Leids Universitair Medisch Centrum

Using equipoise subgroups in observational research

Valid results, but to whom do they apply?

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Clinical equipoise

"a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of different treatment options"

- Ethical requirement for experimental research (specifically randomisation)

- Randomisation → comparability of treatment arms (in expectation)

Examples

1. RCT among patients with Achilles tendon rupture. Randomise between conservative and surgical treatment.

2. RCT among children with trauma accident. Randomise between sending ambulance and sending trauma helicopter.

Equipoise in clinical practice

- For similar patients, with similar indications, different treatments are applied
- Leads to practice variation (that is not due to case-mix differences)

- Good starting point for observational research (‘natural experiment’)
- In case of equipoise → Different treatment options are applied, yet comparability of patients / indications between treatment arms (‘no confounding’)

Proposition: Equipoise leads to comparability

Different treatment options applied, yet comparability of patients / indications between treatment arms (‘no confounding’)

Otherwise, focus on those subgroups in whom there is ‘equipoise’, or…

- PS analysis
- Regression analysis
- Matching
- Restriction
- …

Examples (confounding)

1. Large practice variation in treatment of patients with Achilles tendon rupture: both conservative and surgical treatment are commonly applied.

2. Major differences (severity of) trauma accidents for which either ambulance or trauma helicopter is being sent.

Identify equipoise subgroups

Focus on those subgroups in whom there is equipoise

- E.g., ask a panel of experts: “which treatment would you advise?”
- Disagreement implies equipoise
  - Who are experts (members)?
  - How many experts (size of the panel)?
  - What defines disagreement?
  - What info to provide to the experts?
  - In general: How to set up the panel? (members, size, …)

Bias-variance trade-off

- Bias: the more you narrow it down to similar patients, the smaller the potential for confounding
- Variance (or precision): the more you narrow it down, the fewer patients you can include and the less precise estimates will be
- Efficiency (in the execution of the study): more detailed assessment of equipoise takes more time/effort by panellists

Generalizability of results

"What do we estimate and to whom do results of the study apply?"

In case of identifying equipoise subgroup based on expert panel → estimated treatment effect applies to subgroup of patients for whom panellist would disagree

- Depends on patient characteristics
- Depends on panellist (in contrast to, say, RCT)

Estimated treatment effect need not apply to those for whom panellist would agree…

Examples (generalizability)

1. Substantially large group of patients with Achilles tendon rupture for whom panellists will disagree

2. Group of children/accidents for whom panellist disagree likely small.

Summary

- Clinical equipoise provides a good starting point for observational research of medical treatments
- To increase the degree of clinical equipoise, subgroups can be selected for whom experts disagree regarding recommended treatment (*'confounding control by design'*)
- Using equipoise subgroups affects generalizability of results

An equipoise paradox?

- Equipoise is an (ethical) requirement for RCTs,

  but in case of equipoise you may not need RCTs

  since - in case of equipoise - observational studies are feasible and possibly valid…

- Yet, - in case of (perceived) equipoise - treatment effects are likely small, and small amounts of bias could have a substantial impact on inference and therefore RCTs are required…

When conducting an equipoise subgroup study

- Call it a ‘natural experiment’
- Provide details about the expert panel
- Additional confounding control (in analysis) may be required
- Think about the generalizability (does the study target your aims?)

- Ask yourself the question: why not an RCT?