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Venn Rapporteur

In December 2019, the FDA issued a new draft guidance *Demonstrating Substantial Effectiveness for Human Drug and Biological Products*

The FDA's evidentiary standard for effectiveness has not changed from the one presented in the 1998 *Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.*

However, changes in the types of drug development programs submitted to the Agency have occurred. These include more programs in serious diseases lacking specific treatment and more programs in rare diseases.

These changes created a need for flexibility in the amount and type of evidence needed to meet the substantial evidence standard in such circumstances, hence the new guidance.

Flexibility can affect the design of clinical trials (alternatives to randomized, double-blinded, controlled trials using a superiority design, may be acceptable in given circumstances), the endpoints on which the evidence of effectiveness is based, the quantity of evidence required, the types of mechanistic and pharmacologic evidence and non-clinical evidence that can be used as confirmatory evidence.

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The ICH E9(R1) Addendum

On 20 November 2019, the final draft of the ICH Harmonised guideline E9(R1) "***Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials***" was adopted by the regulatory members of the ICH Assembly under Step 4 of the ICH process and consequently recommended for adoption to the regulatory bodies of ICH regions.

Brief History

The February 1998 ICH E9 "*Note for Guidance on Statistical Principles for Clinical Trials*" set out the principles of statistical methodology applied to clinical trials for marketing applications submitted in the ICH regions.

In October 2014 the ICH Steering Committee adopted a concept paper entitled "*E9(R1):Addendum to Statistical Principles for Clinical Trials on Choosing Appropriate Estimands and Defining Sensitivity Analyses in Clinical Trials*".

This addendum was proposed to provide clarification on ICH E9 and described an agreed framework for planning, conducting and interpreting sensitivity analyses of clinical trial data.

A draft guidance document was prepared and reached step 2 in July 2017. The comments generated by the public consultation were reviewed by the Expert Working Group and led to the final draft being adopted on 20 November 2019.

Purpose & Scope

The addendum aims at filling the need of a common understanding by different stakeholders of the "treatment effect" addressed in a clinical trial. It proposes a **structured framework** aligning the objectives, planning, design, conduct, analysis and interpretation of a clinical trial and strengthening the dialogue between disciplines as well as between sponsor and regulator regarding the treatment effect(s) of interest.

NEWSLETTER AUTHOR

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FDA Guidance for Industry on Adaptive Designs for Clinical Trials of Drugs and Biologics (November 2019)

This new guidance document replaces the first 2010 draft guidance issued by the FDA.

The guidance defines an adaptive design as *a clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial.*

Potential advantages of adaptive designs are: greater statistical efficiency, ethical advantages, improved understanding of drug effects and better acceptability to stakeholders. These advantages come at the price of possible limitations and numerous statistical and logistical challenges.

Challenges of clinical trials using adaptive designs include

- the need of more complex statistical methods to control the type-one error probability (false positives), the risk of biased estimates (and/or confidence intervals) of treatment effect,

- a more complex trial planning with complete pre-specification of the design aspects,

- maintaining the trial conduct and integrity.

- In most cases, intensive simulations will be necessary to identify the best design features (eg. timing and number of interim analyses), the statistical properties of the design (power, type-one error probability and bias) and/or to compare the performances of alternative designs.

Interacting with the FDA is highly recommended when planning an adaptive design, particularly for late-phase, pivotal clinical trials

The Framework

1. Clear **trial objectives** are first defined.
2. They translate in **key clinical questions** of interest.
3. A suitable **estimand** (what is to be estimated) is defined for each question of interest.
4. An adequate method of estimation (the **estimator**) is selected, that will provide a measure of the treatment effect (**estimate**)
5. **Sensitivity analyses** to address the question of the robustness of the inference to deviations from assumptions underlying the estimator are defined.

Intercurrent Events

Intercurrent Events are events occurring after treatment initiation that affect either the interpretation or the mere existence of the measurements associated with the clinical question of interest.

Example of intercurrent events are:

- Discontinuation of assigned treatment
- Use of additional or alternative therapy (introduction or change to background or concomitant therapy, rescue medication, prohibited medication and switching between treatments of interest)
- Terminal events such as death

Note that neither study withdrawal nor other reasons for missing data are in themselves intercurrent events.

Unlike missing data, intercurrent events are not to be thought of as a drawback to be avoided in clinical trials.

Strategies to address intercurrent events

- The **Treatment Policy Strategy**: the occurrence of the intercurrent event is considered irrelevant. The value for the variable of interest is used regardless of whether or not the intercurrent event occurs.
- **Hypothetical Strategies**: specific scenarios in which the intercurrent event would not occur: For example: to address the intercurrent event *use of rescue medication* the question of interest could be defined as the *effect of the treatment if rescue medication was not available*.
- **Composite Variable Strategies**: The intercurrent event is incorporated into the definition of the variable. For example: discontinuation of treatment because of toxicity is considered as a failure if the outcome is success/failure.
- **While on Treatment Strategies:** the values up to the time of the intercurrent event may be considered relevant for the clinical question, rather than the value at the same fixed timepoint for all subjects. An example is palliative pain management for terminally ill cancer subjects.
- **Principal Stratum Strategies**: The clinical question of interest relates to the treatment effect only in the stratum of patients in which a given intercurrent event would occur (or alternatively would not occur). That stratum is called the “principal stratum”. For example: treatment effect on severity of infections in the principal stratum of patients becoming infected after vaccination.

Construction of an Estimand

Four attributes are to be considered when constructing an estimand:

- **The treatment condition of interest** and the alternative treatment condition to which comparison will be made (individual interventions, combinations of interventions administered concurrently, e.g. add-on to standard of care, or overall regimen involving a complex sequence of interventions).
- The **population** of patients targeted by the clinical question: the entire trial population, a subgroup defined by a particular characteristic measured at baseline, or a principal stratum defined by the occurrence (or non-occurrence, depending on context) of a specific intercurrent event
- The **variable** (or endpoint) to be obtained for each patient that is required to address the clinical question. The specification of the variable might include whether the patient experiences an intercurrent event (Composite Variable and While on Treatment strategies).
- A **population-level summary** for the variable should be specified, providing a basis for comparison between treatment conditions.

Example: Type 2 Diabetes Mellitus Trial

From Frank Bretz's presentation at the EFSPI/PSI Workshop on "Estimands and their role in Clinical Trials, September 28, 2015 – Click here

Design: Randomized, 2-arm (drug A and drug B) diabetes trial in patients with type 2 diabetes mellitus (T2DM)

Endpoint: change of HbA1c levels from baseline to after 24 weeks of randomization. HbA1c levels are measured at baseline and at 4, 8, 12, 16, 24 weeks

Patients may switch to rescue medication (and stop study medication) if HbA1c levels are above a given threshold

Assuming (for simplicity) no missing observations and no study treatment discontinuations other than in patient starting rescue medication.

	TREATMENT POLICY ESTIMAND	HYPOTHETICAL STRATEGY ESTIMAND
Population	Intended post-approval population of T2DM patients	
Variable / Endpoint	Change of HbA1c level to baseline after 24 weeks of randomization	
Treatment condition of interest	Effect ***regardless of what treatment was actually received***, i.e. effect of treatment policies 'drug A until start of rescue followed by rescue' versus 'drug B until start of rescue followed by rescue'.	Effect of the initially randomized treatments, ***had all patients remained on their randomized treatment throughout the study without receiving rescue medication***, i.e. effect assuming patients did not receive rescue medication.
Primary statistical model	ANCOVA model using all available data	ANCOVA model Data collected after start of rescue medication are discarded and multiply imputed under a 'missing at random' assumption: borrowing information from patients in the same treatment arm.
Population-Level summary	LS-Mean for between group difference at week 24	LS-Mean for between group difference at week 24
Sensitivity analysis	Include/exclude covariates Include/exclude outliers Relax the normality assumption	Include/exclude covariates Include/exclude outliers Relax the normality assumption Modify the 'missing at random' assumption
Impact on data collection	Patients are followed up for the whole study duration Collection of HbA1c levels post start of rescue medication is needed	HbA1c levels post start of rescue medication are not used in the analysis. Their collection is not necessary

Consequences

The new guidance impacts the way to design clinical trials and to write their protocols. An even closer collaboration between disciplines will be needed to formulate clinical trial objectives, design, conduct, analysis and interpretation. Discussions between sponsor and regulator will determine the treatment effect(s) of interest that a clinical trial should address.

Venn's Methodology and Biometrics experts can support you in defining your estimands, in developing study designs and protocols compliant with ICH E9(R1) and in your discussion with the Regulatory Agencies.

FDA CDER Annual Report "New Drug Therapy Approvals" 2019

In 2019, The FDA CDER approved 48 novel drugs (versus 59 in 2018 and 46 in 2017). Twenty (20) of these 48 novel drugs (42%) were first in class, 21 (44%) were drugs to treat rare or orphan diseases. Expedited development and review pathways were used for 29 (60%) of the 48 novel drugs: Fastrack designation for 17 (35%), Breakthrough Therapy designation for 13 (27%), Priority review for 28 (58%) and Accelerated Approval for 9 (19%).

The most frequent indications were oncologic and neurologic diseases, followed by hematologic and infectious diseases.

33 of the 48 novel drugs approved in 2019 (69%) were approved in the United States before receiving approval in any other country.

Recommended Online Resources

ICH E9(R1): guidance:
https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf
Training:
https://database.ich.org/sites/default/files/E9-R1_EWG_Step2_TrainingMaterial.pdf
EFSPI/PSI European Statistical Meeting on Estimands: 28th Sept 2015:
https://www.psiweb.org/events/past-psi-events/2015/09/28/default-calendar/european-statistical-meeting-on-estimands

FDA draft guidance on Demonstrating Substantial Effectiveness:
https://www.fda.gov/media/133660/download

FDA Final guidance on Adaptive Designs for Clinical Trials of Drugs and Biologics
https://www.fda.gov/media/78495/download

FDA Advancing Health Through Innovation: New Drug Therapy Approvals 2019
https://www.fda.gov/media/133911/download

Get in Touch

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