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

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Speakers & Agenda

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- ECA definition & conditions of use

Emma Hawe

- Methodological considerations

Nicolle Gatto

- Case examples

Nicole Mittmann

- Expectations from agencies

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cadth Canada's Drug and Health Technology Agency

Disclosures

- HK is an employee and shareholder of Novartis. She is also the Editor-in-Chief of the journal Epidemiologic Methods.
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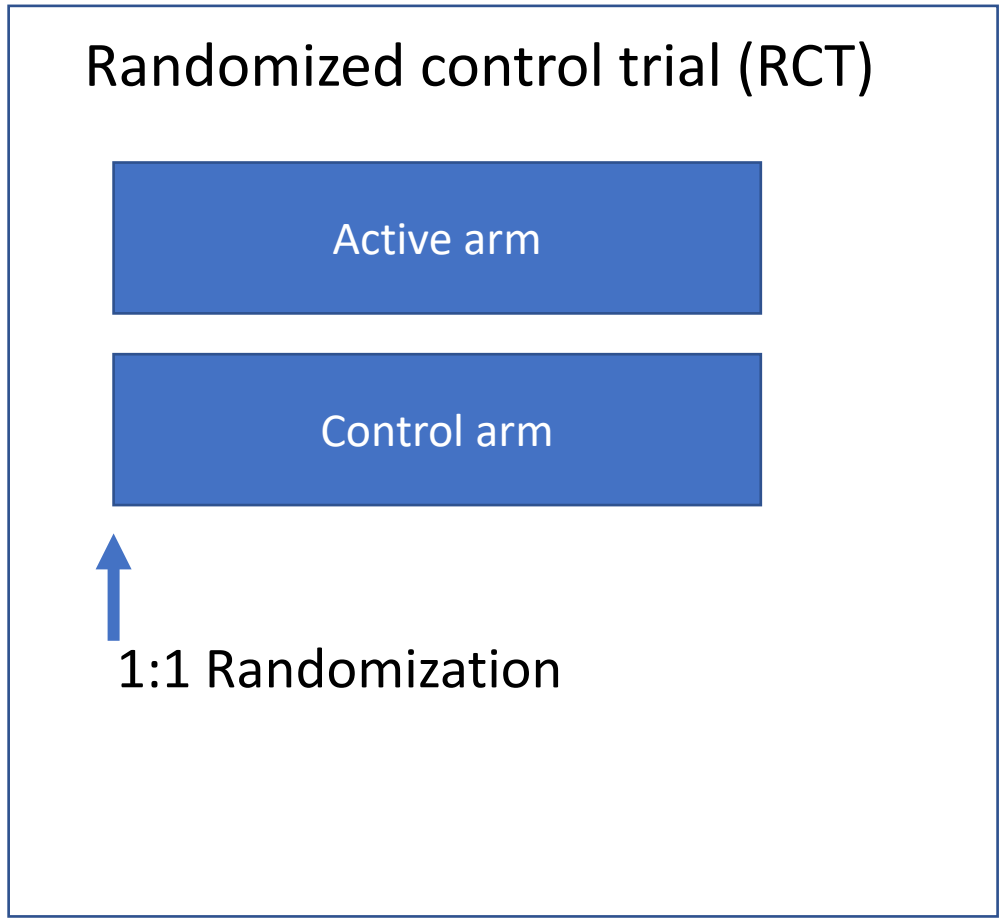
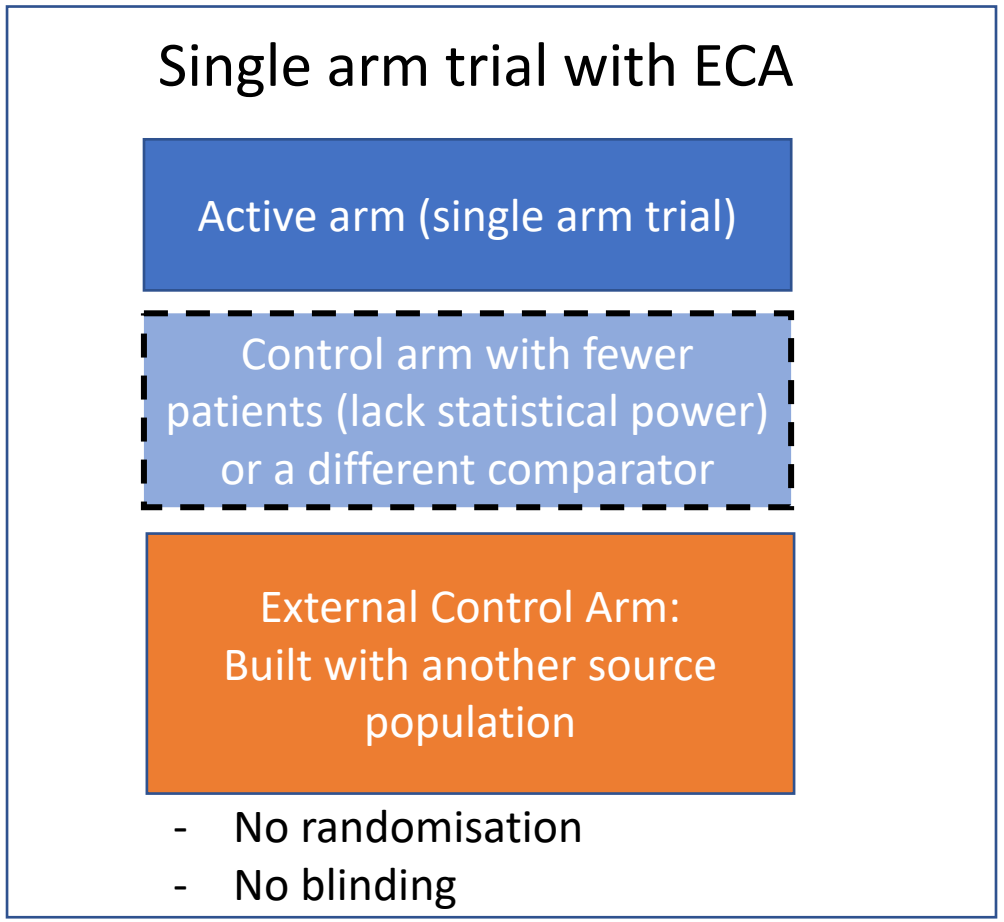
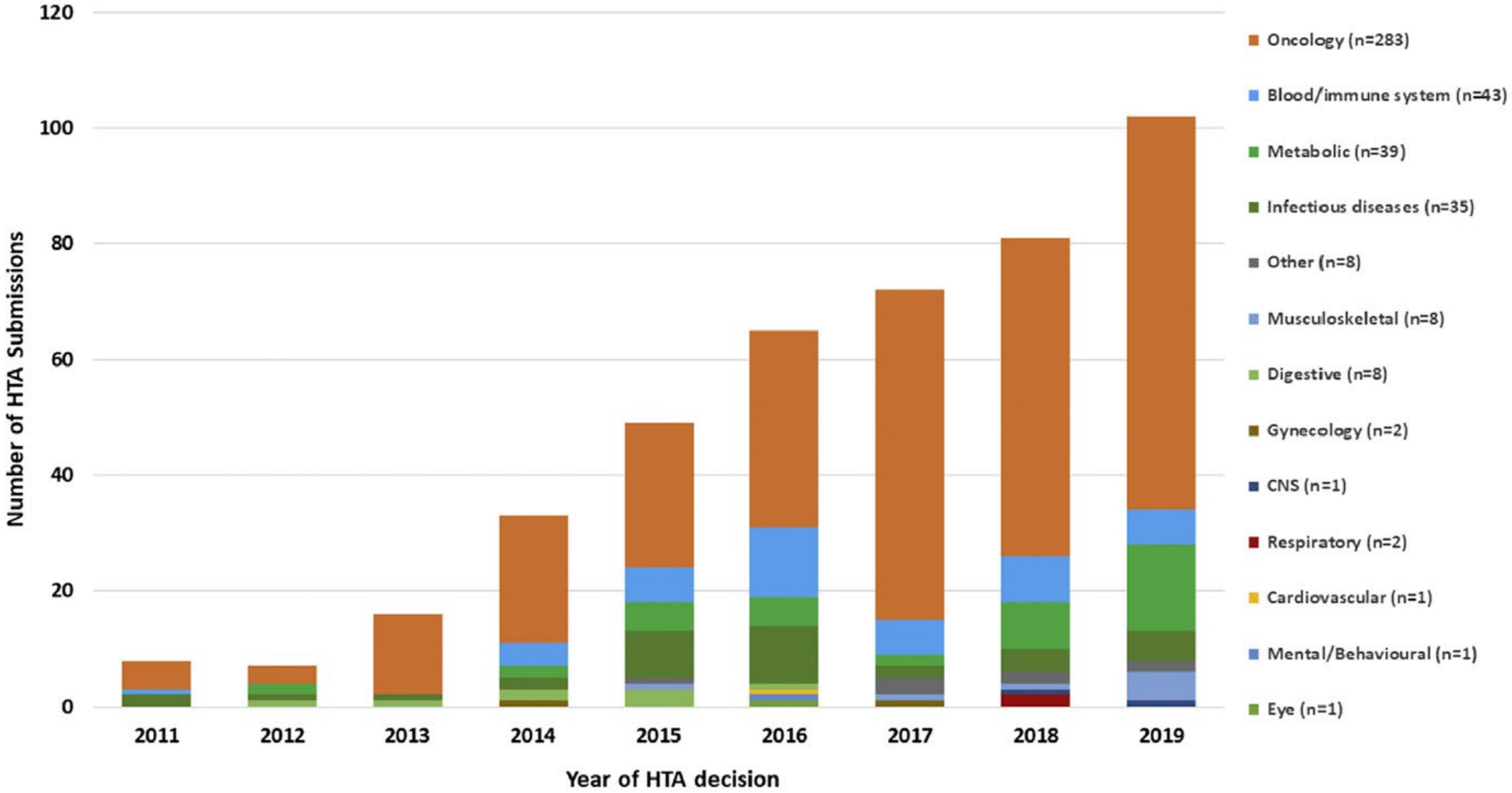
What is an External Control Arm (ECA)?

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





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

**Burger et al. The use of external controls: To what extent can it currently be recommended? Pharm Stat. 2021 Nov;20(6):1002-1016. doi: 10.1002/pst.2120.*

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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