External Control Arms (ECA) in Phase 3 Trials: What Is Needed Now and in the Future to Enable Acceptance With Regulatory and HTA Bodies?
Speakers & Agenda

Helene Karcher
  • ECA definition & conditions of use

Emma Hawe
  • Methodological considerations

Nicolle Gatto
  • Case examples

Nicole Mittmann
  • Expectations from agencies
Disclosures

• HK is an employee and shareholder of Novartis. She is also the Editor-in-Chief of the journal Epidemiologic Methods.

• The views presented are mine and not those of my employers.

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What is an External Control Arm (ECA)?

ECA: a study arm used as (efficacy) comparator to an active arm from a single-arm trial or an RCT with an insufficient comparator.

**Randomized control trial (RCT)**
- Active arm
- Control arm
- 1:1 Randomization

**Single arm trial with ECA**
- Active arm (single arm trial)
- Control arm with fewer patients (lack statistical power) or a different comparator
- External Control Arm: Built with another source population
  - No randomisation
  - No blinding
Increase in single arm trial submissions to HTA bodies (Patel 2021)
Validity issues with External Control Arm (ECA)

The root cause of validity issues comes from having a data source external to a (Phase 3) trial

- Previous RCTs: historical control or synthetic arm
- Real-world data (RWD)

No randomization, no blinding
Sources of bias* and methodological challenges: see Emma’s part

Example of submissions to FDA with ECA: case of selinexor

Selinexor (XPOVIO) in relapsed/refractory multiple myeloma

First NDA submission with
- Single arm trial STORM
- Comparator built on EHR to demonstrate increase in overall survival

Grounds for FDA rejection
- Methodological considerations
  - Eligibility criteria
  - Index date definition
  - Different distributions of baseline characteristics between single arm trial and ECA
- FDA was only made aware of the ECA at the report stage

Second FDA submission with the Phase 3 RCT «BOSTON»

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212306Orig1s000MultidisciplineR.pdf
Upcoming guidances and consultation opportunities

• Soon-to-be-released guidances on ECAs
  • FDA guidance on ECA: “Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products »
  • EMA draft reflection on the use of single arm trials (and ECA)
  • CADTH guidance on May 16th

• Consultation with health authorities
  • E.g., use FDA « Advancing Real-World Evidence Program» established in Oct 2022
    https://www.fda.gov/drugs/development-resources/advancing-real-world-evidence-program?utm_medium=email&utm_source=govdelivery#Eligibility
Take-aways

• ECAs appear to be more welcome than ever in regulatory and HTA submissions

• A solid justification of the need for a single arm trial + ECA is required from regulators and payers
  • Justification: RCT not feasible due to recruitment, ethics, etc.
  • ECAs acceptable in a wide range of indications and conditions

• Transparency, pre-specification and sound science on the choice of data source, outcomes, analytics are necessary for regulatory / HTA success
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• Epidemiologic Methods
  https://www.degruyter.com/journal/key/em/html

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