a committee does not exist it should be established as a pre-requisite before the trial take place.

The local Ethics Committee (s) and the regulatory authority (where applicable) in the country where the trial is to be conducted should review the trial, ensuring that the proposed research is ethical, takes into account the local conditions and requirements, that the local sites are suitable and that circumstances and arrangements for the conduct of the research are appropriate for that country and the study population concerned.

In multicentre studies, a central Ethics Committe could review the study from a scientific and ethical standpoint, and the local Ethics Committe could verify the practicability of the study in their communities, including the infrastructures, the state of training, and ethical considerations of local significance

It should be clear that any Ethics Committee reviewing the trial should be able to withhold approval of the research proposals. When there are objective grounds for considering that the conditions in the request for this authorisation are no longer met, or there is information raising doubts about the safety or scientific validity of the clinical trial, it should be possible to suspend or prohibit the trial notifying the sponsor thereof. [14]

There should be assurance that the review is independent and that there is no conflict of interest that might affect the judgment of members of the Ethics Committee in relation to any aspect of the research. A declaration of possible conflict of interest should be provided by any of the Ethics Committee members.[15]Any members with a special or particular, direct or indirect, interest in a proposal should not take part in its assessment if that interest could subvert the member's objective judgment. Ethics Committees have to be pluralist and representative of all stakeholders, multidisciplinary and independent.[16].Ethics Committee should be so composed as to be able to provide complete and adequate review of the research proposals submitted to them. Membership should include physicians, scientists and other professionals such as nurses, lawyers, ethicists, clergy as well as lay persons including patients' representatives, qualified to represent the cultural and moral values of the community and to ensure that the rights of the research subjects will be respected. When illiterate persons form the focus of a study they should also be considered for consultation in the Ethics Committee decision process. Ethics Committees should include appropriate expertise paediatric and/or mental health disorders or other vulnerable populations or take advice in clinical, ethical and psychosocial problems in these fields when reviewing protocols involving these populations. The Ethics Committee in the country where the trial is to be conducted should have, as either members or consultants, persons with understanding of the community's customs and traditions*." Such persons should be able, for example, to indicate suitable members of the community to serve as intermediaries between investigators and subjects and to advise on whether material benefits or inducements may be*

14 Art. 12 of Directive 2001/20/EC
15 WHO (CIOMS) Guideline 2.
16 Art.19 International Declaration on Bioethics (UNESCO); ICH E6 paragraphs 1.27 and 3

regarded as appropriate in the light of a community's gift-exchange and other customs and traditions".[17]

Expertise used should be documented and recorded by the Ethics Committee. Paediatric expertise requirements, as described in paragraph 8 of European Ethical considerations for clinical trials on medicinal products conducted with the paediatric population, should be complied with [18]

Regulatory action/ action plan

1. *Failure to submit a protocol to an independent* EC *is a serious violation of ethical standards. EU Regulatory Authorities should disregard data obtained in a such unethical manner, when submitted in support of a MAA in accordance with Directive 2001/83 EC or Regulation EC 726/2004.*
2. *Requirements for submission to the national regulatory authority of each country in which the trial is conducted and to the Ethics Committee (s) in those countries must be complied with, and evidence of both submissions and approvals provided. The applicant for a MAA should provide EU Regulatory Authorities with a summary of Ethics Committee, and National Regulatory Authority approvals of each clinical trial supporting the MAA. This information should form part of the clinical study report in accordance with ICH E3.*
3. *EU Regulatory Authorities should identify those studies that may give rise to special ethical concern (e.g. arising from their design, the local regulatory framework within which they are conducted, the vulnerability of the study subjects) and where applicable seek additional assurance that the trials have been ethically conducted.*
4. *Where clear serious concerns are identified the EU Regulatory Authorities should communicate these concerns to the National Regulatory Authority of the Country (ies) concerned.*
5. *The Sponsor ensuring that the clinical trial is reviewed by an appropriate EC should consider the opportunity to submit the clinical trial also to an Ethics Committee (either in an EU or non EU Country) that operates within an established regulatory framework with ethical standards equivalent to those applying in the EU. Evidence of the mechanisms put in place should be provided.*

4.2. Information/Consent procedure

Scientific research as well as any preventive, diagnostic or therapeutic medical intervention involving human subjects is only to be carried out with the prior, free, express, specific, documented and informed consent of the person concerned, based on adequate and comprehensible information [19] provided both in writing (or optionally pictorially for illiterate individuals) and orally. Furthermore, consent should, be given, and may be withdrawn, by the person concerned at any time and for any reason without disadvantage or prejudice. [20] *"Informed consent is documented by means of a written,*

17 WHO (CIOMS) Guideline 3.
18 Art. 4 of Directive 2001/20/EC and Paragraph 8 of EU Ethical Considerations for clinical trials on medicinal products conducted with the paediatric population
19 Art.2 (j), art. 3.2 (b) and art. 4-5 of Directive 2001/20/EC; Art. 5-6, 16 (iv) (v)-17 of Convention on Human Rights and Biomedicine of the Council of Europe (COE); Art. 13-16 of Additional protocol on Biomedical research (COE), 2005; Art. 5 and 9 of Universal declaration on Human genome and Human Rights; Art. 8-9 of International Declaration on Human Genetic Data (2003); Paragraphs 22,24,26,27,28 and 29 of Declaration of Helsinki (2008); Art. 3 (2) of Charter of Fundamental Rights of the European Union (2000); Art. 5 of Universal Declaration on Bioethics and Human Rights (UNESCO , 2005); Paragraph 1.28 and 2.9 of ICH E6
20 Art. 3.2 (e) of Directive 2001/20/EC; Art. 6 of Universal Declaration on Bioethics and Human Rights (Unesco,2005); Art. 14 Additional Protocol on Biomedical research (COE), 2005

signed and dated informed consent form".[21] The trial participant should be given a copy of his/her consent once it is signed. Refusal to give consent or withdrawal of consent to participation in research shall not lead to any form of liability (particularly of a financial nature) and/or to any form of discrimination against the person concerned, in particular regarding the right to medical care [22]. The same level of care and information should be maintained during treatment or investigations.

The informed consent of each subject shall be renewed if there are significant changes in the conditions or procedures of the research or if new information becomes available that could affect the willingness of subjects to continue to participate. [23]

In particular studies alternative ways of documenting the informed consent may need to be established as described below. For persons who are not capable of exercising autonomy, special measures are to be taken to protect their rights and interests. Research on a person without the capacity to consent (children, adults with severe mental disability, [24] or behavioural disorders[25] and research in emergency situations may be undertaken only if the necessary authorisation has been given specifically and in writing by the legal representative or an authority, person or body provided for by law and having received adequate information, taking into account the person's previously expressed wishes or objections.

An adult not able to consent shall as far as possible take part in the information/authorisation procedure.[26] In proportion to age and degree of maturity, the child should participate in the (informed) consent process together with the parents and provide assent. The process of informed consent should be conducted with enough time and at the same time as obtaining consent from the parent(s) or the legal representative, so that the informed consent reflects the presumed will of the minor or of the adults who do not have the capacity to consent. The information process provided to the child and the child's response should be documented. *"Strong and definitive objections from the child should be respected".* [27]

"If a subject is unable to read or if a legally acceptable representative is unable to read an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative"[28]. Mechanisms should be put in place to ensure that the trial subject is aware that they are participating in research.

21 Art. 2 (j) of Directive 2001/20/EC; Paragraph 1.28 of ICH E6, 1995
22 Art. 14 section 2 of the Additional Protocol on Biomedical Research to the Convention on Human Rights and Biomedicine and section 80 of its Explanatory report
23 WHO(CIOMS) Guideline 6
24 Art. 3.2 (d), 4 and 5 of Directive 2001/20/EC; Art. 6 of Convention on Human Rights and Biomedicine of the Council of Europe (COE)
25 WHO (CIOMS) International guidelines n. 15
26 Art. 4 (a), (b) and (c) and art. 5 (a), (b) and (c) of Directive 2001/20/EC; Art. 14 and 15 of Additional protocol on Biomedical research (COE), 2005
27 Paragraphs 7- 7.2 of Ethical considerations for clinical trials on medicinal products conducted with the pediatric population.
28 Paragraph 4.8.9 of ICH E6

"In appropriate cases of research carried out on a group of persons or a community, additional agreement of the legal representatives of the group or community concerned may be sought. In no case should a collective community agreement or the consent of a community leader or other authority substitute for an individual's informed consent"[29]. *"In some cultural contexts an investigator may enter a community to conduct or approach prospective subjects for their individual consent only after obtaining permission from a community leader, a council of elders, or another designated authority. Such customs must be respected. In no case, however, may the permission of a community leader or other authority substitute for individual informed consent"* [30]

The consent process and the information provided should take into account the needs of persons who are unfamiliar with medical concepts and technology[31]. All documentation (information and consent/assent) must be written in a lay-friendly language, using wording appropriate to age, psychological and intellectual maturity and must be designed to protect vulnerable and poorly educated subjects involved in research. Pictorial forms are also recommended for illiterate subjects.

Sponsors and investigators should develop culturally appropriate ways to communicate information that is necessary for adherence to the standard required in the informed consent process*. "Also, they should describe and justify in the research protocol the procedure they plan to use in communicating information to subjects"* [32] *"For collaborative research in developing countries the research project should, if necessary, include the provision of resources to ensure that informed consent can indeed be obtained legitimately within different linguistic and cultural settings"*[33]. Where appropriate, a cultural mediator, familiar with medical terminology, independent from the sponsor and investigator, experienced in the language, social habits, culture, traditions, religion and particular ethnic differences should be available to provide help in the process of obtaining informed consent, but should not consent on behalf of the subject. [34] Nevertheless, cultural diversity and pluralism are not to be invoked to infringe upon human dignity, human rights and fundamental freedoms or to limit their scope.[35]

"*Sponsors and investigators have a duty to refrain from unjustified deception, undue influence, or intimidations"*[36]*and "to renew the informed consent of each subject if there are significant changes in the conditions or procedures of the research or if new information becomes available that could affect the willingness of subjects to continue to participate"* [37]

Regulatory action/ action plan:

1. *Failure to obtain informed consent (and/or assent where applicable) is a serious violation of ethical standards. EU Regulatory Authorities should disregard data obtained in a such unethical manner, when submitted in support of a MAA in accordance with Directive 2001/83 EC or Regulation EC 726/2004.*
2. *The applicant for a MAA should provide EU drug regulatory authorities with a summary of the consent processes used and significant variations of those processes in the clinical trials supporting the MAA and include sample information sheets on consent forms. This information should form part of the clinical study report in accordance with ICH E3.*

29 Art. 6 of Universal Declaration on Bioethics and Human Rights (UNESCO, 2005)
30 WHO (CIOMS) Guideline 4
31 WHO (CIOMS) Guideline 4
32 WHO(CIOMS) Guideline 4
33 WHO (CIOMS) Guideline 4
34 Paragraph 6.3 of Ethical considerations for clinical trials on medicinal products conducted with the pediatric population
35 Art. 12 of Universal Declaration on Bioethics and Human Rights (UNESCO, 2005)
36 WHO (CIOMS) Guideline 6
37 WHO (CIOMS) Guideline 4 and 6

3. *EU Regulatory Authorities should identify those studies that may give rise to special ethical concern regarding the consent process (e.g. arising from the patient population included and their capacity to provide informed consent, the regulatory framework within which they are conducted, the vulnerability of the study subjects) and where applicable seek additional assurance that consent was properly obtained.*
4. *Additional good practice guidelines on the communication of the information to the potential participants in research may be required to better describe some research situations and should be developed, with input from patients' organisations and community groups as well as other experts in ethics and clinical trials.*

4.3. Confidentiality

Any information of a personal nature collected during a clinical trial shall be considered as confidential and treated according to the rules relating to the protection of individuals with regard to the processing of personal data[38]. Process refers to any operation or set of operations performed upon personal data, including collecting, using, accessing, making available, disclosing, transferring, retaining or destroying personal identifiable Information.

"To the greatest extent possible, such information should not be used or disclosed for purposes other than those for which it was collected or consented to, consistent with international law, in particular international human rights law".[39]

Any participant in research shall be entitled to know any information collected on his/her health. Such information or other personal information collected for a research project will be accessible to him/her in conformity with the applicable laws on the protection of individuals with regard to processing of personal data[40].

In accordance with European Directive 95/46/EC, data must be[41]: fairly and lawfully processed, processed in relation to the purposes for which they are collected, adequate, relevant and not excessive, accurate, not kept longer than necessary, processed in accordance with the data subject's rights, secure, not transferred to countries without adequate protection without the subject's consent.

"An investigator who proposes to perform genetic tests of known clinical or predictive value on biological samples that can be linked to an identifiable individual must obtain the informed consent of the individual or, when indicated, the permission of a legally authorised representative. Conversely, before performing a genetic test that is of known predictive value or gives reliable information about a known heritable condition, and individual consent or permission has not been obtained, investigators must see that biological samples are fully anonymized and unlinked; this ensures that no information about specific individuals can be derived from such research or passed back to them". [42]

If research gives rise to information of clinical significance to the current or future health or quality of life of research participants, this information shall be available if they want to receive it. That shall be done within a framework of health care or specific counselling[43],"*In communication of such information, due care must be taken in order to protect confidentiality and to respect any wish of a*

38 Art. 3.2(c) of Directive 2001/20/EC
39 Art. 9 of Universal Declaration on Bioethics and Human Rights (UNESCO, 2005); art. 14 International Declaration of Human Genetic Data; art 8 Charter of fundamental rights of the European Union
40 Art. 26 of Additional Protocol on Biomedical research (COE), 2005
41 Art. 6 of Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data
42 WHO (CIOMS) Guideline 18
43 Art 27 of additional Protocol on Biomedical research (COE), 2005

participant" [including the minor and/or his/her legal representative] *"not to receive such information*", in accordance with national law.[44]"*During the process of obtaining informed consent the investigator should inform the prospective subjects about the precautions that will be taken to protect confidentiality".*[45]

The written information and informed consent form to be provided to subjects should include explanations:

a) of the extent to which the monitor(s), the auditor(s), the Ethics Committe and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorising such access.

b) "*that records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject' identity will remain confidential"*.[46]

Biological sample retention, planned analysis and the need for consent to such use (and reuse) should be in accordance with what is described in the protocol. Samples cannot be used for purposes different of the ones described in the protocol without a new written informed consent

The trial documents should be archived for a duration that takes into consideration the potential need for long-term review, particularly for trials performed in children (long-term safety).

Where personal information is collected, stored, accessed, used, or disposed of, a researcher should ensure that the privacy, confidentiality and cultural sensitivities of the subject and/or the collectivity are respected, most of all when children are involved[47].

Regulatory action/ action plan:

1. *EU Regulatory Authorities should disregard reports which fail to properly protect the confidentiality of the trial subjects, when submitted in support of a MAA in accordance with Directive 2001/83 EC or Regulation No (EC) 726/2004. These reports should be returned to the applicant and the breaches of confidentiality rectified (including removal of confidential information from their database) prior to eventual resubmission.*
2. *EU Regulatory Authorities should identify those studies that may give rise to special concern regarding confidentiality (e.g. arising from the use of genetic information or bio banked samples) and where applicable seek additional assurance that confidentiality has been properly maintained. When requested, the applicant for a MAA should provide EU Regulatory Authorities with a summary of the steps taken to protect confidentiality and the consent obtained to enable the use of and access to the subjects' data.*

4.4. Fair compensation

Article 3.2 (f) of Directive 2001/20/EC requires that provision is made for insurance or indemnity.

44 Art. 10 of Convention on Human Rights and Biomedicine of the Council of Europe (COE); Art. 27 of Additional Protocol on Biomedical research (COE), 2005
45 WHO (CIOMS) Guideline 18
46 Paragraph 4.8.10 of ICH E6
47 Paragraph 18 of Ethical considerations for clinical trials on medicinal products conducted with pediatric population.

Art 31 of the Additional Protocol on Biomedical research of Council of Europe states that "*The person who has suffered damage as a result of participation in research shall be entitled to fair compensation* [48] *according to the conditions and procedures prescribed by law*"

The WHO-CIOMS Guideline 19 recommends that research subjects who suffer injury as a result of their participation should be entitled to free medical treatment for such injury and to such financial or other assistance as would compensate them equitably for any resultant impairment, disability or handicap. In the case of death as a result of their participation, their dependants are entitled to compensation.

"Subjects must not be asked to waive the right to compensation or required to show negligence or lack of a reasonable degree of skill on the part of the investigator in order to claim free medical treatment or compensation. The informed consent process or form should contain no words that would absolve an investigator [or sponsor] f*rom responsibility in the case of accidental injury, or that would imply that subjects would waive their right to seek compensation for impairment, disability or handicap. Prospective subjects should be informed that they will not need to take legal action to secure the free medical treatment or compensation for injury to which they may be entitled. They should also be told what medical service or organisation or individual will provide the medical treatment and what organisation will be responsible for providing compensation".* [49]

Before the research begins, the sponsor, whether a pharmaceutical company or other organisation or institution, should agree to provide compensation for any injury for which subjects are entitled to compensation, or come to an agreement with the investigator concerning the circumstances in which the investigator must rely on his or her own insurance coverage (for example, for negligence or failure of the investigator to follow the protocol, or where government insurance coverage is limited to negligence). In certain circumstances it may be advisable to follow both courses.

"Sponsors should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence". [50]

"Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects involved in research should include explanations of the compensation and/or treatment available to the subject in the event of trial-related injury".[51]

Information shall be provided to the EC and where required to the National Regulatory Authority, on details of any insurance, indemnity or compensation to cover damage arising in the context of the research project[52] (in particular "*provision for indemnity or compensation in the event of injury or death attributable to a clinical trial, and any insurance or indemnity to cover the liability of the investigator and sponsor"*). [53]

In preparing its opinion, the Ethics Committe (and where required the National Regulatory Authority) should consider these provisions[54] and should pay careful attention to waivers of liability in the insurance contract, in particular with respect generally to long term effects and on development for children included in research. However, *"unrecognised congenital defects are generally excluded".* [55]

Regulatory action/action plan

48 Art. 31 of Additional Protocol on Biomedical research (COE) 2005
49 WHO (CIOMS) Guideline 19
50 Paragraph 5.8 of ICH-E6
51 Paragraph 4.8.10 of ICH-E6
52 Art 11 juncto appendix of Additional Protocol on Biomedical research (COE) 2005; Paragraph 3.1.2 of ICH-E6.
53 Art. 6.3 (h) and (i) of Directive 2001/20/EC
54 Art. 6.3 of Directive 2001/20/EC
55 Paragraph 22 of Ethical considerations for clinical trials on medicinal products conducted with paediatric population.

1. *Failure to provide fair compensation by insurance or indemnity is a serious violation of ethical standards. The applicant for a MAA should provide EU Competent Authorities with a summary of the provisions made to provide for the fair compensation of subjects for trial related injury. This information can form part of the clinical study report section on ethical considerations and informed consent.*
2. *EMA and EU Regulatory Authorities should identify those studies that may give rise to special concern regarding insurance, indemnity or compensation for research related injury and where applicable to seek additional assurance that trial subjects' interest have been protected*.

4.5. Vulnerable populations

In the context of this paper, one of the main concerns is the vulnerability of person due to poverty, lack of adequate health care systems or lack of access to medicines,

The definition of vulnerability is based on existing ethical guidelines. Nevertheless vulnerability has to be considered in terms of a condition, or situation affecting persons and making people vulnerable in particular situation rather than considering a specific population as vulnerable (people that are part of a specific population considered vulnerable may or may not be vulnerable).

The key concern is to avoid that vulnerable persons or group are exploited for the benefit of EU patients. At the same time the benefit to the patient of taking part in the study and the ethics of potentially turning them away simply because they fit one of the vulnerable categories needs to be considered. Special care should be paid to the benefit/risk balance and to minimizing risk and burden when clinical trials are conducted in vulnerable populations[56] rThe health needs of the Country should be reflected.

"Vulnerability" is defined as susceptibility of being wounded. Vulnerability is applied both to individuals and to populations. "*Vulnerable persons are those who are relatively (or absolutely) incapable of protecting their own interests*",[57] that means "*individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate*"[58] "*More formally, vulnerable persons may have insufficient power, intelligence, education, resources, strength, or other needed attributes to protect their own interests*" [59]

Example of vulnerable subjects are patients with incurable diseases, or that have serious, potentially disabling or life-threatening diseases, [60] persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, homeless persons, nomads, refugees, prisoners, members of a group with a hierarchical structure, members of the armed forces [61],minors and those incapable of giving consent. Other groups or classes may also be considered vulnerable (e.g. elderly persons, people receiving welfare benefits or social assistance some ethnic and racial minority groups and individuals who are politically powerless) This list is not exhaustive and many other categories not mentioned in this text but that fall in the definition of vulnerable population could be included.

Children

"Children represent a vulnerable population with developmental, physiological and psychological differences from adults, which make age- and development- related research important for their

56 Art 15, 18 and 20 of the Additional Protocol on Biomedical Research of the Council of Europe
57 WHO (CIOMS) Guideline 13
58 Paragraph 1.61 of ICH-E6,
59 WHO (CIOMS) Guideline 13
60 WHO (CIOMS) Guideline 13
61 Paragraph 1.61 of ICH-E6,

benefit".[62] Clinical research on children should be carried out under conditions affording the best possible protection for these subjects, without subjecting paediatric population to unnecessary trials.[63]

Women

Women are not per se a vulnerable group. However, in some societies women are not accorded full rights, either in law or in practice. Therefore, in some cases women may be regarded as being in a position of vulnerability in the sense that they may have a limited capacity to protect their own interests.

In locations where the social, political or economic position of women could be deemed as questionable (whether in law or in practice), this should be considered in the trial protocol and, where appropriate, special provisions for the protection of their rights and welfare should be applied, for example concerning informed consent.

Restrictions in research on vulnerable subjects

Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted, or the conditions they suffer from (e.g. renal insufficiency). "*Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition*".[64]

"*Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research"*.[65]

Research should be undertaken in vulnerable population only when particular conditions are met e.g. whether the results of the research have the potential to produce real and direct benefit to the trial subject, whether research of comparable effectiveness cannot be carried out on individuals capable of giving consent or for example on women who are not pregnant, or on persons who are not deprived of liberty, whether the person undergoing research has been informed of his or her rights and the safeguards prescribed by law for his or her protection, unless this person is not in a state to receive the information, whether the necessary authorisation has been given specifically and in writing by the legal representative, and the person (or pregnant woman) concerned does not object.

Exceptionally and under the protective conditions prescribed by law, where the research may not have the potential to produce results of direct benefit to the health of the person concerned, such research may be authorised, if it can contribute to the benefit of the group concerned whilst fulfilling the other conditions described above. *"Measures of such benefit would include the importance of knowledge gained, severity of the issue to be addressed, commonality of the issue, likelihood of obtaining results from proposed research, and usefulness of benefits obtained"*.[66]

The need for special protection of the vulnerable population rights and welfare should be reviewed and applied, where relevant. Vulnerable subjects should not be recruited into a trial where this was not explicitly foreseen in the trial protocol or other information provided to and approved by the Ethics

62 Recital 3 of Directive 2001/20/EC
63 Recital 4 and art. 1 of Regulation EC/1901/2006 and art. 4 of Directive 2001/20/EC.
64 Belmont Report: ethical principles and guidelines for the protection of human subjects of research, Section D 3.
65 Art. 17 of Declaration of Helsinki (2008).
66 Paragraph 12 of Ethical considerations for clinical trials on medicinal products conducted with paediatric population

Committe. Any special consent procedures or other precautions required should have been explicitly described to the Ethics Committe and approved by them.

The decision to include vulnerable subjects in a trial should be fully justified by the sponsor. "*Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research*"[67].

Regulatory action/action plan:

1. *The inclusion of vulnerable subjects in a clinical trial without the approval of the Ethics Committe and without implementation of the appropriate consent processes is a serious violation of ethical standards.*

   EU Regulatory Authorities should disregard data obtained in such an unethical manner, when submitted in support of a MAA in accordance with Directive 2001/83 EC and Regulation No (EC) 726/2004.

2. *The applicant for a MAA should provide drug regulatory authorities with an adequate and appropriate justification for inviting vulnerable individuals or groups to serve as research subjects and the description of the specific measures and means implemented to protect their rights and welfare, should be included in the protocol and in the clinical study report (in accordance to ICH E3) and should made public in the Public Assessment Report*

3. *EU Regulatory Authorities should identify those studies that may give rise to special ethical concern regarding the inclusion of vulnerable populations and where applicable to seek additional assurance that the inclusion of such populations was justified and their rights and welfare protected.*

4.6. Placebo and active comparator

The capacity of a trial to produce reliable results is a pre-requisite for the ethical justification of that trial. "Research shall neither delay nor deprive trial participants of medically necessary preventive, diagnostic or therapeutic procedures".[68] A clinical trial cannot be justified ethically unless it is capable of producing scientifically reliable results. "In some circumstances it may be acceptable to use an alternative comparator, such as placebo or "no treatment",[69] whilst taking into account that "the rights, safety and wellbeing of the trials subjects are the most important considerations and should prevail over the interests of science and society".[70]

The rationale for the use of placebo in a number of therapeutic areas is not always widely understood. Where such designs are deemed necessary and ethical, failure to follow them can have negative consequences. Either it will lead to such products not being authorised in the absence of adequate evidence of efficacy or if they were to be authorised with a suboptimal trial design this could give rise to the approval of less effective or ultimately ineffective (placebo equivalent) medicines. EU regulators will ensure that the rationale for the use of study designs involving placebo or other comparators is clearly set out and communicated, in order to ensure that such trials could be conducted in the EU.

67 Para.17 of the Declaration of Helsinki (2008) and WHO (CIOMS) Guidance n. 10.
68 Article 23 of Additional protocol on biomedical research (COE), 2005
69 WHO (CIOMS) Guideline 11
70 Paragraph 2.3 of ICH-E6

The use of placebo is permissible in accordance with principles foreseen in the Directive 2001/20/EC, Directive 2005/28/EC, the WHO (CIOMS) Guidelines 8 and 11, paragraph 32 of the Declaration of Helsinki (2008), article 23 of the Additional Protocol on Biomedical Research of the Council of Europe(2005), paragraph 2.1; 2.2; 2.3 and 2.12 of the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95), paragraphs 9.2.1 and 9.2.3 of the guideline on ethical considerations for clinical trials on medicinal products conducted with the paediatric population (2008) and ICH E10 (Choice of Control Group). The CPMP position statement on the use of placebo in clinical trials (28 June 2001 EMEA/17424/01) should also be taken into account.[71]

Studies carried out in countries outside EU/EEA should meet the same ethical principles and standards applied to studies performed in the EEA. Derogation from these principles should not be accepted in particular in the context of the European marketing authorisation procedure.

EU Regulatory Authorities should neither require nor accept study designs, involving placebo or other comparator, which would not be ethically acceptable in the EEA.

"Economic [or logistical] reason for the unavailability of an established effective intervention cannot justify a placebo-controlled study in a country of limited resources when it would be unethical to conduct a study with the same design in a population with general access to the effective intervention outside the study". [72]

Lack of access of patients in communities within, or outside of, the EEA, to the EEA-licensed (or equivalent) comparator cannot be a justification to withhold this treatment option to those patients when participating in a trial regardless of the reasons for the lack of access (e.g. no reimbursement, no national marketing authorisation). Regardless of the location of the trial, all patients participating in these trials should receive the same or a similar standard of care and comparable treatment options as trial participants within the EEA.

EU Regulatory Authorities should verify that the study has been reviewed by the Ethics Committees and that they have determined: whether the use of placebo or other comparator is ethically acceptable in the context of that trial; whether the safety and rights of the subjects have been fully protected and whether prospective subjects would be fully informed about the use of placebo and/or other comparators and available alternative treatments and gave their informed consent (or informed refusal), in accordance with above cited ethical principles. [73]

Regulatory action/action plan:

1. *Sponsors should describe in detail in the protocol and in the clinical study report the justification for the use of placebo and/or choice of active comparator in accordance with the ethical principles referred to above. This information can form part of the clinical study report in accordance with ICH3 and protocol in accordance with ICH E6.*
2. *EU Regulatory Authorities will identify those studies that may give rise to special ethical concern regarding the use of placebo or other comparators and where applicable seek additional assurance that the design was appropriate and ethically acceptable.*
3. *Where it is determined that a study design was not acceptable in accordance with the aforementioned criteria, it should not be accepted in support of a MAA in accordance with Directive 2001/83 EC and Regulation No (EC) 726/2004.*

71 https://www.ema.europa.eu/en/documents/position/emea-position-statement-use-placebo-clinical-trials-regard-revised-declaration-helsinki_en.pdf
72 WHO (CIOMS) Guideline 11
73 WHO (CIOMS) Guideline 11

4. If a sponsor has particular concern about a particular trial design, it is strongly advised to seek scientific advice with Regulators on study design before carrying out the trials

4.7. Access to treatment post trial

Patients' access to innovative medicinal products varies widely. Differences in patients' access mostly reflect differences in the economic situation and social and health care systems of the country or region both inside the EEA and countries outside EU/EEA.

Whether the medicinal product is likely to be available in the community or country where the research study is conducted should be considered by the sponsor, Ethics Committees and National Regulatory Authorities. New medicinal products should be intended for marketing in the countries or regions where the clinical trials are conducted. For the individual patient who participated in a clinical trial continued access to the product that has been identified as beneficial is crucial. It is recognized; however, that post trial access of patients to treatment or medical care provided by sponsor or investigator cannot substitute for shortcomings of national or regional health care systems.

Paragraph 14 of the Declaration of Helsinki requires that the protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits [74]

WHO demands that before consenting, subjects must be "*informed, whether, when and how any products or interventions proven by the research to be safe and effective will be made available to them after they have completed their participation in the research and whether they will be expected to pay for them"*.[75]

Paragraph 33 of the Declaration of Helsinki requires: *"At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits"*.[76]

For the time between end of the trial and the availability of the licensed product on the market, the continuation of treatment by the sponsor needs to be considered, e.g. in the context of compassionate use. The cessation of a beneficial possibly life-saving or -prolonging treatment at or after marketing of the product due to economic reasons, e.g. low personal income of the patients and/or no reimbursement is problematic. Ethical Committees, national regulatory authorities and patients participating in a clinical trial need to be fully informed prior to any decision on their part whether and under what conditions study participants will have access to a treatment that has been shown to be safe and effective for them during the trial taking into account the specific situation in their country or region.

Depending on national or regional healthcare systems, participation in a trial may also offer access to significantly better medical care than would otherwise be available. The cessation of the standard of care available during the trial, once a trial is over, has been widely criticized. Ethics committees, national regulatory authorities and patients participating in a clinical trial need to be fully informed prior to any decision on what post trial medical care or other relevant benefits will be provided by the investigator or sponsor.[77]

74 Para.33 of Declaration of Helsinki (2008)
75 WHO (CIOMS) Guideline 5
76 Para.33 of Declaration of Helsinki (2008)
77 WHO (CIOMS) Guideline 21

Transparency on matters of post trial access to treatment and medical care is paramount for clinical trials submitted to EMA in support of European MAA. The Applicant should describe the situation of trial participants with regard to post trial access to treatment and medical care with respect to the local situation where the trial is conducted. The Applicant should describe what provisions were made for post trial access to treatment and medical care and what information was given to the patients prior to their consent. This information will be summarised in the European Public Assessment Report (EPAR).

Regulatory action/action plan:

1. *The applicant for a MAA should provide EU Regulatory Authorities with a description of the situation of trial participants with regard to post trial access to treatment and medical care depending on their localization and the national or regional health care system. The applicant should describe the provisions made for post trial access to treatment and medical care for study participants depending on their localization and the treatment and medical care otherwise available. This information can form part of the clinical study report section on ethical considerations in accordance with ICH E3.*
2. *EU Regulatory Authorities should identify those studies that may give rise to special ethical concern regarding access to treatment post trial and where applicable to seek additional assurance that the solution was appropriate and ethically acceptable.*
3. *EU Regulatory Authorities will summarize this information in the Public Assessment report.*

4.8. Applicability of data to EEA population

There are several issues relating to the applicability of trials conducted outside EU/EEA to European populations. These involve factors both intrinsic and extrinsic to the study population and EEA population. [78]

These are discussed in the "Reflection Paper on the extrapolation of results from clinical studies conducted outside the EU to the EU population" [xxi79] (Doc. Ref. EMEA/CHMP/EWP/692702/2008) and the ICH 1998 E5(R1) Ethnic Factors in the Acceptability of Foreign Clinical Data (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E5_R1/Step4/E5_R1__Guideline.pdf). [80xxii]

5. Determine the practical steps to be undertaken during the provision of guidance and advice in the drug development phase

The EMA has a role in stimulating innovation and research in the pharmaceutical sector. The Agency gives scientific advice and protocol assistance to companies for the development of new medicinal products and draws up scientific guidelines aimed at helping applicants in the development of medicinal products. The tasks and responsibilities of the Agency under the Paediatric Regulation include the provision of objective scientific decisions on the development plan for medicines for use in children.

78 ICH 1998 E5 (R1) Ethnic Factors in the Acceptability of Foreign Clinical Data
79 Reflection paper on the extrapolation of results from clinical studies conducted outside the EU to the EU population EMEA/CHMP/EWP/692702/2008
80 ICH 1998 E5(R1) Ethnic Factors in the Acceptability of Foreign Clinical Data

European pharmaceutical legislation (and that in other regions of the world also) requires clinical trials to be performed prior to the granting of a marketing authorisation. The analytical, pharmaco-toxicological and clinical requirements in respect of testing of medicinal products are set out in the Annex 1 of Directive 2001/83/EC. Additional requirements and incentives apply to encourage the conduct of clinical trials for the development of medicines for the treatment of children and for the treatment of patients with rare diseases. These requirements may increase the number and scope of clinical trials being conducted, not all of which can or need to be carried out in Europe. Clinical trials conducted in the EEA should comply with applicable laws and regulations. In addition, applicants intending to submit in the EEA are advised to consult with EEA regulators about the design and ethical conduct of clinical trials prior to their commencement when it is planned to conduct those trials in countries outside EU/EEA. EEA regulators should ensure that every opportunity is taken prior to the commencement of clinical trials to influence their design and ensure their ethical conduct.

Several operational or technical considerations lead to the conduct of clinical trials in a widening range of countries:

- Availability of patients willing to participate in clinical trials, and with the relevant disease profile,
- Availability of qualified investigators willing and available to conduct the trials,
- Preparation for MAA, in those other countries,
- Lower costs in some countries,
- More rapid approval of trials,
- Willingness of patients to participate in trials due to the trial facilitating access to higher standard of care and / or medication(s) not otherwise available to them,
- Small number of relevant patients existing in Europe,
- Availability of patients who are naïve to treatment,
- Difficulty in recruiting patients due to differences in standard of care across developed countries.

These issues or other circumstances influencing the location of clinical trials outside the EEA should be clearly identified. The applicant should provide the rationale for the location of such clinical trials and detail its plan for addressing ethical and operational issues related to its proposed development plan.

Agency working groups should take into consideration the circumstances driving the location of trials when considering requests for advice, establishing requirements for the conduct of trials or developing guidelines and should:

- highlight these circumstances and their related risks
- try to minimise the risk by recommending some corrective actions or other alternatives for the drug development plan or clinical trials proposals
- make the applicant aware of those potential issues before the trial is conducted whenever possible, or before the MA application
- clearly identify the potential impact on the ethical aspects of trials and the quality of clinical data to be generated.

5.1. Assessment of therapeutic needs in the EEA and relationships with its drug development plan

When addressing the targeted indication(s) and its applicability to the European population, both the applicant and EMA parties/ committees should specifically consider the following issues that could influence the decision to conduct trials outside the EU:

- Condition(s) less frequent in the EU/EEA than in other non-EEA countries
- Small number of affected subjects worldwide due to the rarity of the condition (e.g. rare diseases)
- Applicability of the targeted drug claim in the European population when the disease is predominant mainly outside Europe (e.g. tropical diseases)
- Different therapeutic needs in the European population
- Clinical data to be generated may be of little relevance to the European population (e.g. notable difference in disease management).

When applicable according to the procedure applied for, the applicant should consider the relevance of its clinical program, in relation to:

- Applicability of the proposed indication and the therapeutic needs of the European population
- Prevalence of the condition in non-EEA countries and in EEA countries.

The consequences of drug development with clinical trials conducted outside the EEA (completely or partially) should be considered with regards to:

- Limitations of data extrapolation from non-EU patients to the EEA
- Impact of the geographic source of patients on the efficacy and safety results and their extrapolation the European population in the context of disease management (e.g. national characteristics of disease management and patient care)
- Validity of the selected comparators (active or placebo) for enabling assessment of the Risk/Benefit balance of the product for the European population
- Pre-specified subgroup analyses based on ethnicity and/or regions of the world
- Evaluation of the level of adherence to standard background treatment regimes for a specific disease
- Take into consideration possible differences in genetic profiles which could influence the drug response.

Where a scientific advice, guidance or assessment relates to an application for a scientific opinion in the context of article 58 of Regulation No (EC) 726/2004 the considerations should relate to the population for which the medicinal product is to be used, rather than the EU population.

5.2. Issues related to feasibility of clinical trials

The applicant should provide any available information on its development plan:

- Details on the planned locations of the trials planned in the EEA and outside
- Criteria for the selection of the non-EEA countries

As such information may be limited or unavailable in the early phases of drug development, the applicant could provide a commitment to comply with general regulatory/GCP and ethical principles. Applicants are encouraged to seek follow-up advice when the drug development plan become clearer and clinical trials outside of the EU/EEA are foreseen

A feasibility assessment for recruiting the targeted number of patients in a clinical trial should be provided in order to allow consideration of the possible consequences on the future MAA and results interpretation. This feasibility assessment should include as a minimum:

- Recruitment plan for patients in the EEA and outside
- Selection criteria and numbers of centres per country or regions outside the EEA
- Duration of trial recruitment and expected impact of comparability of results over time in case of very long recruitment (e.g. duration of recruitment longer than 3 years for rare disease).

5.3. General measures to assure data quality when conducting trials outside the EU

Issues that may have an impact on the quality of data to be generated should be clearly identified and resolved when possible:

- Duration of the study
- Complexity of the trial design, e.g.: requirement for blinding / shipments of samples (e.g. tissues)/ specific or high level of technology platforms required (e.g. MRI)/ frequency of biological/radiological monitoring/capability for storing clinical trials materials
- Restricted access to specific tests and laboratory with possible impact on final data quality (e.g. testing of HIV resistance)
- Access to active comparators/ placebo/ age-appropriate formulation at the national level or when provided by the applicant
- Differences in Patients-Reported Outcomes
- Limitations for long term follow up of patients after treatment (active comparator and study drug) discontinuation
- Anticipated quality of data monitoring and training of investigators

Specific measures to be taken into consideration in order to assure the quality of results should include:

- Identification of limitations in extrapolating data from non-EU patients to the EEA populations, such as different ethnicities, underlying specific conditions
- Different local epidemiology of infectious pathogens and / or disease pathology
- Appropriateness of study design in accordance with the European guidelines and the most up to date scientific recommendations and ethical requirements
- Choice of claim for superiority versus non inferiority in relation to a proper identification of therapeutic needs and respective recruitment capacity in the EEA and outside
- Identification of standards of care for the targeted disease among countries

- Drug and study acceptability by the patients in the targeted countries and by the national ECs
- Research responsive to the health needs and priorities of the population or community in which it is carried out.

5.4. Considerations for designing clinical trials:

The applicant should pay particular attention when designing trials outside the EEA in order to avoid generating data not relevant for the intended purpose:

- Study design:
  - Risk of futility when efficacy assessment based on an inaccurate statistical hypothesis (e.g. inappropriate claim of superiority due to an underestimation of disease outcome in the countries outside the EEA)
  - Choice and access to active comparators and availability of other therapeutics required for best disease management in the selected countries
  - Level of overall standard of care in the targeted countries
  - Stopping rules in case of lack of efficacy or safety issue
  - Existence and responsibilities of the independent Data and Safety Monitoring Board and/ or Data Monitoring Board
  - Availability of a local accredited laboratory in the Country where the study is performed to provide testing of samples.
- Analysis of factors potentially impacting on the ability to extrapolate the clinical trial results to the EU population, such as:
  - Sources of data variability

    disease outcome and management

    parameters impacting the drug effect variability

    standards of patients management care

    specific measures for assessment of treatment adherence in some specific cases
  - Validation of outcome measure, to be used in the non-EEA population (e.g. Quality Of Life scoring)
  - Implementation and interpretation of biomarkers and surrogate end-points

Regulatory action/action plan:

1. *Clinical trials are conducted not only for submission to the EEA but also to many other regulators worldwide. In order to minimise risk of non-approvability of the application due to the choice of study populations not applicable to the EU/ EEA population or trial designs not acceptable in the EEA sponsors should seek EU scientific advice prior to the conduct of those trials.*
2. *EMA Committees and working Parties evaluating requests for Scientific Advice, Orphan designation, and Paediatric Investigation Plans and National Regulatory Authorities when applicable should systematically consider the issues raised in this reflection paper and apply the proposals during their assessments and recommendations/opinions provided to the applicants.*

3. *Applicants should clearly explain why data from the patient populations selected are applicable to the EEA population unless the product is intended to be used outside the EEA.*

6. Determine the practical steps to be undertaken during the marketing authorisation phase

Submission, validation, assessment and inspection of the clinical trials contained in the Marketing Authorisation Application

Recital 16 of Regulation (EC) No 726/2004 states that, with respect to clinical trials conducted outside the Community on medicinal products destined to be authorised within the Community, at the time of the evaluation of the application for authorisation, it should be verified that these trials were conducted in accordance with the principles of good clinical practice and the ethical requirements equivalent to the provisions of the said Directive.

Article 6(1) of the same regulation requires that "*the application include a statement to the effect that clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC.*"

Article 56 (4) of the same regulation foresees that "*the Committee for Medicinal Products for Human Use may, if they consider it appropriate, seek guidance on important questions of a general scientific or ethical nature.*"

As a consequence, the Marketing Authorisation evaluation should ensure that these GCP principles have been applied to all clinical trials submitted in the dossier, and, that ethical guidance is sought if required.

Furthermore, an application for Marketing Authorisation for medicinal products for any population shall be regarded as valid only if requirements of the Article 7 of the European Paediatric Regulation are met.

6.1. Points to consider during the assessment process: identify assessment issues and processes

Background

Three scenarios are considered:

- The first relates to acceptability of foreign data for the EU, from a scientific viewpoint. This is already adequately covered elsewhere (see section 4.8).
- The second relates to concern over the conduct of the study, and data reliability – this should trigger requests for clarification from the applicant, and also discussion with inspectors as to whether a GCP inspection may be appropriate or required (see 6.2).
- The third relates to concern over the design of studies in relation to acceptability in Europe. Such concerns may relate to the use of placebo or duration of use of placebo, poorly optimised background therapy, use of inappropriate comparator, inappropriate investigations, lack of consent etc.. This aspect is addressed below.

Review procedures

- At the time of the application, information should be provided on where each clinical trial was performed and on how relevant ethical requirements were met.
- As part of the review of the MAA, assessors should consider whether or not there are major ethical concerns relating to the studies that have been included in the dossier to support the MAA. Assessors should confirm in the Assessment Report that they have not identified any major ethical issues in their assessment of the studies, that the studies have been approved by the relevant Ethics Committe and by the National Regulatory Authority, that the sponsor has provided the statement that the studies have been conducted as set out in Annex 1 of Directive 2001/83, and that they have not identified any major concerns regarding the conduct of the study. Particular attention should be paid where vulnerable patients are included within the trial population, and/or trials are conducted in low to middle income countries, and/or where no EEA Ethics Committee has reviewed and approved the study/studies for trials performed outside the EU.
- In considering the design of studies, assessors should consider international guidelines for biomedical research involving human subjects where it is recommended that research is responsive to the health needs and priorities of the population or community in which it is carried out and any intervention or product developed or knowledge generated will be made reasonably available for the benefit of that population or community. Applicants are encouraged to provide such information, in so far as it is possible. Whilst it will not always be possible for assessors to conclude definitively, questions or concerns in relation to this area may be included in the List of Questions to the applicant

The EU assessment report should reflect:

1. That it has been determined that all clinical trials were conducted in accordance with the principles of good clinical practice and the above mentioned ethical requirements ,
2. Any ethical concerns that have been raised,
3. How these ethical concerns have been addressed and whether they had an impact on the assessment of the quality, safety and efficacy of the product,
4. Whether the CHMP has sought additional ethical advice, if felt necessary
5. A summary of the reasons for and outcome of any GCP inspections requested (these may be routine or triggered) summarised,
6. Discussion of applicability of data to the EU/EEA population

Actions to take if there are concerns over the ethics of studies

1. Where the assessor is concerned that a study may not have been conducted ethically, the assessors should first seek further clarification from the applicant who should be given the opportunity to justify their position.
2. The CHMP should develop appropriate links with experts in ethics in relation to clinical trials who could advise on such issues, as appropriate. It is proposed that CHMP should establish a pool of experts to advise, when requested, on the ethical aspects of clinical trials. A structure similar to a SAG might be envisaged. It is essential that if actions were to follow CHMP's assessment of a study as 'not conducted in accordance to the appropriate ethical requirements', the assessment and any conclusions should be robust.

Consequences of a study being considered unethical

1. If, (after taking appropriate advice), the CHMP concludes that a study has not been carried out in accordance with the appropriate ethical requirements, the CHMP must conclude upon additional steps. No single solution will be applicable to all situations, as issues are likely to be complex.
2. Therefore the European Medicines Agency /CHMP must have a number of possible tools at its disposal. These may include the following:
    2.1. Assessment of the application excluding data from the studies or part of the studies deemed unethical. Additional analyses may be required. This could result in an application that is not approvable.
    2.2. Publishing the circumstances and details of studies which were found not to have been conducted in accordance with ethical requirements.
    2.3. A graded system of potential actions. Such a system should be developed (see 6.3).
3. Regulatory authorities should have some degree of discretion over how, when and if to take action, taking into account the circumstances of the trial, and the nature and severity of the issues that have been identified, as well as the medical need for the product.

Regulatory action/action plan

1. *The European Medicines Agency should establish a pool of experts to advise the CHMP in its assessment of the ethical aspects of clinical trials submitted within the MAA, and define their membership, required expertise, mandate and procedures, and the process by which the CHMP, EMA or other Agencies' scientific committee, may consult them. Such consultation would only be required where ethical concerns had been identified and could be on general matters of principle involved in establishing requirements and guidance, or specific cases involving particular trials and products.*
2. *EU Regulatory Authorities should develop a system and adequate guidance for review of MAA dossiers, to facilitate identification of studies of potential ethical or GCP concern(s). This review should cover both the time of validation of the Marketing Authorisation Applications and the assessment. Appropriate training in application of this system will be provided.*

6.2. Inspections: Triggers for inspection to be identified by assessor

GCP inspection is an important tool for monitoring compliance with requirements. A programme of routine inspections is required to ensure that information is available to the regulator on a regular basis and in the absence of any particular concern triggering a specific inspection to investigate the issues giving rise to concern.

Inspection triggers:

During the review of an application for a marketing authorisation, concerns can be raised by CHMP related to the compliance of the study conduct with current local and international legal and regulatory provisions, and to the reliability of the data submitted.

Several criteria may act as triggers for a GCP inspection; most of these criteria are study-related aspects while others relate to the fact that the study was conducted in countries outside the EU.

Study-related triggers for an inspection are in general focused around four main issues:

1. Existence and characteristics of trial subjects, distribution of subjects.

2. Quality and administration of investigational medicinal products.
3. Efficacy and safety evaluation criteria and data.
    3.1. Data with abnormal variation or distribution
    3.2. Unexpectedly low levels of (S)AE reporting compared to other sites or sources.
4. Ethical and regulatory aspects of study and trial team.

If a study has been conducted in country(ies) outside EU/EEA, additional triggers may be identified during the review process. Some of these triggers may be:

1. Design of the study raises ethical concerns. Whilst these specific points relate to trial design, which is apparent from the review process without inspection, they may sometimes raise a more general concern about the conduct of the trial.
2. Conduct of the study raises ethical concerns
3. Lack of familiarity or concerns with/unawareness of the local legislative regulatory or ethical framework on the part of EU Regulators
4. The study was conducted mainly/solely outside EEA
5. Concern about the stability of IMP in a non-temperate climate

In case of concerns identified during the review of an application for Marketing Authorisation, questions should be addressed to the sponsor. The concern will also be discussed between assessors and inspectors, and an inspection may be initiated whenever required. Inspections may also be requested as part of a programme of routine inspections.

Regulatory action/action plan

1. *The criteria used as the basis for both routine and triggered GCP inspections and the process for identifying triggers for GCP inspections should be further developed and systematised.*
2. *Frameworks for contact with National Regulatory Authorities, to gain/share information on the GCP compliance and local inspection, in the countries where clinical trials take place as well to conduct joint inspection should be developed.*

6.3. Actions available in response to non compliance

This reflection paper seeks to reinforce the regulatory framework for the conduct of ethical, scientifically valid clinical trials, and the protection of trial subjects. Ideally such measures would ensure that significant non-compliance would not occur. The processes available to address situations where requirements have not been followed, should strive to further refine and reinforce the framework for the conduct of trials and the understanding of requirements by all involved. The range of actions available should also include activities that involve communication, education and refinement as the preferred course. In some circumstances this will not be possible, or appropriate, not least because by the time of the MAA, the clinical trials in question are generally completed and little can be done to remedy deficiencies in the conduct of those particular trials.

Trial subjects and their communities also need to be assured that their rights and welfare will be supported and reinforced by regulators, both locally, and internationally as the entire process of development of medicines relies on the willingness of individuals to participate in clinical trials.

Particular emphasis should be given to trials conducted in countries outside EU/EEA. The role and authority of the Ethics Committees and National Regulatory Authorities in the countries where the trials are conducted should be supported. When non compliance with GCP regulatory obligations and ethical concerns are detected, action should include communication with the National Regulatory Authority concerned. This action should be proportionate to the consequences of the observed violation on the rights and welfare of the trial subjects and of the deficiencies on the data integrity.

There is the need to define and to make public the consequences of non compliance with GCP and above mentioned ethical concerns in designing, conducting, recording and reporting of the clinical trials included in the MAA.

Non compliance which significantly affects the rights, safety or well being of the subjects or the quality and integrity of the data reported is not acceptable, and will result in rejection of data and/or other regulatory actions.

Regulatory options should include the following:

Information and possible action by regulators of countries outside EU/EEA

Information on non-compliance should be made available to the Regulatory Authority in the country in which the trial non-compliance has been identified and to other regulators in the international network, (subject to appropriate confidentiality arrangements if applicable).

Request for additional information or action by the sponsor

The sponsor may be asked to supply additional information or explanation, conduct further analyses or data collection/review, or to commission further monitoring or independent audits of a wider range of sites.

Inspection or re-inspection

(Further) sites involved in the same trial/and or further trials and/or sponsor site/Marketing Authorisation Holders may be inspected to determine the extent of non-compliance.

Rejection of data/exclusion of trial/negative opinion

Data obtained from clinical site(s) or from a trial found to be seriously non compliant with GCP and/or ethical requirements should be excluded from use in support of the MAA.

Education and Facilitation

Applicants and/or Marketing Authorisation Holders may be informed of non-compliance and advised on how this can be remedied for future trials, and in some cases action may be possible for the trial in question.

Warning

The EMA may issue a formal warning reminding Applicants and/or Marketing Authorisation Holders of their GCP obligations relating to the conduct of clinical trials in accordance with above mentioned ethical and GCP requirements

Transparency regarding clinical trial conduct and compliance including non-compliant Marketing Authorisations

The EPAR should describe any serious non-compliance encountered and discuss the steps taken as a consequence. This should be done whether the CHMP opinion is positive or negative or the application is withdrawn prior to the opinion.

Suspension of the Marketing Authorisation/Urgent Safety restriction /Revocation of the Marketing Authorisation

Suspension/Urgent safety restriction/revocation of the Marketing Authorisation are considered where the non-compliance is identified after the MA has been granted in accordance with the legislation, guidance and rules applicable.

Penalties

The possibility of applying specific penalties should be considered and the mechanism for application of those penalties identified.

Regulatory action/action plan

1. *EU Regulatory Authorities should develop a clear and detailed system for regulatory actions in case of non compliance with ethical and GCP requirements.*
2. *Where clear serious concerns are identify the EU Regulatory Authority should communicate these concerns to the National Regulatory Authority of the Country(ies) concerned.*

6.4. Transparency, including improvement of Public Assessment Report content and consistency

The European Medicines Agency publishes on its website (www.ema.europa.eu) a full scientific assessment report called a European Public Assessment Report (EPAR) for every medicine granted a central marketing authorisation by the European Commission. Similarly, Public Assessment Reports are published on National Agencies' websites or the Heads of Medicines Agencies website (www.hma.eu) for medicines nationally authorised through the decentralised or mutual recognition procedures.

Regulation (EC) No 726/2004 requires that competent authorities verify that clinical trials, in particular when carried out outside the European Union, were conducted in accordance with the principles of good clinical practice and the ethical requirements equivalent to Directive 2001/20/EC.

The outcome of the process improvement for review of MAA dossiers and identification of studies of potential ethical or GCP concern proposed in the above section 5.1 should be made publicly accessible. Transparency on Regulatory Authorities' GCP review during Marketing Authorisation procedures is necessary because of public and patients' right to information about medicines and their development, including regarding good clinical practice in the conduct of clinical trials which is an important factor in patients' willingness to participate in trials and their trust in medicines.

The Public Assessment Report summarises the quality, safety and efficacy data evaluated and the outcome of that evaluation during the marketing authorisation processes in order to ensure that consistent and appropriate information is provided to the public on the clinical trials included in the MAA. Public Assessment Report are produced to standard formats and their content based on the CHMP Assessment Report (AR) or Reference Member State (RMS) AR after deletion of commercially confidential information.

The CHMP or RMS assessment reports are obtained from the assessments at the different phases of the marketing authorisation procedures. The application of GCP and ethical requirements and steps taken to confirm this, or any related issues should be reflected in the Public Assessment Reports.

For example, guidance to assessors outlines the nature of clinical trial information that should be included in the assessment report at Day 80 and in the CHMP assessment report/EPAR. (see Guidance Document – Day 80 Clinical Assessment Report https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/day-80-assessment-report-overview-guidance_en.pdf).

Inclusion in the guidance of the items listed below, and the consistent application of this, will substantially improve the content of assessment reports and hence the Public Assessment Report in respect of ethical and GCP compliance.

The CHMP or RMS assessment report and the Public Assessment Reports should address the following aspects:

- The steps taken to evaluate and provide assurance regarding the ethical conduct of the trials should be described as should any significant deficiencies and how they have been addressed.
- The standard GCP review should be summarised in an annex to the CHMP or RMS Assessment Report and to the Public Assessment Report, It should list, for each clinical trial submitted the protocol identification and title, start and end date, identification of the sponsor, of the countries where each trial was conducted and the numbers of subjects recruited in each country. The nature of the patient population should also be described (age and gender and any particular considerations of vulnerability). The standards to which the trials were conducted should be identified. This summary should be based on information to be supplied, electronically, by the applicant.
- During the course of the assessment, any relevant ethical issue such as access to treatment post trial, use of placebo or treatment interruptions, choice of active comparators, treatment of vulnerable populations should be highlighted as part of the assessment of the individual trial.,
- The justifications for the study designs, choice of comparators and selection of study populations, should be provided with particular emphasis on those studies that involve increased ethical sensitivity due to their design, indication, patient population or location of conduct. The applicability of the trial to the EEA population should be discussed where relevant.
- A comment that "no ethical issues were identified" may be sufficient where applicable.
- If available, information on Patients' involvement in study design should be communicated,
- When a GCP inspection is performed, the reason(s) for inspection should be described. The outcome and consequences on the assessment of a MAA should be further elaborated. Relevant information from the inspection report may be made publicly accessible.
- When GCP/ethical concerns have been raised, the assessment report should present the issue, describe any external expertise sought and the advice received, and discuss the ethical aspects and their consequences on the assessment of the quality, safety and efficacy of the product.
- The actions taken should be reflected in the Public Assessment Reports.

Regulatory action/action plan

1. *The CHMP or RMS assessment report and the Public Assessment Reports should describe clearly the clinical trials included in the Marketing Application dossier, listing the trials and details concerning their conduct. The applicant should provide tabular listings of this information to facilitate this process.*
2. *The CHMP or RMS assessment report and Public Assessment Reports should describe the assessment of the ethical issues and GCP compliance of the trials in the MAA, steps (including inspection) taken to confirm this and expert advice sought. They should confirm that the trials are considered to have fulfilled requirements, or, if that is not the case should describe the circumstances and details of studies which have been found not conducted in accordance with ethical requirements and GCP, and the actions taken as a consequence*

3. References

i Charter of Fundamental Rights of the European Union (2000)
http://www.europarl.europa.eu/charter/default_en.htm
ii Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine. European Treaty Series – No 164. Oviedo, 4 IV 1997
http://conventions.coe.int/treaty/en/treaties/html/164.htm
iii Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research (Strasbourg 2005) http://conventions.coe.int/treaty/en/treaties/html/195.htm
iv Universal Declaration of Human Rights of 1948, http://www.un.org/en/documents/udhr/
v Convention for the protection of Human Rights and fundamental Freedoms (COE, 1950) ,
http://www.echr.coe.int/nr/rdonlyres/d5cc24a7-dc13-4318-b457-5c9014916d7a/0/englishanglais.pdf
vi United Nations High Commissioner for Human Rights: Convention on the Rights of the Child (20/11/1989).
http://www.ohchr.org/english/law/pdf/crc.pdf
vii UNESCO. Universal Declaration on Bioethics and Human Rights (2005)
http://portal.unesco.org/en/ev.php-RL_ID=31058&URL_DO=DO_TOPIC&URL_SECTION=201.html
viii Universal Declaration on the Human Genome and Human Rights (UNESCO, 1997) http://portal.unesco.org/en/ev.php-URL_ID=13177&URL_DO=DO_TOPIC&URL_SECTION=201.html
ix International Declaration on Human Genetic Data (UNESCO, 2003) http://portal.unesco.org/en/ev.php-URL_ID=17720&URL_DO=DO_TOPIC&URL_SECTION=201.html
x CIOMS-WHO International Ethical Guidelines for Biomedical Research Involving Human Subjects (Geneva 2002) ,
http://www.cioms.ch/frame_guidelines_nov_2002.htm
xi World Medical Association. Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. Revision 2008
http://www.wma.net/en/30publications/10policies/b3/index.html
xii Opinion n.17 of the European Group on Ethics in Science and New Technologies to the European Commission : "Ethical aspects of clinical research in developing countries" http://ec.europa.eu/european_group_ethics/docs/avis17_en.pdf
xiii EU Ethical considerations for clinical trials on medicinal products conducted with the paediatric population (2008)
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/ethical_considerations.pdf
xiv ICH E6 Guideline on Good Clinical Practice (1995), https://www.ema.europa.eu/documents/scientific-guideline/ich-guideline-good-clinical-practice-e6r2-step-5_en.pdf
xv Clinical investigation of medicinal products in the paediatric population. ICH E11.
CPMP/ICH/2711/99. http://www.emea.europa.eu/pdfs/human/ich/271199EN.pdf
xvi DIRECTIVE 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use
http://eudravigilance.emea.europa.eu/human/docs/directives/Dir2001-20_en.pdf
xvii DIRECTIVE 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2005:091:0013:0019:en:PDF
xviii DIRECTIVE 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2001L0083:20070126:EN:PDF
xix REGULATION (EC) No 1901/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004
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xx Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31995L0046:EN:HTML
xxi Reflection Paper on the extrapolation of results from clinical studies conducted outside the EU to the EU population" (Doc. Ref. EMEA/CHMP/EWP/692702/2008)
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