

Gender and Informed Consent in Clinical Research: Beyond Ethical Challenges

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ABSTRACT: Informed consent for clinical research is both a communication process and a document to inform individuals about relevance, scope, benefits and risks of their involvement in research and to obtain consent for participation in a study. Critical issues arise when the research involves particularly vulnerable subjects, such as women in some circumstances (i.e. specific physiological conditions, namely, fertility, pregnancy, breastfeeding, or socio-economic vulnerabilities). If, on one hand, participation of particularly vulnerable subjects in clinical research requires special care and safeguards to protect the person's rights and reduce risks of undue inducement and therapeutic misconception; on the other, a vulnerability-based exclusion would result in discrimination and a barrier to possible health benefits deriving from advances in scientific research. In this context, gender-related issues may become a huge challenge in terms of appropriateness, completeness and clarity of information and freedom of consent. This article will explore ethical issues surrounding women's participation in clinical research, with a specific focus on gender considerations in informed consent, through a narrative review of soft law at the European level and beyond on this topic. Concerns on the role of the male/female partner in the informed consent process will also be addressed.

KEYWORDS: Informed consent; vulnerability; gender; fertile women; pregnant/breastfeeding women

SUMMARY: 1. Introduction – 2. Women as research actors and participants – 3. Fair inclusion of women in clinical research: the US experience – 4. Ethical research conduct – 5. Rethinking women's specificities in clinical research: from "vulnerability" dimensions to "scientific complexity" – 5.1. Fertility condition in women – 5.2. Safety of clinical research with women: before, during and after pregnancy – 5.3. Maternal and foetal health in pregnancy: balancing benefits and risks – 5.4. The impact of socio-economic conditions on freedom and self-determination – 6. A gender approach to informed consent – 7. Sensitive issues related to the acquisition of informed consent – 7.1. The role of the pregnant woman's partner in the informed consent process – 7.2. An ethical reflection on pregnancy/breastfeeding and the role of the man's pregnant partner or of childbearing potential in the informed consent process – 8. Conclusions.

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This essay is developed within the European project "Improving the guidelines for Informed Consent, including vulnerable populations, under a gender perspective" (i-CONSENT), funded by the European Union framework program H2020 (Grant Agreement n. 741856).

1. Introduction

Autonomy of a subject in the decision to participate in clinical research is of major importance, being the informed consent the document that allows an individual to voluntarily decide whether or not to enrol in a clinical study. However, relevant issues arise when the research involves particularly vulnerable subjects, such as women in some situations (i.e. specific physiological conditions, namely, fertility, pregnancy or breastfeeding, or socio-economic factors affecting their freedom and self-determination). Gender¹ issues in communication and understanding of the potential benefits and risks related to any clinical study can seriously challenge the appropriateness, completeness and clarity of information and of obtaining informed consent. Hence, a participant-tailored approach to communication is required for an effective consent process.

There are very few International and European guidelines and recommendations focusing on a gender-tailored approach to informed consent, in terms of effective communication strategies to facilitate understanding of benefits and risks related to particularly vulnerable subjects' involvement in clinical research. Scattered references to this topic can be found in documents addressing women's participation in clinical trials or in ethical guidelines for research involving human subjects: in this context, it is possible to devise a number of common ethical standards, as well as problematic issues where disagreement or gaps still remain. However, particular attention is devoted to raising awareness on safety methods and identifying special sections within consent forms with inclusion/exclusion criteria relating to pregnant/breastfeeding women or of childbearing potential. There is often consideration for cultural or social aspects, which may lead to gender vulnerabilities, but these observations are not translated in specific procedures to be implemented in the informed consent process.

This article provides a narrative review of guidelines, recommendations and opinions issued by International Organizations, European institutions, International and European bioethics/research ethics committees, scientific societies, national bioethics/research ethics committees in selected countries (Austria, Belgium, France, Germany, Italy and United Kingdom). The analysis is not limited to the European context, but it is also extended to the United States, with regard to topics which are still not clearly defined (i.e., how to improve access of women in clinical research) and thus needing further analysis. Moreover, Canada was taken into account as an illustrative case, due to interesting developments with regard to gender considerations in the informed consent process. Resources were gathered by monitoring the websites of key International, European and national bodies in this field.

¹ In this article, the word "sex" will be used to refer to the biological dimension (sexual difference between males and females) and "gender" for the psychological, social and cultural dimensions, which influence men and women's behaviours in their decision to participate in clinical research, requiring a differentiated approach in the informed consent process. The two words are confused and often overlap in soft law. The evolution in the notion of gender beyond sexual binarism (the so-called gender or post-gender theories or ideologies) will not be taken into account in this context, as it does not pertain to the object of this review.

2. Women as research actors and participants

At the European level, not many guidelines shed light on the relationship between the protection of women's health and the need for "gender-oriented clinical trials": up to date, very few National Bioethics Committees in Europe have addressed this topic by developing a thorough reflection on the shortcomings of a low-rate participation of women in research, with a clear emphasis on the benefits and risks of their inclusion/exclusion from clinical research. In Italy, the Italian Committee for Bioethics (NBC) raised awareness on this issue in its *Opinion on Pharmacological Trials on Women*², in which it focused on the state-of-the-art of pharmacological experimentation from a gender perspective and highlighted key bioethical problems in this field, within the context of avoiding any form of discrimination and promoting gender equality in healthcare and research. The issues relating to pharmacological experimentation on pregnant women were not considered in the scope of the document. The NBC stressed that in clinical research women are referred to as "weak subjects", or at least they seem to be not subjected to adequate consideration, which should take into account their specificity both from a quantitative point of view (rates of women enrolled in trials compared to men) and a qualitative point of view (data analysis with regard to sexual differences)³. Moreover, the Opinion discussed interesting outcomes concerning a number of studies being conducted in Italy on female pathologies, where the involvement of women is directly linked to the nature of the pathology. The data provided by the Italian Observatory on drug experimentation showed a progressive increase in studies specifically carried out on women, especially in phases II and III. However, women's involvement is mainly identified in relation to therapeutic strategies for specifically female diseases, such as breast cancer and the control of the post-menopausal osteoporosis. There are other areas in which the NBC devised a lack of pharmacological trials on female pathologies as well: particularly with regard to the substitutive hormonal treatment in postmenopausal women, where there are many risks of heart attack or breast cancer or cardiovascular toxicity of the chemotherapy drugs used to treat breast cancer. Although, the most critical under-representation is identified in those trials on drugs for diseases affecting both men and women: clinical research falls short on considering women's specific biological traits and their changing health condition, with a higher risk of suffering medication side effects. This is due to sex-based differences in pharmacokinetic and pharmacodynamics characteristics of drugs. Many researchers have not devoted adequate efforts to look into sexual differences relevant for the study of symptoms, assessment of diagnosis and efficacy of treatments. In this regard, the Italian Committee set out a number of bioethical recommendations, which recalled the importance of implementing the key "ethical principle of fairness of a pharmacological trial on both men and women, in real conditions of equality, without unjustified exclusion, while stressing the necessity of identifying and removing the causes of this unfairness"⁴. Along with considering specific age-related vulnerabilities in pharmacological trials, it is equally fair and right to place the same emphasis on gender differences, which are likely to lead to diverse research results and require tailored trial approaches. The NBC called for an increased level of women participation in research, es-

² ITALIAN COMMITTEE FOR BIOETHICS (NBC), *Opinion on Pharmacological trials on women*, 2008.

³ ITALIAN COMMITTEE FOR BIOETHICS (NBC), *Opinion on Pharmacological trials on women*, 2008, p. 7.

⁴ ITALIAN COMMITTEE FOR BIOETHICS (NBC), *Opinion on Pharmacological trials on women*, 2008, p. 17.



pecially in studies aimed at better understanding women health conditions (i.e. common diseases, specific risk factors etc.), taking into account changes in their psychological, social and cultural conditions, in order to devise gaps in those areas of the health care system where new and variable female needs are poorly taken care of. It also pointed out that an improved involvement of women would guarantee an effective condition of equality of care with respect to men, since a lack of sex-differentiated data results in a form of discrimination for women's health. According to the Italian Committee, the promotion of women's participation in clinical research should rely on providing adequate information on the negative consequences deriving from a lack of differentiated trials, as well as on the social importance of their enrolment in clinical research. Another way to devote greater attention to gender issues in trials is to foster the involvement of women as research actors (both as researchers and representatives of patient associations) and in ethics committees, so as to enable their active participation in the definition of research protocol procedures and, most interestingly, in the informed consent process. In this context, the Austrian Bioethics Commission at the Federal Chancellery published, in 2008, *Recommendations with Gender Reference for Ethics Committees and Clinical Studies*, in which it provided guidance on how to ensure a gender balance in the composition of ethics committees and identified a number of requirements for a gender approach to clinical research⁵. There are no specific recommendations regarding a differentiated approach to informed consent for women and men. It only emphasizes the need for an ethics committee to assess the appropriateness of the method of obtaining informed consent.

As for European soft law, reference is made to women's peculiarities in the general context of health, however, clear and specific guidelines or policies focusing on inclusion/exclusion criteria for women in clinical research (beyond reporting the lack of gender-based stratified data in this area) have not been issued yet. Among the awareness-raising guidelines, it is noteworthy to recall the *Note for Guidance on General Considerations for Clinical Trials*, published by the European Medicines Agency (EMA) in 1998, highlighting that "women of childbearing potential should be using highly effective contraception to participate in clinical trials"⁶. In 2003, based on the conclusions of a European working group including female researchers and representatives of the pharmaceutical industries, it issued the *Note for Guidance on the Clinical Development of HIV-Medical Products*⁷ in which the EMA made recommendations for envisaging study protocols pointing out gender-based data analysis with a male-female comparative approach, alongside calling for statistically significant women's enrol-

⁵ The Austrian Bioethics Commission recommended that "action be taken to: 1) ensure an even balance of the sexes in the composition of ethics committees and that such measures be applied equally with regard to all legally required representatives in an ethics committee; 2) guarantee the inclusion of men and women of all ages according to acknowledged scientific principles (prevalence of the disease) in all biomedical and other research projects and to accept the exclusion of women of childbearing potential in exceptional cases only.; 3) ensure that the inclusion of women of childbearing potential in clinical trials (with due consideration to international guidelines) be formulated and discussed and that rules be provided which make provision for a women-friendly study design of the projects that are submitted"; 4) it also stressed that "the exclusion of women or men of any age from clinical trials should require a detailed justification". See AUSTRIAN BIOETHICS COMMISSION, *Recommendations with Gender Reference for Ethics Committees and Clinical Studies*, 2008, paragraphs 18, 20-22.

⁶ EUROPEAN MEDICINES AGENCY (EMA), *Note for Guidance on General Considerations for Clinical Trials*, 1998, p. 11.

⁷ EUROPEAN MEDICINES AGENCY (EMA), *Note for Guidance on the Clinical Development of HIV-Medical Products*, 2003.

ment and appropriate medical training adapted to this protocol design. In 2005, the EMA published *ICH-Gender considerations in the conduct of clinical trials*, which reviewed the International Conference on Harmonization (ICH) guidelines dealing with women issues⁸. The EMA stressed the fact that “while women appear to be participating in all phases of study development, participation is lower in early phases (phase 1 – 1 / 2)”⁹. Although, these trials are important for determining safety, efficacy and changes in dosage based on gender effects. Nevertheless, unlike special consideration for age-related specificities in other documents, it argued against “the need for a separate ICH guideline on women as a special population in clinical trials”, and stated that “relevant ICH¹⁰ and regional guidelines should be consulted for guidance on demographic considerations, including gender, in the design, conduct and analysis of clinical trials”, while stating that “this issue may be revisited if future experience suggests a change from current practice”¹¹. Considerations on relevant information to be included in a gender-based informed consent process are not provided.

The European Parliament adopted a Resolution of 14 February 2017 on promoting gender equality in mental health and clinical research (2016/2096 (INI)), which noticed that although the European Medicines Agency (EMA) recognized the importance of taking into account sex-related differences in drug response, it has not developed specific strategies aimed at investigating these differences¹². Therefore, it urged EMA to take action in this field by drawing up separate guidelines for women as a special population in clinical trials.

At the international level, guidance on women participation in research is embedded in the *International Ethical Guidelines for Health-Related Research Involving Humans* (as revised in 2016), prepared

⁸ INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE (ICH), *Sex-related Considerations in the Conduct of Clinical Trials*, 2004 (revised in 2009).

⁹ EUROPEAN MEDICINES AGENCY (EMA), *ICH-Gender Considerations in the Conduct of Clinical Trials*, 2005, p. 4.

¹⁰ INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE (ICH), *ICH Harmonised Tripartite Guideline. E4: Dose-Response Information To Support Drug Registration*, 1994; INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE (ICH), *ICH Harmonised Tripartite Guideline. E3: Structure and Content of Clinical Study Reports*, 1995; INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE (ICH), *ICH Harmonised Tripartite Guideline. E8: General Considerations for Clinical Trials*, 1997; INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE (ICH), *ICH Harmonised Tripartite Guideline. E2E: Pharmacovigilance Planning*, 2004; INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE (ICH), *ICH Harmonised Tripartite Guideline. M3 (R2): Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*, 2009; INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE (ICH), *ICH Harmonised Tripartite Guideline. E2C (R2): Periodic Benefit-Risk Evaluation Report*, 2012; INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE (ICH), *ICH Harmonised Guideline. M4E: The CTD – Efficacy Guidance for Industry* (as revised in 2017).

¹¹ EUROPEAN MEDICINES AGENCY (EMA), *ICH-Gender Considerations in the Conduct of Clinical Trials*, 2005, pp. 3-6.

¹² The European Parliament recognized that “specific strategies to implement guidelines for the study and evaluation of gender differences in the clinical evaluation of drugs have not been developed by the European Medicines Agency (EMA), despite the fact it has acknowledged that ‘some of the factors that influence the effect of a medicine in the population may be important when considering potential differences in response between men and women’ and that ‘gender-specific influences can also play a significant role in drug effect’”. See *European Parliament resolution of 14 February 2017 on promoting gender equality in mental health and clinical research (2016/2096 (INI))*.

by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO). Guideline n° 18 focuses particularly on women as research subjects, informed consent and childbearing potential issues: it emphasizes the need to foster the inclusion of women in clinical research and protect their autonomy in the decision-making process, deeming individual informed consent an imperative requirement¹³. However, this last aspect may become problematic for those women with cultural backgrounds where the community dimension prevails over the individual one. Most likely, it will constitute a reason for reluctance to participate in clinical trials; hence, resulting in an exclusion criterion for specific population subgroups. This issue, as well as fertility and pregnancy aspects, will be further discussed later on.

In 2010, the Department of Gender, Women and Health (GWH) of the World Health Organization (WHO) published a document on *Gender, women and primary health care renewal*¹⁴, which highlighted the fact that gender biases permeate health research through: 1) the lack of sex-disaggregated data; 2) designing research methodologies that are not tailored to gender and other social disparities; 3) methods used in clinical trials for new drugs that exclude women and girls from study populations and lack a gender perspective; 4) gender imbalance in ethical committees, research funding and advisory bodies; 5) differential treatment of women scientists¹⁵. It firmly argued that research failing to examine the role of sex and gender in health is both “unethical” and “unscientific”. Moreover, the WHO underlined that individuals need to be given information to enable meaningful participation, not always through the written word, but by using communication modes that are suitable to women and men. Health literacy initiatives would constitute an important component of empowerment.

¹³ Guideline n° 18 states that “women must be included in health-related research unless a good scientific reason justifies their exclusion. Women have been excluded from much health-related research because of their child-bearing potential. As women have distinctive physiologies and health needs, they deserve special consideration by researchers and research ethics committees. Only the informed consent of the woman herself should be required for her research participation. Since some societies lack respect for women’s autonomy, in no case must the permission of another person replace the requirement of individual informed consent by the woman”. See COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, 2016, Guideline n°18, p. 69.

¹⁴ WORLD HEALTH ORGANIZATION (WHO) Department of Gender, Women and Health (GWH), *Gender, women and primary health care renewal: a discussion paper*, 2010. For an overview of WHO’s work on the issues related to women and health, see also: WORLD HEALTH ORGANIZATION (WHO), *Guidelines for Good Clinical Practices (GCP) for trials on pharmaceutical products*, 1995a; WORLD HEALTH ORGANIZATION (WHO), *Women’s Health: improve our health, improve our world* (WHO Position Paper, Fourth World Conference on Women), 1995b; WORLD HEALTH ORGANIZATION (WHO), *Women’s Health and Development Family and Reproductive Health, Gender and Health: Technical Paper*, 1998; WORLD HEALTH ORGANIZATION (WHO), *Standards and operational guidance for ethics review of health-related research with human participants*, 2011.

¹⁵ The WHO also stressed that “in the European Union, efforts at including the gender perspective into health research had been effective with regard to increasing women participation in science (research by women), but not as effective in tackling problems of research for and about women”. See WORLD HEALTH ORGANIZATION (WHO) Department of Gender, Women and Health (GWH), *Gender, women and primary health care renewal: a discussion paper*, cit., p. 49.

3. Fair inclusion of women in clinical research: the US experience

The report *Women's Health Research: Progress, Pitfalls, and Promise* issued by the US Institute of Medicine. Committee on Women's Health Research (2010) reviews the process of exclusion/inclusion of women with regard to clinical research in the United States¹⁶. In 1977, the Food and Drug Administration (FDA) excluded women of childbearing potential from participating in phase I and early phase II trials, because of thalidomide and diethylstilboestrol tragedies. This was meant to avoid the possibility of exposing a foetus to a drug that had not satisfied preliminary safety and efficacy testing. Therefore, women of childbearing potential were allowed to participate in clinical trials only after evidence of a drug's effectiveness in humans was obtained (that is, in late phase II and phase III trials) and following data analysis from animal reproductive studies to check whether the drug caused birth defects; yet, women resulted in being underrepresented in the later phases as well.

In 1985, the Public Health Service Task Force on Women's Health Issues concluded that "the historical lack of research focus on women's health concerns had jeopardized the quality of health information available to women and the health care they receive"¹⁷. From the publication of that report, there have been pivotal changes in women's health research, especially with regard to government support, policy and regulations leading to the development of new scientific knowledge about women's health. This commitment was heightened by the establishment of specific offices on women's health in several government agencies. In 1986, the National Institutes of Health (NIH) designed a policy, which recommended for the inclusion of women in clinical research. Alongside Government reports, also documents from other organizations, including the Institute of Medicine (IOM), have emphasized the need to foster and monitor women participation in health research. Previously, little clinical research on women's health had been carried out, due to existing concerns about risks of possible foetal exposure to an experimental substance, the variability in hormonal status in women, comorbidities and legal issues. Nevertheless, perplexities remained that if FDA approved drugs on the basis of clinical trials in which women were underrepresented, their effectiveness and safety in women would not be known. In 1993, the NIH Revitalization Act basically strengthened existing NIH policies, but with a number of key changes: *inter alia*, the necessity of fulfilling the requirement for inclusion of adequate numbers of women, in order to guarantee a valid analysis by sex for phase III trials and detect differences in intervention effects, while making clear that cost should not be allowed as an acceptable reason for excluding this population group. In the same year, the FDA reversed its 1977 guidelines barring women of childbearing potential from participating in clinical research and published a *Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs*. The Guideline focused on the inclusion of women in clinical research under specific criteria and a sex-based analysis of data¹⁸. The Committee on Women's Health Research noticed

¹⁶ U.S. INSTITUTE OF MEDICINE, Committee on Women's Health Research, *Women's Health Research: Progress, Pitfalls, and Promise*, Washington (DC), 2010.

¹⁷ U.S. INSTITUTE OF MEDICINE, Committee on Women's Health Research, *Women's Health Research: Progress, Pitfalls, and Promise*, cit., p. 1.

¹⁸ The FDA Guideline hinged upon "1) encouraging inclusion of women in phase I and II studies; 2) requiring inclusion of women in efficacy studies; 3) requiring analysis of data on sex differences; 4) boosting consideration

a gradual, although existing shift from a disease-centred approach to women's health and related research – merely focusing on disorders associated with the female reproductive system – to a woman-centred approach, which included other burdensome diseases in women's life (e.g. where differences between women and men are more evident in terms of frequency, seriousness, causes or manifestations, treatments or outcomes, morbidity or mortality). This broader concept of woman's health has equally shown variations in the extent of diseases among women from different socio-demographic groups, as well as an uneven distribution of benefits stemming from research developments and novel treatments. Research has also expanded to encompass studies that take into account not only biological sex as a determinant of disease, but also gender, in the sense of emphasizing the importance of social, psychological and behavioural influences. Nevertheless, women representation, consideration and reporting of sex and gender differences in the design and analyses of studies are still inadequate. This hampers advances in women's health research and its translation into clinical practice. The Committee, therefore, recommended mainstreaming women's health research, namely routinely assessing differences between men and women, as well as subgroups of men and women in all health research. It also urged the FDA¹⁹ to enforce compliance with the requirement for sex-stratified analyses of efficacy and safety for medical products (drugs, devices and biologics) that are coming to the market, alongside considering those analyses in regulatory decisions²⁰.

4. Ethical research conduct

The principle of justice is of paramount importance in conducting an ethical research, especially when recruiting eligible participants to be enrolled in clinical trials. In the context of this article, it may be translated in the researcher's duty to refrain from contributing to inequalities with regard to research designs not adequately taking into account gender-based needs and characteristics in the management of the trial process; or ensuring completeness and accuracy of the information conveyed to research participants, through gender-tailored communication strategies, sensitive to different literacy levels (this is directly linked to guaranteeing free and informed consent). Protecting privacy and confidentiality is another key rule stemming from the principles of respect for the person, and beneficence according to which the latter should be informed about the use of personal data, in order to avoid any harm deriving from the publication of sensitive information. Nevertheless,

of effects of menstrual cycle on drug effect, effects of exogenous hormone therapy on drug effect, and effect of drug on the effects of oral contraceptives, when feasible". See U.S. FOOD AND DRUG ADMINISTRATION (FDA), *Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs*, 1993.

¹⁹ U.S. GOVERNMENT ACCOUNTABILITY OFFICE, *Women's Health: FDA needs to Ensure More Study of Gender Differences in Prescription Drugs Testing*. HRD-93-17, 1992; U.S. GOVERNMENT ACCOUNTABILITY OFFICE, *Women Sufficiently Represented in New Drug Testing, but FDA Oversight Needs Improvement*. GAO-01-754, 2001; U.S. FOOD AND DRUG ADMINISTRATION (FDA), *FDA Report. Collection, Analysis, and Availability of Demographic Subgroup Data for FDA-Approved Medical Products*, 2013; U.S. FOOD AND DRUG ADMINISTRATION (FDA), *Collection of Race and Ethnicity Data in Clinical Trials*, 2016.

²⁰ U.S. INSTITUTE OF MEDICINE, Committee on Women's Health Research, *Women's Health Research: Progress, Pitfalls, and Promise*, cit., p. 13.

the WMA *Declaration of Helsinki*²¹ does not specifically refer to women peculiarities in relation to ethical principles for medical research, not even with regard to informed consent. These principles are also included in other crucial international legal instruments in the field of bioethics and research ethics.

In the context of an ethical management of informed consent, it is important to recall that, in 2015, the Committee on Ethics of the American College of Obstetricians and Gynecologists issued the *Opinion n° 646 on Ethical Considerations for Including Women as Research Participants*, in which the responsibilities of researchers were clearly specified, pointing out a set of criteria for an effective disclosure of information in the informed consent process, with a particular emphasis on how to communicate benefits and risks when dealing with pregnant women²².

5. Rethinking women's specificities in clinical research: from "vulnerability" dimensions to "scientific complexity"

Institutional guidelines are generally keen on not considering women as vulnerable subjects, since this may fuel reticence towards their inclusion in research and hinder the possibility for them of reaping the benefits deriving from participation. However, there are a number of circumstances in which they could be vulnerable in research, such as studies with female sex workers, trafficked women, refugees and asylum seekers; or the case of women who live in a cultural context where they are not permitted to consent on their own behalf for participation in research, but require permission from a spouse or male relative. When women in such situations are potential participants in research, researchers need to exercise special care²³. Particularly, CIOMS guidelines address major ethical challenges to informed consent deriving from women's conditions of social vulnerability²⁴. Caution must

²¹ WORLD MEDICAL ASSOCIATION (WMA), *Declaration of Helsinki* (as amended), 2013.

²² According to the ACOG, "the researcher has an obligation to disclose to women and discuss with her all material risks affecting her; in the case of a pregnant woman, this includes all material risks to the woman and her foetus. Disclosure should include risks that are likely to affect the patient's decision to participate or not to participate in the research. Anything beyond minimal risk must be weighed carefully against the potential benefits to the woman (and the foetus, in the case of a pregnant woman) when the advisability of participation is considered. Because the process of informed consent cannot anticipate all conceivable risks, women who develop unanticipated complications should be instructed to contact the researcher or a representative of the institutional review board immediately". See THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS (ACOG), Committee on Ethics, *Ethical Considerations for Including Women as Research Participants. Opinion n. 646*, 2015, p. e102.

²³ COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, Commentary on Guideline n° 15, 2016, p. 58.

²⁴ The Commentary on Guideline n° 18 stresses the fact that "in many societies women remain socially vulnerable in the conduct of research. For example, they may suffer negligence or harm because of their submission to authority, their hesitancy or inability to ask questions, and a cultural tendency to deny or tolerate pain and suffering. When women in these situations are potential participants in research, researchers, sponsors and ethics committees must take special care in the research design, assessment of risks and benefits, as well as the process of informed consent, to ensure that women have the necessary time and appropriate environment to make decisions based on information provided to them". See COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, Commentary on Guideline n° 18, cit., p. 69.

be used if vulnerable subjects are enrolled in studies; their proposed participation in a research project must always be justified specifically. The general rule is that potential research participants should be the least vulnerable necessary to achieve the goals of the study and appropriate protection should be ensured in these specific cases, in order to guarantee the dignity and safety of women consenting to participate in research²⁵. The concept of vulnerability is also mentioned in other international documents, such as in articles 19 and 20 of the *Declaration of Helsinki* (as revised in 2013) and Article 8 of the *UNESCO Universal Declaration on Bioethics and Human Rights* (2005), which calls for both a “negative” duty to refrain from causing harm and a “positive” duty to promote solidarity and to share the benefits of scientific progress, highlighting the close relationship between respect for the integrity and dignity of persons, on one hand, and the vulnerability of persons, on the other, and recognizes special vulnerabilities of women and girls (“gender-related vulnerabilities”) concerning treatment in healthcare delivery and research, as they are “particularly exposed to the whole range of social, cultural, economic, educational and political determinants of vulnerability”²⁶. Beyond social and cultural patterns leading to vulnerable conditions for women, there are biological reasons: as recalled by the Italian NBC, female subjects’ involvement in clinical trials has traditionally been deemed problematic, due to their physiological peculiarities (notably enzymatic and hormonal differences), variations during childbearing and non-childbearing age (i.e. menstrual cycle, pregnancy, breastfeeding, menopause), as well as the possibility of reliance on contraception, in order to avoid pregnancy or for therapeutic reasons; however, estrogens and progestins modify women’s metabolism; particularly, estrogens may also interfere with the way genes work. This kind of variability is likely to affect the collection of clear data in mixed sex trials, with an ensuing negative impact on the statistical relevance of the research study. In addition, a possible pregnancy in fertile women is considered another problematic issue for the pharmaceutical industry, as experimental drugs could harm the foetus not only during an unexpected pregnancy while a trial is underway, but also after the end of the process. Therefore, these possible negative effects discourage investments in research involving women, because of the extensive time required for the study development, as well as the rise in insurance costs to cover the emergence of negative consequences. In this regard, CIOMS guidelines point out that “pregnant women must not be considered vulnerable simply because they are pregnant”, although recognizing that “specific circumstances, such as risks to the foetus, may require special protections”²⁷. This view has been strongly stressed by the Committee on Ethics of The American College of Obstetricians and Gynecologists, which argues that one of the reasons for systematically excluding women from research is their perceived status as “vulnerable”, and goes as far as suggesting that “pregnant women in research trials should be defined as ‘scientifically complex’ rather than a ‘vulnerable’ population”²⁸. This position relies on the fact that vulnerable individuals

²⁵ COUNCIL OF EUROPE, COMMITTEE ON BIOETHICS (DH-BIO), *Guide for Research Ethics Committee Members*, 2012, p. 10.

²⁶ UNITED NATIONS EDUCATIONAL, SCIENTIFIC AND CULTURAL ORGANIZATION (UNESCO), International Bioethics Committee of UNESCO (IBC), *The Principle of Respect for Human Vulnerability and Personal Integrity*, 2013, pp. 5-9.

²⁷ COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, Commentary on Guideline n° 15, cit., p. 58.

²⁸ THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS (ACOG), Committee on Ethics, *Ethical Considerations for Including Women as Research Participants. Opinion n.646*, cit., p. e102.

are those with a compromised ability to protect their interests and provide informed consent, whereas pregnant women do not, as a group, fall within this definition. They have the decision-making capacity to opt for participating or not in specific research studies. Nevertheless, pregnant women are a “scientifically complex” group, in the sense that they require tackling a mix of physiological and ethical complexity, which stems from “the need to balance the interests of the pregnant woman and the foetus. Maternal and foetal interests usually align, as appropriate care of the woman is necessary for the health of the foetus, but these interests may diverge in the setting of research, especially when it is not focused on concerns of pregnancy or foetal health”²⁹. Moreover, cultural issues and the scientific knowledge gap between researchers and participants, directly affecting the latter’s capacity to clearly understand the underlying risks related to their specific health condition should be carefully weighed, especially in these sensitive circumstances. The importance of taking into account the physiological conditions of women is equally highlighted in a set of ICH guidelines³⁰. If on one hand classifying women as “vulnerable” in specific contexts should not limit their participation in research and restrict the potential value of findings beneficial for their health; on the other, leaving such a categorization aside must not lead to an under-estimation of risks, protection needs and necessary safeguards peculiar to women’s health condition.

5.1. Fertility condition in women

International and European guidelines tend to acknowledge the ethical importance of including women of childbearing potential in clinical studies. It would be unjust to exclude them from clinical studies, since this hampers their chance to reap the benefits of new knowledge obtained from these studies and may result in the impossibility to safely use drugs not tested on women of this group, without adequately protecting the foetus – in case of pregnancy – as they could take drugs available on the market and risk exposure would not be avoided, with potentially dangerous consequences. A number of guidelines place a great emphasis on the self-determination of fertile women in making their own autonomous decision to enrol in clinical studies, as long as they have been duly informed about the specific degree of risk involved in participation. The need to protect the interests and health condition of women often overrides an appropriate consideration of foetus protection measures: according to CIOMS, “access to a pregnancy test, to effective contraceptive methods and to safe abortion must be guaranteed before exposure to a potential teratogenic or mutagenic intervention. The informed consent process must include information about the risk of unintended pregnancy. Moreover, if the pregnancy is not terminated, women must be guaranteed a medical follow-

²⁹ THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS (ACOG), Committee on Ethics, *Ethical Considerations for Including Women as Research Participants. Opinion n.646*, cit.

³⁰ ICH Guidelines call for “including demographic variables, such as age, sex etc. in research protocols and identifying menstrual status as a possible relevant factor. Where studies are sufficiently large, data should be presented according to these subgroups. At the summary level, the demographic characteristics of patients across all efficacy studies should be provided. Adverse events, extent of exposure and safety-related laboratory measurements and vital signs, etc. should include demographic data such as the age and sex of patients”. See INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE (ICH), *ICH Harmonised Tripartite Guideline. E3: Structure and Content of Clinical Study Reports*, 1995.

up for their own health and that of the infant and child”³¹. Nevertheless, as stated in the UK *Guidelines on the practice of ethics committees in medical research with human participants*, “since all contraceptive methods have a very small failure rate, the inclusion of potentially fertile women in pharmacological studies creates a teratogenic risk”³². Risk exposure may be high or low; its extent varies according to single studies. Even in the case of women of reproductive age (i.e. not pregnant), the Royal College of Physicians recommends that such risks should be discussed with their partners, also assessing the opportunity to request the latter’s consent. It equally encourages researchers to provide appropriate advice concerning contraception precautions and about the existing option of “emergency contraception” if precautions have been omitted. Nevertheless, this possibility is ethically problematic, since it is likely to deter women not willing to run the risk of jeopardizing a potential pregnancy and harming the foetus from participating in high-risk trials, entailing an underrepresentation of specific groups of women. An ethical assessment of the frequency of a health condition in a particular age group also deserves specific consideration, in order to determine whether a study of a disease could be carried out without involving such individuals, because it is rare in this category of women (i.e. old-age diseases). Women who become pregnant during research are removed from the study in cases where a drug or biological product is known to be mutagenic or teratogenic. As a consequence, medical care and follow-up are required throughout their pregnancy, in order to detect and monitor any foetal anomalies. In studies where there is no evidence of a potential harm to the foetus, women who become pregnant are usually not advised to leave the trial, but are given the opportunity to continue or end their participation. Sometimes it may be appropriate for a woman to stay in the study for safety monitoring, despite being removed from the drug study³³. Other guidelines are more cautious about the inclusion of women of childbearing potential in clinical studies and embrace a balanced approach, which takes into account benefits and risk for both the woman and the foetus: for instance, the Italian NBC emphasized the ethical and social relevance of fertile women participation, “provided that an adequate protection of the unborn child can be guaranteed”³⁴, alongside recommending a preliminary consultation about the trial, during which clear and accurate information on the goals of the study is provided, as well as a classification of potential benefits and risks that the study may involve for the participant, while highlighting the risks for the foetus in case of pregnancy. Whenever risks for the foetus are envisaged, the NBC underlined the importance of the woman’s clear statement of a conscious and responsible commitment to honour abstinence from sexual activity, in order to avoid pregnancy. The NBC also highlighted that the informed consent must be guaranteed, giving women a fair amount of time and appropriate environmental conditions to decide, and that their individual consent cannot be replaced by the partner’s consent. Nevertheless, in cases of possible interactions between experimental treatments and the contraceptive methods being used (e.g. certain drug trials can make hormonal contraceptive ineffec-

³¹ COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, Commentary on Guideline n° 18, cit., p. 70.

³² ROYAL COLLEGE OF PHYSICIANS, *Guidelines on the practice of ethics committees in medical research with human participants*, 2007, p. 61.

³³ COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, Commentary on Guideline n° 18, cit., p. 70.

³⁴ ITALIAN COMMITTEE FOR BIOETHICS (NBC), *Opinion on Pharmacological trials on women*, cit., p. 18.

tive), the NBC recommends that the woman (and her partner) receive adequate information; recruitment should follow only if a commitment is clearly expressed in the informed consent “to avoid starting a pregnancy during the time of the trial and, in some cases, also for a certain time afterwards, a time to be defined according to the typology of the trials. The woman, on her part, must be available to carry out checks (pregnancy tests) that allow the experimenters to verify the conditions of safety to proceed”³⁵.

A necessary reliance on contraception to avoid pregnancy, as a requirement for participation in clinical research, can become ethically problematic especially when such prescriptive contraceptive methods clash with moral and religious beliefs, resulting in a possible barrier to research enrolment decision-making.

The use of contraception is a highly controversial and ethically sensitive issue in the Italian debate, as in many cases where fertile women are involved research sponsors consider it a mandatory requirement for participation. Despite the existence of a variety of stances on this topic, which reflects an ethical pluralism in our current society, it is possible to identify two main positions that oppose this mandatory requirement: a first one upheld by those who criticize the expectation of the pharmaceutical industry that women should use hormonal contraceptives, as this requirement would restrict women’s freedom, intended as self-determination (e.g. the possibility to choose among different options); others also argue that relying on hormonal contraceptives as a mandatory requirement is not morally acceptable, since it would be detrimental to the freedom and responsibility of research participants, but inspired by a different perspective. This position, supported by those who believe in the inseparability of the unitive and procreative dimensions of the marital act, claims that the woman’s explicit commitment to avoid pregnancy is sufficient, and that she should be able to choose birth control methods, respectful of her lifestyle and values, including abstaining from sexual intercourse³⁶. The NBC’s balanced approach aimed at protecting both the woman and the foetus is also upheld by the Austrian Bioethics Commission, which stressed that clinical trials on fertile women should be conducted in ways that avoid posing risks to the unborn child, while recommending the formulation of rules for a woman-friendly study design of research projects³⁷.

5.2. Safety of clinical research with women: before, during and after pregnancy

Both at the international and European levels, particular consideration is devoted to the significance of clinical research involving pregnant women, insofar as it improves knowledge of conditions and treatments of diseases related to pregnancy. These diseases may affect the woman, the foetus or both.

In this context, CIOMS highlighted the fact that a systematic exclusion of pregnant and breastfeeding women from clinical research leads them to take prescription/non-prescription drugs, which often lack sufficient safety and efficacy evidence, with ensuing potentially high maternal, fetal or neonatal

³⁵ ITALIAN COMMITTEE FOR BIOETHICS (NBC), *Opinion on Pharmacological trials on women*, cit., p. 19.

³⁶ ITALIAN COMMITTEE FOR BIOETHICS (NBC), *Opinion on Pharmacological trials on women*, cit., pp. 12-13.

³⁷ AUSTRIAN BIOETHICS COMMISSION, *Recommendations with Gender Reference for Ethics Committees and Clinical Studies*, cit.

risks³⁸. As recalled by the Committee on Bioethics of the Council of Europe in the *Guide for Research Ethics Committees*, research conducted on pregnant women may or may not have a potential direct benefit and is allowed only when studies of comparable effectiveness cannot be carried out on other persons; for research with potential direct benefit, the risk-benefit assessment must consider the specific situation of pregnancy, whereas research without potential direct benefit “must contribute to the ultimate attainment of results capable of conferring benefit to other women in relation to reproduction or to other fetuses. However, in such research the criteria of minimal risk and minimum burden are compulsory”³⁹. In addition, if involving breastfeeding women, particular care is recommended to avoid any adverse impact on the health of the child. The issue of “minimal risk” was particularly raised in the US ethical debate in relation to the definition provided in federal regulations (according to which, the likelihood and degree of harm or discomfort anticipated in the research, should not be greater than those experienced in daily life or during the performance of routine physical or psychological examinations). It was unclear whether “daily life” referred to that of the general population or of individual participants. Relying on the participant’s daily life as the standard might make a higher level of risk acceptable; hence, the general population standard is advised⁴⁰. Although, CIOMS underlined that “when the social value of the research for pregnant or breastfeeding women or their foetus or infant is compelling, and the research cannot be conducted in non-pregnant or non-breastfeeding women, a research ethics committee may permit a minor increase above minimal risk”⁴¹. This last aspect requires research ethics committees to act with particular caution: the safety of persons who consent to research must always be the primary concern of research ethics committees and researchers; as a general rule, this implies that all risks be carefully weighed against expected benefits. In any case, relying on evidence from prior animal experimentation is absolutely necessary⁴².

³⁸ The Commentary on Guideline n° 19 specifies that “physicians prescribe medications for pregnant and breastfeeding women, but most often do so in the absence of studies involving such women and without adequate evidence of safety and efficacy. Such routine treatment includes medications that may have a prospect of serious harm to the foetus, such as radiation or chemotherapy for cancer. A direct consequence of the routine exclusion of pregnant women from clinical trials is their use of medications (both prescription and non-prescription) lacking data from clinical trials about the potential individual benefits and harms to themselves, their fetuses and their future children. Therefore, after careful consideration of the best available relevant data, it is imperative to design research for pregnant and breastfeeding women to learn about the currently unknown risks and potential individual benefits to them, as well as to the foetus or nursing infant”. See COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, Commentary on Guideline n° 19, cit., p. 72.

³⁹ COUNCIL OF EUROPE, COMMITTEE ON BIOETHICS (DH-BIO), *Guide for Research Ethics Committee Members*, cit., p. 46.

⁴⁰ THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS (ACOG), Committee on Ethics, *Ethical Considerations for Including Women as Research Participants. Opinion n. 646*, cit.; U.S. NATIONAL BIOETHICS ADVISORY COMMISSION, *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries, Report and Recommendations*, Bethesda, Maryland, vol. I., 2001.

⁴¹ COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, Guideline n° 19, cit., p. 71.

⁴² THE FRENCH NATIONAL CONSULTATIVE ETHICS COMMITTEE FOR HEALTH AND LIFE SCIENCES (CCNE), *Cooperation in the field of biomedical research between French teams and teams from economically developing countries. Report*, 1993.

The Royal College of Physicians identified a number of specific criteria for pregnant/breastfeeding women inclusion in research, in an attempt to balance the requirements of protecting the safety and health of both the mother and the foetus or infant with potential benefits stemming from research advancements⁴³.

In this regard, the Committee on Ethics of the American College of Obstetricians and Gynecologists dealt with the type of information to be provided in case of pregnancy exposure to more than minimal risk in the course of a study⁴⁴. In the context of safety concerns before enrolling in clinical trials on investigational medicinal products, the European Clinical Trial Facilitation Group (CTFG) issued recommendations related to embryo-foetal risk mitigation and risk assessment during preconception and early stages of pregnancy⁴⁵. The CTFG stressed the need to clearly provide in the trial protocol the analysis of embryofetal risk for clinical trials with investigational medicinal products (IMPs), including recommendations for the level of contraception and frequency of pregnancy testing, as well as detailed information on the possibility for interaction between the investigational medicinal product or non-investigational ones and hormonal contraceptives, since this may reduce the efficacy of the contraception method. However, as emphasized by the Committee on Ethics of the American College of Obstetricians and Gynecologists, “concerns about the potential for pregnancy in research trial participants have led to practices involving overly burdensome contraception requirements (such as the use of intrauterine devices or bilateral tubal occlusion), which are out of proportion to the actual risks of experimental drugs or interventions”⁴⁶. Therefore, it advises consultation with an obstetrician-gynecologist or other gynecologic care provider regarding the efficacy and risk of contraception measures, since investigators generally fail to consider what is actually “reliable”: the required methods, which are often prescriptive and potentially coercive, have their own inherent risks and may not meet the woman’s preference. Highly burdensome contraception could be inappropriate based on the principles of respect for autonomy, beneficence and justice. In this sense, a woman should be allowed to choose a birth control method, including abstinence, according to her needs

⁴³ According to the Royal College of Physicians, “pregnant or breastfeeding women should not participate in non-therapeutic research that carries more than minimal risk to the foetus or infant, unless this is intended to elucidate problems of pregnancy or lactation; while, as a general rule, therapeutic research should only be undertaken in pregnant or breastfeeding women with a view to: 1) improving the health of the mother without prejudice to that of the foetus or breast-fed baby; or 2) enhancing the viability of the foetus; or 3) aiding the baby’s healthy development; or 3) improving the ability of the mother to nourish it adequately”. See ROYAL COLLEGE OF PHYSICIANS, *Guidelines on the practice of ethics committees in medical research with human participants*, cit., p. 62.

⁴⁴ The Committee on Ethics of the American College of Obstetricians and Gynecologists points out that “pregnant women who enrol in a research trial and experience a research related injury should be informed about their therapeutic options, including those related to the pregnancy. When a pregnancy has been exposed to more than minimal risk in the conduct of research, the woman should be encouraged to participate in any available follow-up evaluations to assess the effect on her and her foetus or child”. See THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS (ACOG), Committee on Ethics, *Ethical Considerations for Including Women as Research Participants. Opinion n. 646*, cit.

⁴⁵ CLINICAL TRIAL FACILITATION GROUP (CTFG), *Recommendations related to contraception and pregnancy testing in clinical trials*, 2014.

⁴⁶ THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS (ACOG), Committee on Ethics, *Ethical Considerations for Including Women as Research Participants. Opinion n. 646*, cit., p. e100.

and values. In addition, in the Committee's view, "requiring specific contraception in a woman not sexually active violates a commitment to respect her as a person"⁴⁷. This ethical position is in line with the concerns raised by the Italian Committee for Bioethics. As part of the consent process, the woman should be duly informed of all types of risks (including those risks impacting on her decision to enrol or not enrol in research), that could be affecting her and/or her foetus in case of pregnancy. If new scientific information arises during the research, this information should be conveyed to participants as soon as possible. In this case, the CoE Committee on Bioethics (DH-BIO) recommends that participants be told whether the research ethics committee has asked researchers to prepare revised information/new consent forms regarding modifications to the project. At this point, as at any stage in the course of the research, subjects' right to withdraw consent must be respected⁴⁸. For clinical trials including pregnant women because the medicinal product is intended for use during pregnancy, follow-up of the pregnancy, foetus and child is essential, even for several months after the end of the study. If experimentation is carried out on breastfeeding women, "excretion of the drug or its metabolites into human milk should be examined, where applicable; in this case, their babies should also be monitored for the effects of the drug"⁴⁹.

5.3. Maternal and foetal health in pregnancy: balancing benefits and risks

As discussed earlier, conducting clinical trials on pregnant women is an ethically problematic issue, since maternal and foetal risks are deeply interconnected and the decision to enrol this category of women in research presupposes balancing the possible risk of foetal harm with the potential for benefit and the importance of the information to be gained on the health of women and fetuses⁵⁰. Particularly, it may be highly problematic to decide whether to enrol in research directed at benefiting the mother in which the possibility of foetal loss cannot be excluded; in this case, it is a matter of weighing maternal welfare against foetal risk, as for studies of epilepsy or psychosis in pregnancy⁵¹. In this context, it is noteworthy mentioning the controversial bioethical debate surrounding the status of the foetus, recalled by the NBC: some argue that when balancing the possible damage to the foetus (considered not yet to have dignity "in the strong sense") with the potential direct benefits to women, primary consideration should be given to the latter, since an *a priori* exclusion of women to protect the foetus would result in injustice in research, given that women would not have the same opportunities as men in the treatment of certain diseases; others argue that where clinical research is likely to jeopardize the foetus's life and health (according to this stance, the foetus is recognised as a subject having dignity "in the strong sense"), even only hypothetically or potentially, it is ethically advisable for these women not to participate in trials, since the risk to the new life overrides the po-

⁴⁷ THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS (ACOG), Committee on Ethics, *Ethical Considerations for Including Women as Research Participants*. Opinion n. 646, cit., p. e103.

⁴⁸ COUNCIL OF EUROPE, COMMITTEE ON BIOETHICS (DH-BIO), *Guide for Research Ethics Committee Members*, cit.

⁴⁹ EUROPEAN MEDICINES AGENCY (EMA), *Note for Guidance on General Considerations for Clinical Trials*, cit., p. 10.

⁵⁰ THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS (ACOG), Committee on Ethics, *Ethical Considerations for Including Women as Research Participants*. Opinion n. 646, cit., p. e101.

⁵¹ ROYAL COLLEGE OF PHYSICIANS, *Guidelines on the practice of ethics committees in medical research with human participants*, cit., p. 63.

tential benefits to the women⁵². The accuracy and clarity of the information provided in these sensitive contexts is key to ensuring the prospective participants' full understanding of the potential benefits and the extent of risk at stake.

When dealing with pregnant women, another ethically sensitive issue concerns foetal protection within disease prevention research: investigation into pathological conditions (such as toxoplasmosis, deformities, etc.) or treatments specifically aimed at the foetus may equally be the focus of research studies. The primary goals of these interventions is to improve the health of children by intervening before birth to correct or treat prenatally diagnosed abnormalities. However, since this leads to unavoidable consequences for the woman's health and bodily integrity, it cannot be carried out without consideration of her wellbeing and without her explicit consent⁵³.

5.4. The impact of socio-economic conditions on freedom and self-determination

Social and economic vulnerabilities may interfere with the self-determination of individuals and lead to a remarkably increased exposure to a number of risks: some contextual aspects that fuel social vulnerability in research concern poverty and low educational levels, difficulty in accessing healthcare (i.e. whenever transnational research projects are involved), as well as the interaction between gender and marginalised racial and ethnic backgrounds⁵⁴. In this regard, the French National Consultative Ethics Committee for Health and Life Sciences (CCNE) highlighted the special status of women in some developing countries, that generates "a situation of inequality in the gender relationship", which deserves particular attention, since it could compromise an actual understanding of health issues⁵⁵. Respect for free and informed consent acknowledges that potential research participants must not be coerced or unduly influenced by use of inducements (both direct or indirect) or threats. For instance, the IBC discussed cases of poor women in developing countries deciding to enrol in trials after being informed that their children would be entitled to receive necessary medical treatments in this context. Therefore, these women's ability to provide a valid consent was in doubt, given their concern for their children's health. In addition, they become vulnerable to any risks involved in clinical trials, since they are likely to underestimate these aspects due to other priority interests. As recalled by the CoE Committee on Bioethics (DH-BIO), "it is extremely difficult to achieve a complete lack of influence, but influence that would lead individuals to accept a higher level of risk than would otherwise be acceptable to them, would be considered undue. This kind of influence may be financial in nature, but could also include, for instance, attempts to influence family members" (as in the case of vulnerable women accustomed to social conditioning to submit to authority), or veiled

⁵² ITALIAN COMMITTEE FOR BIOETHICS (NBC), *Opinion on Pharmacological trials on women*, cit., pp. 12-13.

⁵³ The ACOG made clear that "it is impossible to enrol the foetus in a clinical study without affecting the pregnant woman either physically (i.e. in the case of surgical treatments) or pharmacologically (as when drugs given to women cross the placenta to treat the foetus)". See THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS (ACOG), Committee on Ethics, *Ethical Considerations for Including Women as Research Participants. Opinion n. 646*, cit., p. e105.

⁵⁴ UNITED NATIONS EDUCATIONAL, SCIENTIFIC AND CULTURAL ORGANIZATION (UNESCO), International Bioethics Committee of UNESCO (IBC), *The Principle of Respect for Human Vulnerability and Personal Integrity*, cit., p. 27.

⁵⁵ THE FRENCH NATIONAL CONSULTATIVE ETHICS COMMITTEE FOR HEALTH AND LIFE SCIENCES (CCNE), *Disparity in access to health care and participation in research on a global level-ethical issues. Opinion n°78*, 2003, p. 19.

threats (for example by researchers, medical staff or healthcare providers) to deny access to services to which individuals would otherwise be entitled, or expectation of any other retaliatory response from senior members of a group with a hierarchical structure in case of refusal to participate in a trial. Therefore, special care is needed in situations where participation in a research project may be the only way to access health care⁵⁶. The CoE Committee on Bioethics (DH-BIO) does not refer to gender issues in this specific context. In principle, the involvement in a clinical trial is a benevolent act, which should not be induced by monetary or other forms of compensation, in order to avoid exploitation⁵⁷. Although, it is considered ethically acceptable and appropriate to reimburse individuals for any costs associated with participation in research, including transportation or lost wages. A number of research ethics committees also believe that participants should receive compensation for their time devoted to research participation; however, WHO recommends that payments should not be so large, or free medical care or other forms of compensations so extensive, as to provide prospective participants with incentives to consent to research enrolment against their better judgment or to undermine their understanding of the research⁵⁸. However, determining the ethical acceptability of compensation is problematic, as the possibility it may exert an undue inducement to participate in research depends on a number of different variables, such as prospective subjects' economic status. An ethical consideration of informed consent must focus on comprehension and free consent, as both elements are an essential part of the person's self-determination: it is all the more important when dealing with vulnerable categories of women that potential participants are given clear information in language, which is understandable to them, particularly when subjects with linguistic or cognitive limitations are involved. This is a necessary aspect for freedom in consenting. In addition, the Committee on Ethics of the American College of Obstetricians and Gynecologists advises those in charge of providing information "to be cognizant of participants' beliefs and values during the informed consent process"⁵⁹.

6. A gender approach to informed consent

In the context of informed consent, the issue regarding comprehension of information conveyed by investigators or practitioners is often raised in developed countries where illiteracy can be a minor problem, but where inability to understand is due to the complexity and length of documents submitted to research participants (however, also in clinical practice). More than empowering subjects through clear information, these documents may be interpreted as a way to protect healthcare professionals from being accused of delivering incomplete information. The International Bioethics Committee (IBC) of UNESCO, therefore, recalls the importance of the clarity of the text submitted and its content, which should include necessary and sufficient information to decide either to con-

⁵⁶ COUNCIL OF EUROPE, COMMITTEE ON BIOETHICS (DH-BIO), *Guide for Research Ethics Committee Members*, cit., 10.

⁵⁷ EUROPEAN GROUP ON ETHICS IN SCIENCE AND NEW TECHNOLOGIES (EGE), *Ethical aspects of clinical research in developing countries*, 2003, p. 13.

⁵⁸ WORLD HEALTH ORGANIZATION (WHO) Department of Ethics, Equity, Trade and Human Rights, *Standards and operational guidance for ethics review of health-related research with human participants*, cit., p. 14.

⁵⁹ THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS (ACOG), Committee on Ethics, *Informed Consent. Opinion n°439*, 2009, p. 3.

sent or refuse to consent. This must be done in a language that is accessible to person concerned. Other ethical challenges stem from the fact that in many cases, particularly in scientific research, it may be necessary to document in a written form that consent has been obtained. However, the implementation of this request is likely to face problems, in certain situations: for instance, in societies with an oral tradition, where the value of oral consent is unquestionable; as a consequence, written form consents can be considered as a lack of trust or even as an insult; or in illiterate groups of people, “where a sign at the bottom of a page may not reflect a real agreement with the content of the document”⁶⁰. Hence, there is wide recognition that, in principle, despite the need of an assiduous effort towards the possibility of obtaining written consent, based on the context, it is appropriate to explore other ways of demonstrating that consent has been actually and consciously expressed. Nevertheless, the IBC does not specifically apply literacy issues to gender considerations. In this context, the German Working Party of research ethics committees⁶¹ has developed and published samples for informed consent, which are documents for clinical trials with medicinal products on healthy volunteers or patients and for collecting materials for biobanking, recommended to sponsors. Even though they are not adapted to gender, these documents stress that the oral information process must take account of the background and abilities of the person concerned.

In Canada, a set of initiatives have been carried out to provide guidance on women enrolment in clinical research by issuing a number of documents in this area, which are particularly interesting for their major focus on tailoring the informed consent process to female peculiarities in terms of communication skills: particularly, in 2006, the Canadian Working group on Women and Health Protection published a document on *The Inclusion of Women in Clinical Trials: Are We Asking the Right Questions?*, placing a strong emphasis on the need to adapt consent forms to women’s specificities and literacy levels and overcoming the “pro-forma” model⁶².

The Working Group therefore recommended that efforts be made to ensure consent forms are “userfriendly”, without leaving out important informational content in order to be able to give an actual consent, well aware of the potential benefits and risks related to enrolment. In addition, Canadian guidelines raise awareness about the possibility of gender-based differences in how the informed consent process is carried out, due to potential gender and class-based diversities in doctor-patient relationships. These guidelines equally stress the importance of making “reader-friendly” summaries of trial protocols easily available and envisaging the development and use of multiple means of communication (i.e. Internet, print, oral, multiple languages, etc.), to ensure all women can have ac-

⁶⁰ UNITED NATIONS EDUCATIONAL, SCIENTIFIC AND CULTURAL ORGANIZATION (UNESCO) IBC, *Report On Consent*, 2008, p. 35.

⁶¹ WORKING PARTY OF RESEARCH ETHICS COMMITTEES IN GERMANY, *Merkblatt zur Verwendung der Mustertexte für die Patienten-/Probanden-information und – einwilligung empfohlen vom Arbeitskreis Medizinischer Ethik-Kommissionen gemäß Beschluss*, 2008.

⁶² The Canadian Working Group on Women and Health Protection clarified that “this requires attention both to informed consent material, and the informed consent process. Given literacy levels of women and the complexity of forms, there are concerns about women expressing truly authentic consent to trial participation. And even with women who are print literate, other factors related to expectations of medical care, understanding of random assignment, placebos, and of probability, can compromise the ability to give truly informed consent”. See CANADIAN WORKING GROUP ON WOMEN AND HEALTH PROTECTION, *The Inclusion of Women in Clinical Trials: Are We Asking the Right Questions?*, 2006, p. 26.

cess to complete and accurate information, combined with related materials⁶³. All these tools are meant to guarantee full understanding of the research process with a gender perspective. Institutional documents particularly underline a number of key elements pertaining to the consent process, whenever enrolling women of childbearing potential: in this case, clinical trial participants should be duly informed, alongside all other risks, about the potential risks of reproductive and foetal toxicity, including teratogenicity and about pregnancy prevention, so that prospective subjects understand how and when to take precautions (i.e. use of reliable methods of contraception and/or abstinence, pregnancy testing) to prevent pregnancy, if necessary within the trial. Moreover, Health Canada recommends that a statement on the effectiveness of contraception methods should be included in all informed consent forms requiring contraceptive guidance, as well as a clear list of the contraceptive methods suggested. Whenever relevant information is not available from reproductive toxicity studies, the informed consent form should explicitly note that embryo-foetal risk cannot be excluded⁶⁴.

7. Sensitive issues related to the acquisition of informed consent

7.1. The role of the pregnant woman's partner in the informed consent process

Clinical studies involving female or male reproductive health may raise issues surrounding the potential effect of the study on the participant's partner. According to the ACOG Committee on Ethics, "in the absence of a few specific scenarios, requiring participation consent from a woman's partner is neither warranted nor ethically justified"⁶⁵ (for instance, in cases of general medical care or whenever pregnancy decisions are involved). It is deemed appropriate if there is a risk of the partner's exposure to an investigational agent and this is likely to carry more than a minimal risk or if data regarding him will be collected; or if testing of a partner is required for a woman to participate in a study (eg. semen analysis or testing for a sexually transmitted infection). Beyond these circumstances, the consent of the woman's partner is not advisable, since it may hinder the woman's decision with regard to health issues.

Conversely, a more balanced position is expressed by CIOMS: even if it firmly states that a partner can never replace the consent of the woman, whenever the latter expresses willingness to seek her partner's advice before making a decision with regard to potential participation in research, this possibility should be granted⁶⁶.

⁶³ CANADIAN WORKING GROUP ON WOMEN AND HEALTH PROTECTION, *The Inclusion of Women in Clinical Trials: Are We Asking the Right Questions?*, cit., pp. 26-27.

⁶⁴ HEALTH CANADA, *Guidance Document: Considerations for Inclusion of Women in Clinical Trials and Analysis of Sex Differences*, 2013, p. 5.

⁶⁵ THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS (ACOG), Committee on Ethics, *Ethical Considerations for Including Women as Research Participants. Opinion n. 646*, cit., p. e103.

⁶⁶ COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, Guideline n° 19, cit., p. 72.

7.2. An ethical reflection on pregnancy/breastfeeding and the role of the man's pregnant partner or of childbearing potential in the informed consent process

The Belgian Advisory Committee on Bioethics has dealt twice with the topic of pregnant women's participation in research: in 2004, it issued a first *Opinion regarding experiments on pregnant and breastfeeding women*⁶⁷ and, in 2015, a second one on *The Ethical implications of the "Statute" of the Pregnant Partner of a Male Participant in a Clinical Trial*⁶⁸, in which it provided a detailed description of key ethical and legal issues related to the informed consent process in the context of pregnancy. In its *Opinion n° 31 regarding experiments on pregnant and breastfeeding women*, the Belgian Advisory Committee on Bioethics, noted that research ethics committees should take into account the various stages of pregnancy that are linked with a totally different set of risks (i.e. possible effects on germ cells or the implantation of fertilized eggs cells, potential teratogenic effects, possible embryotoxic effects and the impact on the physiological changes caused by pregnancy) when assessing protocols for experiments on pregnant women. Hence, in terms of safety, an appropriate analysis of the many underlying issues should differentiate the different stages involved in the process: before conception; the first week of the pregnancy; the second week up to and including the eighth week; the second and third trimesters and the delivery. Research involving pregnant women may be conducted for different reasons, which raise a number of specific ethical issues, ranging from research into problems specific to pregnancy (i.e. pregnancy-related pathological complications such as repeated miscarriages) to physiological or physiopathological research (for instance, concerning circulatory changes during pregnancy). In this case, both the mother and the child may benefit from the study and its results, since they are relevant to the goals of the research. In other cases, trials can be carried out to look into pathological conditions that are not linked to pregnancy, but that occur in pregnant women and, therefore, result in diagnostic or therapeutic problems (for instance, the diagnosis or treatment of hyperthyroidosis). Here, concern is mostly for any adverse effects on the unborn child that could be caused by the drug used; whereas, the benefits to the foetus are generally less important. The Belgian Committee equally recalled different types of research directed at benefitting the foetus (i.e. pathological conditions generally affecting the foetus). These studies may also include investigations into the extent to which treatment can protect mother-to-child transmission of HIV virus⁶⁹.

In the context of interactions between gender and multicultural issues, emphasis was placed on the fact that an over-representation of women belonging to socially disadvantaged or minority groups should be avoided, as their decision to enrol in a trial may be influenced by receiving free medical care. Likewise, they should not be systematically excluded either; nevertheless, it is important to make sure they actually have fully understood the consent form presented to them⁷⁰.

⁶⁷ BELGIAN ADVISORY COMMITTEE ON BIOETHICS, *Opinion n° 31 of 5 July 2004 regarding experiments on pregnant and breastfeeding women*, 2004.

⁶⁸ BELGIAN ADVISORY COMMITTEE ON BIOETHICS, *Opinion n° 62 of 12 October 2015 on the Ethical Implications of the "Statute" of the Pregnant Partner of a Male Participant in a Clinical Trial*, 2015.

⁶⁹ BELGIAN ADVISORY COMMITTEE ON BIOETHICS, *Opinion n° 31 of 5 July 2004 regarding experiments on pregnant and breastfeeding women*, cit., p. 2.

⁷⁰ BELGIAN ADVISORY COMMITTEE ON BIOETHICS, *Opinion n° 31 of 5 July 2004 regarding experiments on pregnant and breastfeeding women*, cit., p. 5.

Moreover, considerable attention has been focused on the role of the man's fertile or pregnant partner in the consent process. This issue arises from the fact that some drugs being tested in clinical trials are potentially toxic for gametes or foetuses, resulting in possible consequences for any offspring conceived during the study. The Belgian Committee addressed this topic in the context of toxicity caused by the sperm of a male participant or when toxicity affects the gametes of a male participant. Its focus was on whether it would be necessary to request the pregnant partner's consent prior to research participation. Because of the sensitiveness of this issue, the Committee underlined the importance of a thorough and adequate informed consent process, with the duty to inform the male participant in a complete, clear and understandable manner regarding the potential medical risk of the test product for both the participant himself and his partner. In this perspective, it is primarily the responsibility of the sponsor to limit the risks related to the study to a minimum. In addition, a number of specific recommendations are made on the informed consent process⁷¹. However, no compulsory requirement to obtain the consent of the male participant's fertile or pregnant partner is suggested. The Italian NBC does not specifically address the issue of acquiring consent from a male participant's partner, but equally recommends that the informed consent and commitment to avoid procreation should apply to men participating in a clinical trial, which carries a risk of harm to the foetus through their gametes⁷².

8. Conclusions

In order to improve the informed consent process with a gender perspective, it is important to envisage a set of ethical standards focusing on women's specificities in clinical research, which could contribute to overcoming current ethical challenges, that were discussed in this paper in relation to their inclusion: first, possible interactions between changes in women's physiological conditions and the use of experimental pharmaceuticals should be clearly conveyed in the informed consent process, with regard to the implications related to the fertility condition and the possible pregnancy and possible damages to the embryos and foetuses. The informed consent must highlight benefits and any possible risks (specifying the extent, envisaged or potential) for embryos and foetuses in case of pregnancy. Second, a fertile woman should be aware and fully informed of methods to avoid pregnancy before, during and after the trial (the period of risk is to be defined and communicated according to the type of trial). This information should be clearly provided by the researcher, respecting the woman's choices and moral or religious convictions. Communicating contraception requirements should also include referring to any inherent risks related to its use.

⁷¹ According to the Belgian Advisory Committee on Bioethics, the informed consent process should include: "1) the period of risk exposure; 2) that the pregnancy of the partner or a refusal to use double contraception are considered to be exclusion criteria; 3) that the participant is encouraged to inform his partner about his participation in a clinical trial; and that the sponsor of the clinical trial formally declares to be prepared to answer the questions of the participant's partner". See BELGIAN ADVISORY COMMITTEE ON BIOETHICS, *Opinion n° 62 of 12 October 2015 on the Ethical Implications of the "Statute" of the Pregnant Partner of a Male Participant in a Clinical Trial*, cit., p. 10.

⁷² ITALIAN COMMITTEE FOR BIOETHICS (NBC), *Opinion on Pharmacological trials on women*, cit., p. 19.

Indeed, the woman should be given a fair amount of time and appropriate environmental conditions to make her free and informed decision and be aware of the possibility for her to revoke consent, at any time, during research, as well as informed of any envisaged risks also after experimentation.

Third, definitions of minimum risk and burden or above this minimum threshold should be provided in the context of clinical research, especially when dealing with fertile, pregnant or breastfeeding women. This information should be clearly explained and communicated before any decision to participate is made.

Fourth, for clinical trials including pregnant women, follow-up of the pregnancy, foetus and child is essential, even for several months after the end of the study. This safety requirement should be clearly communicated during the informed consent process.

If research is carried out on breastfeeding women, participants should be adequately informed of the need to monitor the possible excretion of the drug into human milk, as well as their babies for the effects of the drug. Fifth, pregnant or breastfeeding women should be encouraged to involve their partners in the informed consent process. The degree of involvement of partners may be adapted to participation risks and requires the elaboration of adequate criteria, which need to be explicitly mentioned before experimentation.

Equally, men participating in research which is potentially toxic for gametes or foetuses should not only receive clear and detailed information on the risks linked to their enrolment, but also be requested to involve their fertile or pregnant partners in the consent process. Criteria for their involvement should also be defined.

Sixth, researchers must make sure that women from vulnerable social contexts, and with low literacy levels, have fully understood all benefits and risks related to clinical research enrolment and freely consented to participate. They should devise adequate tools to verify appropriate comprehension levels of what is at stake through a participant-tailored approach to communication.

Caution is especially needed whenever low-income women are enrolled in research, in order to make sure they have not been coerced (through social conditioning or pressures by medical staff or research team) or unduly influenced (financially or offering better healthcare) to participate, in ways that would lead these women to accept a higher level of risk than would otherwise be acceptable to them. It is of paramount importance to verify that there is no underestimation of such aspects due to other priority interests.