EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

The ICH E9 Addendum on "Estimands and Sensitivity Analysis in Clinical Trials"

Issues with the previous way of planning trial and opportunities with the new framework

16th Annual Meeting of the ISCTM

Presented by Florence Butlen on 20 February 2020
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Outline

- The insufficiency of the previous way of planning clinical trials
- The aspects and opportunities of the new framework

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- The insufficiency of the previous way of planning clinical trials
- The opportunities with the new framework

How to understand treatment effects?

- For regulatory approval a medicinal product should have therapeutic efficacy and a positive risk-benefit.
- Treatment effects are estimated from clinical trials.
- In addition to evidence that is statistically compelling evidence of efficacy, assessment of efficacy considers the magnitude of the beneficial treatment effects.

The previous framework

Clinical questions were usually characterised following the PICO frame elements.

Element
Patient
Intervention
Comparator
Outcome

The previous framework

Clinical questions were usually characterised following the PICO frame elements.

Element	Example of reasonable definition
Patient	Patients with diagnosis of Major Depressive Disorder and a certain severity at baseline
Intervention	Experimental drug X
Comparator	Placebo
Outcome	Difference in severity score after 6 weeks between patients with MDD assigned to experimental treatment X and placebo.

In an ideal trial…

CASE STUDY

Lurasidone for the Treatment of Major Depressive Disorder With Mixed Features: A Randomized, Double-Blind, Placebo-Controlled Study

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CASE STUDY

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Trisha S
Caroline

METHOD

Patients

This multiregional study enrolled outpatients 18–75 years of age with a diagnosis of major depressive disorder based on DSM-IV-TR criteria, which was confirmed with the Structured Clinical Interview for DSM-IV Disorders–Clinical Trial version, modified to record the presence of mixed symptoms (27) and administered by an experienced and qualified rater. Patients were required to have a current major

CASE STUDY

METHOD

Patients

After a washout period of at least 3 days, patients were randomly assigned, in a 1:1 ratio via an interactive voice/web response system, to receive 6 weeks of treatment with lurasidone or placebo. Study medication was provided in blister packs as

symptoms (27) and administered by an experienced and qualified rater. Patients were required to have a current major

CASE STUDY

METHOD

Lura

Dis Patients

Efficacy Assessments

The primary efficacy endpoint was mean change from baseline to week 6 in MADRS total score. The key secondary

symptoms (27) and administered by an experienced and qualified rater. Patients were required to have a current major

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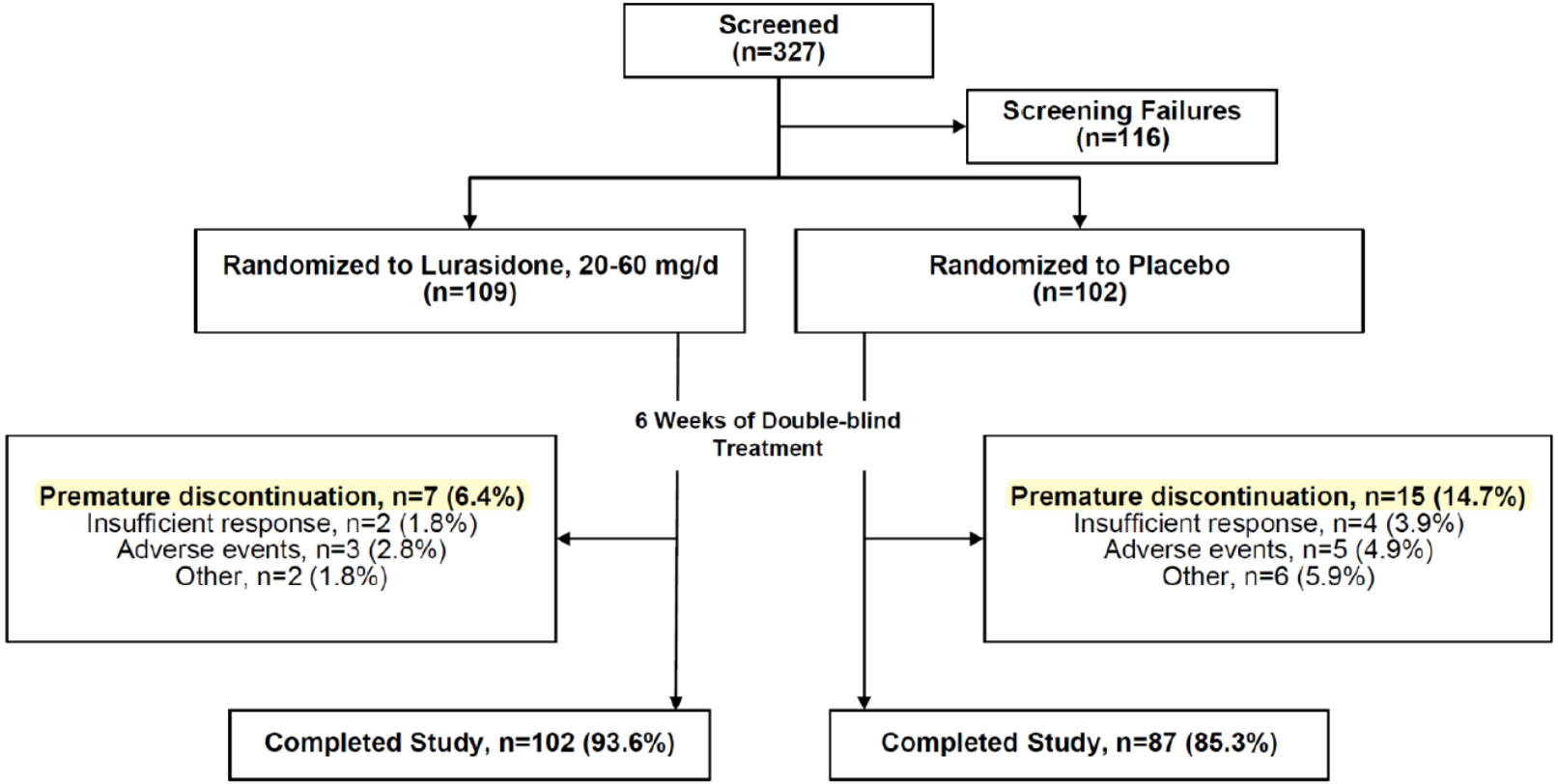


Statistical Analysis

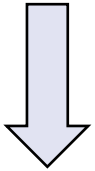
The safety population included all patients who were randomized and received at least one dose of study medication. The intent-to-treat population consisted of randomized patients who received at least one dose of study medication and had at least one postbaseline MADRS or CGI-S assessment. The primary (MADRS) and key secondary (CGI-S) efficacy endpoints, as well as the YMRS, were assessed using a mixed model for repeated-measures analysis including fixed effects for treatment, visit, and pooled center; baseline score as a covariate; and a treatment-by-visit interaction term. An un-

CONCERNS WITH CURRENT PRACTICE

- **intention to treat principle:** the effect of a treatment is assessed by evaluating on the basis of the planned treatment regimen rather than the actual treatment given.
- subjects allocated to a treatment group should be followed up, assessed and analysed as members of that group **irrespective of their compliance to the planned course of treatment**.

CONCERNS WITH CURRENT PRACTICE

- Concerns with the **misalignment** between trial objective, design, planning, conduct, analysis and interpretation in current practice
- There is a risk that:
  - the study will not be designed appropriately to address its objective;
  - the statistical analyses will be misaligned to the trial objective and the target of estimation;
  - the treatment effect that is reported will be incorrectly interpreted, which risks misleading decision makers.



The statistical analysis should be aligned to the agreed target of estimation and not the other way round..

Outline

- The insufficiency of the previous way of planning clinical trials
- The aspects and opportunities of the new framework

Addendum to ICH E9 –Statistical Principles for Clinical Trials ICH E9(R1).

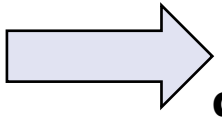
- A new framework for clinical trials.
- To improve the planning, design, analysis and interpretation of clinical trials
- Clear trial objectives should be translated into key scientific questions of interest by defining suitable estimands.
- Having specified an estimand (=WHAT TO ESTIMATE), the addendum addresses impact on trial design, conduct and analysis (=HOW TO ESTIMATE).

Addendum to ICH E9 –Statistical Principles for Clinical Trials ICH E9(R1).

- To align the **target of estimation** with choices on how to handle **intercurrent events**, and on data collection, analysis, **handling of missing** data and **sensitivity analysis**.
- To improve discussions on the suitability of designs and the interpretation of results.
  - **between disciplines** (medics, statisticians, etc).
  - **between sponsor and regulator**

Target of estimation

- Should be relevant to decision makers (e.g. regulators, HTA bodies, payers, prescribers and patients):



Different treatment effects might be relevant to different decision makers.

- Should be clear from the study protocol

Intercurrent events

- Events that occur after treatment initiation and that complicate the description and interpretation of treatment effects:
  - use of an alternative treatment, perhaps a rescue medication;
  - discontinuation of treatment;
  - terminal events such as death.
- **intercurrent events** are addressed in the scientific question of interest.
- External validity : clinical trials are less representative if avoiding the occurrence or the impact of intercurrent events that will occur in clinical practice

MISSING DATA

- greater precision on what is labelled as ‘missing data’.
- patients who discontinue assigned treatment, start another treatment, or die will have sometimes been treated generically as ‘missing data’ causing problems for analysis and inference.
- planning which data need to be collected and hence which data, when not collected, present a missing data problem to be addressed.

Sensitivity analysis

- The addendum gives a revised definition for sensitivity analysis
- With an agreed estimand, and a pre-specified statistical analysis that is aligned to that estimand, sensitivity analysis can focus on sensitivity to deviations from assumptions in respect of a particular analysis, rather than sensitivity to the choice of analytic approach.
- Analyses currently labelled as ‘sensitivity analyses’ can in fact have different targets of estimation (estimands), so that consistent results between analyses should not necessarily be expected.

Any questions?

Further information

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