Position on Revision of Clinical Trials Directive

The EIWH welcomes the Commission's intention to revise the European Clinical Trials Directive 2001/20/EC (CTD) and awaits impatiently the draft proposal.

Disappointingly for the research community and patients alike, the 2001 Directive failed in some ways to create an optimal environment for clinical research in Europe. Rather than facilitating innovation, the current legislation impeded the development of innovative collaborative research by the imposition of an excessively complex bureaucratic process.

The EIWH considers the CTD revision not only an opportunity to incorporate lessons learned from the past, but also to examine ways in which this European regulatory instrument may be better adapted to future research needs. We are particularly eager to see a move towards "personalised medicine" tailored to individual biological and environmental circumstances for patients of all ages. It goes without saying that the safety of patients during the Clinical Trial is of utmost importance and indeed the patient's interest must be the central concern both during and after a trial.

The EIWH wishes to focus its comments on two very specific issues:

Women in clinical trials
Older people and clinical trials

Women in clinical trials

Historically the research community has been reluctant to include women in clinical trials for safety reasons. Following the Thalidomide tragedy in the 1950s, women of childbearing age were excluded from trials due to the fear of exposing the unborn child to investigational procedures. Gradually this ban has been relaxed as women were better able to control their fertility.

Today, we know that sex differences, being male or female, encompass much more than reproductive organs. There is an increasing recognition that both biological factors and gender affect health - for women and men. Awareness is rising that a person's sex may differentially influence genetic predisposition, the impact of both environmental and biological risk and protective factors, time of onset, symptoms and

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the progression of many diseases. Sex may also influence the effectiveness of medication and its duration. All this knowledge has increased our understanding of a range of diseases and consequently enhances our ability to intervene more effectively.

It has become apparent that many physiological and pathological functions are influenced by sex-based differences in biology. "Differences also exist at the basic cellular and molecular levels".[1]

Some treatments work differently in women and men, but the proportion of treatments for which men and women respond differently is yet unknown. The broader issue really centers on biological factors, possibly defined by genes or gene expression that may directly or indirectly modify the effect of specific treatments on specific individuals.[2]

We would therefore urge that in the revision of the Directive the Commission takes the following points into consideration:

Make inclusion of women in clinical trials explicit and the numbers included statistically relevant to allow for systematic analysis of sex differences.

In addition to including women in clinical trials in numbers that match the prevalence of the disease in the general population, the trial must be constructed in such a way that it allows for a **systematic analysis of sex differences.** It is a common misunderstanding that taking sex into account by adjustment in statistical analyses is all that is needed to exclude sex differences. This procedure only eliminates the possibility that sex is a confounding factor. Stratified analyses should be carried out separately for men and women to take into account the fact that a treatment may not only have a different effect in men and women, but that secondary factors influencing efficacy, treatment adherence and side effects may also be different. Furthermore we should not only be recruiting both men and women into studies, but ensuring that even at the molecular level we are using both male and female cells.

A recent Nature article argues that "gender inequalities in biomedical research are undermining patient care". The article calls for the "sex bias in basic research and clinical medicine to end".[3]

The GenderBasic project funded under FP6 has developed recommendations and tools for the improved integration of sex and gender differences in biomedical and health-related research.[4]

In 2006 EMA published the document entitled "ICH - Gender considerations in the conduct of clinical trial" which summarises the different ICH guidelines that refer to women and reviews the regulatory environment for women in trials worldwide. The EMA document states that while women appear to be participating in all phases of study development, participation is lower in early Phase I and I-II studies. However, these are the studies in which safety, safe dosage range and side effects are

[1] Exploring the biological contributions to human health: Does sex matter? Institute of Medicine http://www.nap.edu/catalog/10028.htm

[2] Inclusion of women in clinical trials
Jesse A Berlin and Susan S Ellenberg http://www.biomedcentral.com/1741-7015/7/56

[3] Nature vol 465, issue no 7299, 10 June 2010

[4] http://www.genderbasic.nl/

determined. Leaving such examination until a later date, the authors of an article in Epidemiology Community Health warn "that when women are excluded, any specific dosing requirements for them will remain undiscovered until much later in the drug development process, if ever."[5]

Some examples:
In cardiovascular disease (CVD), the leading cause of death for both men and women, the differences are especially noticeable and can endanger the life of women. Women present different symptoms from men and these are not readily recognised as diagnostic standards were mainly established in men. This means that often potential life-saving treatment is given too late. More women die after a heart attack than men. Stroke is another such example. "The European Heart Health Strategy, co-funded by the Commission, reviewed 62 randomised clinical trials and analysed them for gender-specifity, concluding that women are generally under-represented and only half of the trials reported the analysis of the results by sex/gender".[6] On the other hand, osteoporosis has rarely been recognised or studied in men as it was considered a condition affecting post-menopausal women.

Differences are also observed in the field of auto-immune diseases: lupus, rheumatoid arthritis, and multiple sclerosis, some psychological disorders: schizophrenia, autism, eating disorders, asthma and several types of cancer, sex differences in sensory perception and pain, and the manifestations of Alzheimer's. Several studies document that men and women respond differently to medicines and therapies. It appears that women have a higher susceptibility to adverse drug reactions (ADRs). According to Rademakers "Female patients have a 1.5- to 1.7-fold greater risk of developing an ADR, including adverse skin reactions, compared with male patients."[7]

Improve participation of older people in clinical trials
Older people are generally excluded from clinical trials; the cut off age is around 65 years. Therefore the evidence base for clinical decision-making in older people is poor, although older people are the biggest users of health services including medicines.

Between 2010 and 2030, the number of Europeans aged over 65 will rise by nearly 40%, posing challenges for healthy ageing and healthcare budgets. People 65+ will account for 30% of the EU population compared with 17% in 2008.
Women make up the largest proportion of the older population and are the heaviest users of medicines. The fastest growing age group is 85+ and is mostly female.

Older people use more than 30% of prescribed medicines and more than 40% of over the counter medicines. Moreover, in some countries, they account for up to 60% of total pharmaceutical expenditure. In addition, the percentage of older people who take several medicines for various chronic conditions is high and on the increase. Older people also have the highest risk to develop Adverse Drug Reactions (ADRs). In Europe, ADRs cause 20% of physicians' visits as well as up to 30% of hospital admission. Older people show different pharmacokinetics, the way a medicine moves through the body and pharmacodynamics and have different ADRs from younger adults. Some conditions are specific to older people.

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[5] Epidemiol. Community Health. 2006 November, 60(11), 911-913, BMJ Publishing Group Ltd, European Medicines Agency policies for clinical trials leave women unprotected by Maria Teresa Ruiz Cantero, Maria Angeles Pardo

[6] European Heart Network Annual report 2010

[7] Rademaker M, Department of Dermatology, Health Waikato, Hamilton, New Zealand. rademaker@xtra.co.nz
American Journal of Clinical Dermatology [2001, 2(6):349-51]).

Despite the above, medicines are not routinely tested for the specific use in older people.

Recognising this lack in addressing the needs of an ageing population, the European Medicine Agency (EMA) published its geriatric medicines strategy in February 2011. This is a welcome step in the right direction.

The strategy aims to:

- ensure that the medicines used by older people are of high quality and are studied appropriately in the older population, both before and after authorisation;
- improve the availability of information for older people on the use of medicines[8]

Many older people place a high value on their quality of life and ability to live autonomously. This means that clinical research in older people may require different endpoints. Older people are usually subject to several diseases at one time and this requires special attention to avoid medicines counter- or interacting with each other, harming the patient.

The diseases burden and loss of function increases considerably with advancing age and there are differences in health status between the 'younger' older person and the 'frailer' older person. Additionally a person can be 'old' at age 60 and relatively 'young' at 80.

All these factors highlight the need for special attention to be given to the development and use of medicines for older people.

The revision of the CTD is an opportunity to take account of the differences between men and women, as well as age-specific factors and include both men and women and older people in trials to improve the treatment.
Incorporating sex, gender and age into clinical research is good science and an imperative as we move into the age of more personalised medicine and keeping Europe research on the forefront of innovation as outlined in the 2020 Strategy.

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[8] www.**ema**.europa.eu/**ema**/index.jsp?curl=pages/