

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Diversity in CNS Clinical Trials

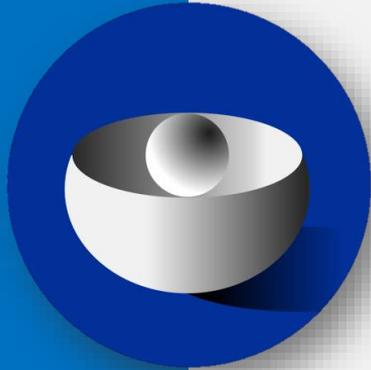
EMA REGULATORY COMMENT

ISCTM/ECNP 2021 Joint Session

Presented by Florence Butlen-Ducuing on 30 September 2021

An agency of the European Union





- **No CoI**
- **Personal views, not from EMA or one of its scientific Committees/WPs**

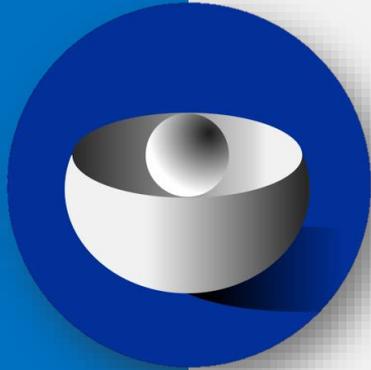


Diversity: a range of many people or things that are very different from each other



What it means for drug development clinical trials ?

- Efficacy and safety may differ among population subgroups depending on sex, age, ethnicity, genetic background...
 - Women may respond differently than men, members from one ethnic group may respond differently than those from another one...
- Diversity of clinical trial participants to help ensure that
 - trial population is representative of the patients who will use the medicine
 - results are generalisable.



OUTLINE

- ✓ **Example of sex-related differences in CNS disorders**
- ✓ **Implications for drug research and development**



Sex: a binary biological variable based on the presence of either X or Y in the 23rd chromosome pair and refers thereby to characteristics that are genetically determined.



Gender:

describes characteristics of women, men and other non-binary categories that are socially constructed (norms, roles and relations).



Women in CNS Clinical trials

[nature](#) > [nature reviews drug discovery](#) > [comment](#) > [article](#)

COMMENT | 05 July 2021

Implications of sex-related differences in central nervous system disorders for drug research and development

Research on sex differences in central nervous system disorders has developed substantially in recent years. Here, we discuss selected examples and the implications for drug development.

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Sex-related differences

- ❑ Many medical conditions, including several CNS disorders.
- ❑ Not yet fully understood, multifactorial
- ❑ Prominence of Women in some CNS Disorders (AD, depression, meningioma, some pain disorders, migraine, panic disorder or multiple sclerosis..)
- ❑ Women tend to be less affected than men in other CNS Disorders (PD, ADHD, ASD..)
- ❑ Type and course of symptoms
- ❑ Responses to medications
- ❑ Clinical scales/Biomarkers
- ❑ **Various reasons: Genetic/ lifestyle risk factors / Hormonal fluctuations**



Implications of sex-related differences for drug research and development



Implications for drug discovery



Implications for drug response



Implications for clinical trials

Implications for drug discovery



- ❑ Several animal models demonstrated sex-specific differences
- ❑ Fewer preclinical studies in female animals
- ❑ To start preclinical research with mixed-sex cohorts and examine data for potential sex differences.
 - ❑ If no clear sex differences : mixed-sex cohorts and then mixed clinical trials.
 - ❑ If data suggest a sex difference: studying cohorts of each sex may be considered in preclinical and clinical settings



Implications for drug response



- To obtain PK/PD data for both sexes
- To consider if human dose finding studies should include or not a design for potential sex differences
- To try and find the optimal dose
- Safety:
 - Differences in PK/PD characteristics may also be associated with different adverse drug reactions in both sexes
 - To consider label changes based on post-marketing data?

Implications for clinical trials

Trial design Questions



1

Adequate representation of men and women

Proportional rep in CTs compared to disease prevalence rates

2

Sex-adjusted clinical scales

✓ Scales for many diseases are not sensitive to sex differences in baseline performance, disease course and symptoms

3

Sex-adjusted biomarkers

✓ Whether and how different outcome measures based on sex should be used within the same trial?

4

Patient stratification based on sex

- ✓ Stratification by sex is not a formal requirement
- ✓ When to conduct separate analysis for male and female ?
- ✓ Early stratification to allow for a pivotal trial in only one sex?

Continuous dialogue between stakeholders

- ❑ Research in women and men
- ❑ Pre-clinical Models
- ❑ Sex-adjusted clinical tools/adjusted outcome Measures/BMs
- ❑ Sex-adjusted clinical trial methodology
- ❑ Interactions between stakeholders ++





Any questions?

Further information

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