ETHICS COMMITTEE
MEDICAL UNIVERSITY VIENNA

GUIDELINES REGARDING THE INCLUSION OF WOMEN IN CLINICAL RESEARCH

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AIM OF THE GUIDELINES

The guidelines describe the requirement for the inclusion of women in biomedical and behavioral research involving human subjects (i.e. clinical research) - including clinical drug trials.

Clinical research is defined as

- Patient-oriented research, including mechanism of human disease, therapeutic interventions, clinical drug trials and development of new technologies
- Epidemiologic and behavioral studies
- Outcomes research and health services research

Since a primary aim of clinical research is to provide scientific evidence leading to improve standard of care and/or a change in health policy, it is important to determine whether the intervention or therapy being studied affects women or men differently.

DEFINITION OF THE POPULATION

The population of concern in this guideline includes women of child-bearing potential and post-menopausal women.

A decision to enroll pregnant or lactating women in a specific research project must be individualized and based on a careful risk/benefit assessment taking into consideration the nature and severity of the disease, the availability and results of preclinical animal data, the availability and risks associated with alternative therapy, the stage of pregnancy and the potential for harm to the fetus or infant.

GENERAL RESEARCH INVOLVING HUMAN SUBJECTS

Policy

It is policy of the Ethics committee that both genders should be included in all biomedical and behavioral research projects involving human subjects in scientifically appropriate numbers. Women of childbearing potential should not be routinely excluded from participation in clinical research, but appropriate measures to exclude potential fetal damage must be taken (see below).

If one gender is excluded, the reason must be clearly stated in the study protocol.

One gender can be excluded because one of the following applies:

- Inclusion is inappropriate with respect to their health
- Research question is relevant to only one gender
- Prior evidence strongly suggests no gender difference
- Data exists for excluded gender
- Subject selection is constrained due to purpose of the research
- Other scientific reasons

Cost is not an acceptable reason for exclusion.

CLINICAL DRUG TRIALS

Statement of purpose

It is important to ensure that women are enrolled in clinical trials at all stages of drug development in order to define the risks and benefits associated with drug therapy in this segment of the population. Since physiological changes and hormonal levels during years of child-bearing potential and menopause, as well as the use of oral contraceptives or hormone replacement therapy, may affect the efficacy and safety of a drug, the influence of these parameters should be studied during drug development.

General principle

Drugs should be studied prior to approval in subjects representing the full range of patients likely to receive the drug once it is marketed. Although in most cases, drugs behave in a qualitatively similar manner in demographic (sex, age, race) and other (concomitant illness, concomitant drugs) subsets of the population, there are many quantitative differences, for example, in dose-response, maximum size of effect, or in the risk of an adverse event. Optimal use of drugs requires identification of these factors so that appropriate adjustments in dose, concomitant therapy and monitoring can be made.

The intention of this guideline is to encourage the inclusion of women, especially those of child-bearing potential at the earliest stages of drug development, in order to ensure that potential sex-related differences are being identified and taken into consideration when generating appropriate data to inform both physicians and potential users concerning sex-related characteristics of a new drug.

The Ethics Committee is committed to a policy of enrolling women in the earliest stages of drug development, but is also concerned about potential fetal exposure and potential fetal damage. It is our opinion that exclusion of women from early trials is not necessary because in accordance with good medical practice, appropriate precautions against becoming pregnant and exposing a fetus to a potentially dangerous agent during the course of a study will be taken by women participating in

clinical trials. It is also expected that women will receive adequate counseling about the importance of such precautions prior to entry into the trial. Details are to be addressed in the Patient Information and Informed Consent Form.

Scope of the guideline

This guideline is directed principally toward new active substances (including biological products and radio pharmaceuticals), as well as new uses, new formulations, or combinations of approved drugs that are likely to be used by women.

Policy

The guideline proposes the inclusion of women in clinical trials from the earliest stages of drug development.

INCLUSION OF BOTH GENDERS IN CLINICAL TRIALS

Patients of both genders should be included in the same trials, if possible in numbers adequate to allow detection of clinically significant sex-related differences in drug response

If there is a scientific reason to include only one gender in a study, this must be clearly stated in the protocol.

For example in some cases it may be appropriate to conduct studies in a single gender - e.g. to evaluate the effects of phases of the menstrual cycle on drug response – (see above).
Although it may be reasonable to exclude certain patients at early stages because of characteristics that might make evaluation of therapy more difficult (e.g., patients on concomitant therapy), such exclusion should usually be abandoned as soon as possible in later development so that drug-drug and drug-disease interactions can be detected. Thus, for example, there is ordinarily no good reason to exclude women using oral contraceptives or estrogen replacement therapy from clinical trials. Rather they should be included and differences in response between them and patients not on such therapy examined.

PRECAUTIONS IN CLINICAL TRIALS INCLUDING WOMEN OF CHILDBEARING POTENTIAL

In accordance with good medical practice, clinical protocols should include measures that will minimize the possibility of fetal exposure to the investigational drug. These would ordinarily include providing for the use of a reliable method of contraception for the duration of drug exposure (which may exceed the length of the study), and use of pregnancy testing prior to initiation of study treatment and at monthly intervals during treatment, depending on the length of the study.

It is also expected that women will receive adequate counseling about the importance of utilizing a reliable method of contraception and will be fully informed about the current state of animal reproductive studies and any other information about the teratogenic potential of the drug. This is essential when there exists a possibility that the new drug product may lessen the effectiveness of a hormonal contraceptive agent. In this case, patients should be advised to use a supplementary, non-hormonal method of contraception for the duration of the drug exposure.

In all cases, the Informed Consent document and the Investigator's Brochure should include all available information regarding the potential risk of fetal toxicity. If no relevant information is available, the informed consent should explicitly note the potential for fetal risk. In general, it is expected that reproductive toxicity studies will be completed before women of childbearing potential are enrolled in large scale and/or long-term Phase II and III studies during which significant drug exposure may occur.

POTENTIAL EFFECTS ON FERTILITY

Where abnormalities of reproductive organs or their function have been observed in experimental animals, the decision to include patients of reproductive age in a clinical study should be based on a careful risk-benefit evaluation, taking into account the nature of the abnormalities, the dosage needed to induce them, the consistency of the findings in different species, the severity of the illness being treated, the potential importance of the drug, the availability of alternative therapy, and the duration of therapy. Where patients of reproductive potential (this should apply to both genders) are included in studies of drugs showing reproductive toxicity in animals, the clinical studies should include appropriate counseling on the utilization of reliable methods of contraception, monitoring, and/or laboratory studies to allow detection of these effects.

Long-term follow-up will usually be needed to evaluate the effects of such drugs in humans. Patients should be made aware of the findings in animals, and the need for long-term follow-up, prior to study entry.