International Federation
of Pharmaceutical
Manufacturers & Associations

IFPMA

Expert Conference on the Revision of the Declaration of Helsinki

December 6th, 2012
Cape Town, South Africa

Introduction

- **Biopharmaceutical companies are committed to high-quality ethical research**
  - Principles on Conduct of Clinical Trials and Communication of Clinical Trials Results *(PhRMA, 2009)*
- **IFPMA was invited to participate in this meeting and provide industry expert input on potential revisions to the Declaration of Helsinki in 2014**
- **Keeping in mind that the original purpose of the Declaration of Helsinki was to serve as a set of guiding principles for physicians investigators, IFPMA has developed points for consideration on the following topics:**
  - Use of placebo in clinical trials
  - Use of comparators based on differences in standard of care and availability of medicines between developed, emerging and developing countries
  - Conduct of clinical trials in vulnerable patient populations
  - Post-study access to medical care

- **Use of placebo in clinical trials**
  - Principle 32
- **Use of comparators based on differences in standard of care and availability of medicines between developed, emerging and developing countries**
  - Principles 32 and 35
- **Conduct of clinical trials in vulnerable patient populations**
  - Principles 9 and 17
- **Post-study access to medical care**
  - Principle 14

Use of Placebo in Clinical Trials

Background

- **Placebo-controlled trials allow researchers to reliably evaluate safety and efficacy of an experimental treatment while minimizing the number of necessary participants exposed to the treatment**
- **Regulatory authorities often require the use of placebo as a comparator in clinical trials**
- **The use of placebo as an acceptable comparator for new treatments tested in clinical trials is acknowledged and addressed by:**
  - Council for International Organizations of Medical Sciences (CIOMS)
    - International Ethical Guidelines for Biomedical Research Involving Human Subjects *(2002, Guideline 11)*
  - The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)
    - Choice of control group and related issues in clinical trials E10 *(2000)*
  - Presidential Commission for the Study of Bioethical Issues
    - Moral Science. Protecting Participants in Human Subjects Research (*2011, Recommendation 12)*

Use of Placebo in Clinical Trials

Points for Consideration

- **Potential scientific, regulatory, and ethical issues associated with the use of placebo or any other appropriate comparator should be carefully assessed in the context of each trial**

- **When a proven effective therapy exists, and the use of placebo as comparator is scientifically necessary and ethically acceptable, it might be valuable, in some instances, to address in the protocol:**
  - Rationale for selecting placebo as the appropriate single or add-on comparator
  - The potential consequences for participants in the placebo arm of not receiving a proven effective therapy *(when placebo is used as the single comparator)*
  - Safeguards whenever appropriate *(*for example: *rescue medication, randomized withdrawal design with patient discontinuation criteria, data and safety monitoring board)*

- **The concept of not exposing patients receiving placebo in clinical trials to *"any risk"* of serious harm should be defined more clearly in the Declaration of Helsinki**

- **Use of placebo in clinical trials**
  - Principle 32
- **Use of comparators based on differences in standard of care and availability of medicines between developed, emerging and developing countries**
  - Principles 32 and 35
- **Conduct of clinical trials in vulnerable patient populations**
  - Principles 9 and 17
- **Post-study access to medical care**
  - Principle 14

Use of Comparators Based on Differences in Standard of Care and Availability of Medicines

Background

- **Selection of comparators based on local or regional standards of care is accepted and acknowledged by:**
  - Council for International Organizations of Medical Sciences (CIOMS)
    - Introduction and Commentary on Guideline 11 *(2002)*
  - Nuffield Council on Bioethics (NCOB)
    - The ethics of research related to healthcare in developing countries *(2002, paragraph 7.29)*
  - National Bioethics Advisory Commission (NBAC)
    - Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries (*2001, Volume I)*
  - Presidential Commission for the Study of Bioethical Issues
    - Moral Science. Protecting Participants in Human Subjects Research (*2001, Recommendation 12)*
  - Council of Europe (CoE)
    - Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research *(2004, paragraph 120)*

Use of Comparators Based on Differences in Standard of Care and Availability of Medicines

Points for Consideration

- **Selection of an active comparator when conducting multiregional trials in developed and emerging or developing countries should take into consideration:**
  - Whether the comparator can be considered scientifically and ethically acceptable for the patient population/s regardless of where the study is conducted
  - Healthcare needs of the country
  - Medical and logistical infrastructure
  - Medical practices
  - Compliance with local regulations
  - Genetic differences that may alter responses to medications
- **The concept of *"best proven intervention"* should be reconsidered to address internal discrepancies within the document *(e.g. between principles 32 and 35)*, and to achieve better alignment with other major ethical guidance documents**
  - *"Best proven"* could be defined as *"established effective intervention"* or *"best locally proven intervention"* (e.g. referenced to the local standard of care)

- **Use of placebo in clinical trials**
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- **Use of comparators based on differences in standard of care and availability of medicines between developed, emerging and developing countries**
  - Principles 32 and 35
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  - Principles 9 and 17
- **Post-study access to medical care**
  - Principle 14

Clinical Trials in Vulnerable Patient Populations

Background

- **The inclusion of vulnerable patient populations in clinical trials often raises concerns about their:**
  - Reduced ability to protect their own interests
  - Limited capacity or freedom to consent or to decline to consent
- **Vulnerable patient populations include a diverse group of people who may benefit from the development of new medical treatments, for example:**
  - Pregnant women
  - Extreme of ages *(e.g. children, elderly)*
  - Those with impaired cognitive functions
  - Persons with life-threatening diseases or in emergency clinical situations
  - Those who are in a dependent situation or deprived of liberty
  - Those who may lack access to health care
- **The inclusion of vulnerable patient populations in clinical trials is acknowledged and addressed by:**
  - Nuffield Council on Bioethics (NCOB)
    - The ethics of research related to healthcare in developing countries *(2002, paragraphs 4.19-4.21)*
  - Council for International Organizations of Medical Sciences (CIOMS)
    - International Ethical Guidelines for Biomedical Research Involving Human Subjects *(2002, Guideline 13)*

Clinical Trials in Vulnerable Patient Populations

Points for Consideration

- **Clinical trials in vulnerable patient populations are necessary to generate rigorous and reliable information about potential benefits and risks of treatments, and to increase the validity of the results**
- **When conducting clinical trials in vulnerable patient populations particular attention should be given, for example, to:**
  - Ethical justifications for their inclusion
  - Risks of undue influence, abuse or coercion
  - Respect for their dignity, rights, safety and welfare, local norms and culture
  - Expertise and experience required to conduct the clinical study
  - Challenges of the consent/assent process
  - Role of legal/authorized representative
- **Sustained collaboration between patients' associations and communities, industry, academia, regulators, and disease advocacy groups is important to encourage participation by vulnerable patient populations in clinical trials, while ensuring their full protection as research participants**

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Post-study Access to Medical Care

Background

- **Limited clarity is provided in the Declaration of Helsinki or other ethical guidance documents about:**
  - What constitutes post-study medical care
  - Which population/s should receive post-study access to medical care
  - Who is responsible to provide post-study access to medical care
  - When post-study access to medical care could/should end
- **Our comments relate to post-study access to study medications**

Post-study Access to Medical Care

Points for Consideration

IFPMA

- **Post-study access to medicines being studied for an approved indication is the responsibility of the applicable government agency or other payer as per usual healthcare programs**
  - Sponsor is not responsible for any continued healthcare costs for diseases/conditions that continue beyond the end of such study
- **The sponsor may offer post-study access to the study medication in circumstances (*for example, life-threatening diseases, clinical emergencies)* where no appropriate alternative therapies are available locally:**
  - Subject to local legal and regulatory requirements
  - Guided by best available evidence for a favorable benefit/risk profile
  - Plan for post-study access (including discontinuation) should be guided by the documented pre-trial agreement and any potential modifications
- **In cases where the sponsor plans to provide post-study access to the study medication, supply may be discontinued if:**
  - In the sponsor's opinion, new information becomes available that affects negatively the previous benefit/risk assessment of the medication
  - The reviewing agency rejects the request for marketing authorization based upon an assessment of benefit/risk and there are no further plans to seek authorization
  - In all circumstances, the sponsor will work with relevant local authorities and caregivers in the best interest of the research participants