Non-randomised evidence for economic evaluation

IMPACT-HTA WP6

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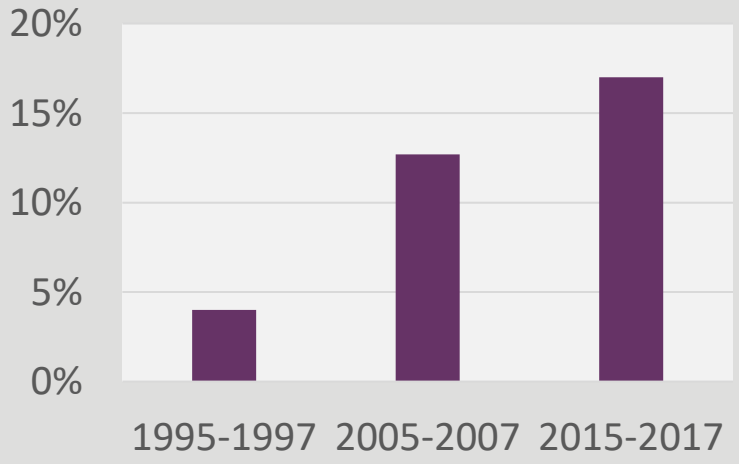
What evidence do we need to make decisions about which health technologies become available to patients?

- Internal validity is key: the **gold standard** for generating evidence about new drugs are **randomised controlled trials**.
- Increased interest in the use of **non-randomised studies** for market access and coverage decisions for new medicines.
- **Empirically grounded recommendations** on the use and interpretation of evidence from non-randomised studies are needed.



FDA approvals based on non-randomised studies (1995-2017) [1]

Sources: [1] Zhang et al. *JAMA Netw Open.* 2020

What did we do?

Empirically assess effect estimates obtained from randomised vs. non-randomised studies

- Do randomised and non-randomised studies agree about therapeutic effect of drugs and its magnitude?
- **Meta-epidemiological study** [1]: what is the impact of a specific study characteristic on the effect estimate it produces?
- Measure how often the two study types agreed about therapeutic benefit and effect size; pool discrepancies across all clinical questions.

Largest analysis to date: **346 clinical questions** with matched randomised and non-randomised studies; **2,747 unique contributing studies**

Develop recommendations for the use of non-randomised evidence to estimate treatment effects in HTA

- Pragmatic review of empirical evidence on internal validity of non-randomised studies and specific methods: meta-epidemiological study and other studies.
- Pragmatic review of **existing best-practice recommendations**.
- **Workshop** with European HTA bodies and regulators from 8 countries

Set of **13 recommendations** across **6 domains,** aimed at evidence developers and HTA bodies

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Source: [1] Sterne et al. *Stat Med.* 2002

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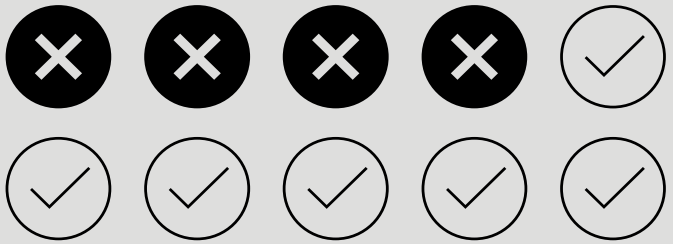
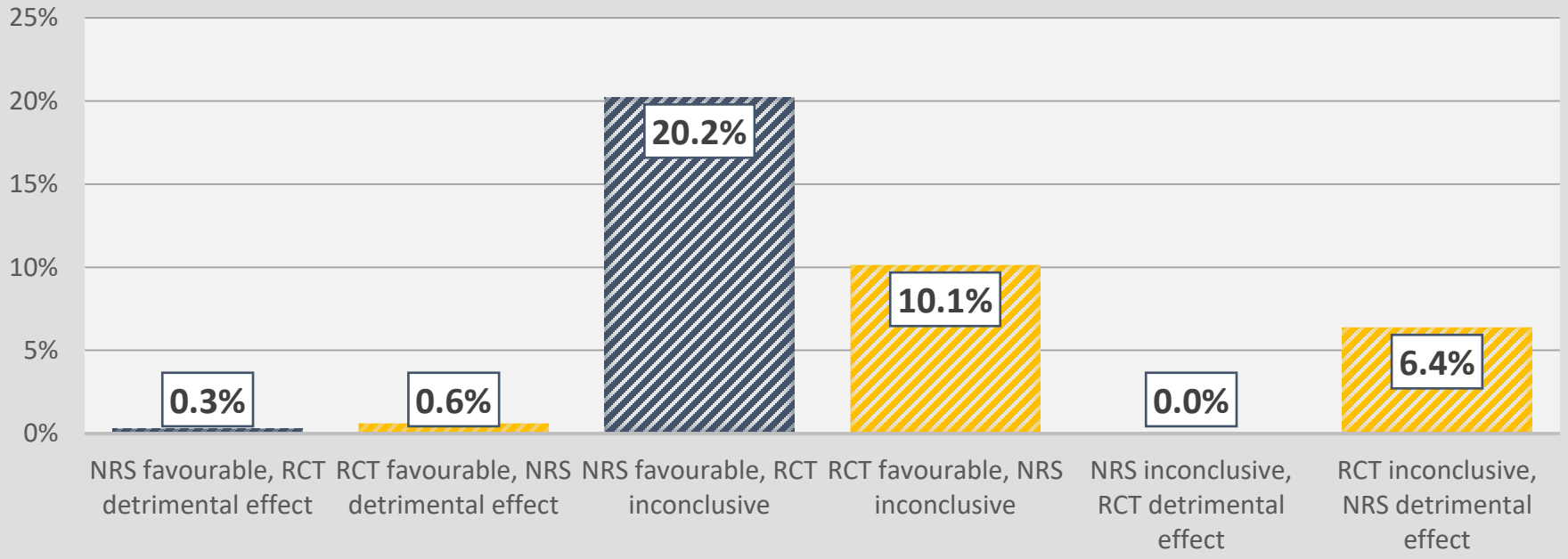
Do randomised and non-randomised studies agree about therapeutic effect of drugs?

Non-randomised and randomised studies led to **different conclusions** about whether a drug has therapeutic benefit for close to **4 in 10** of the 346 clinical questions analysed





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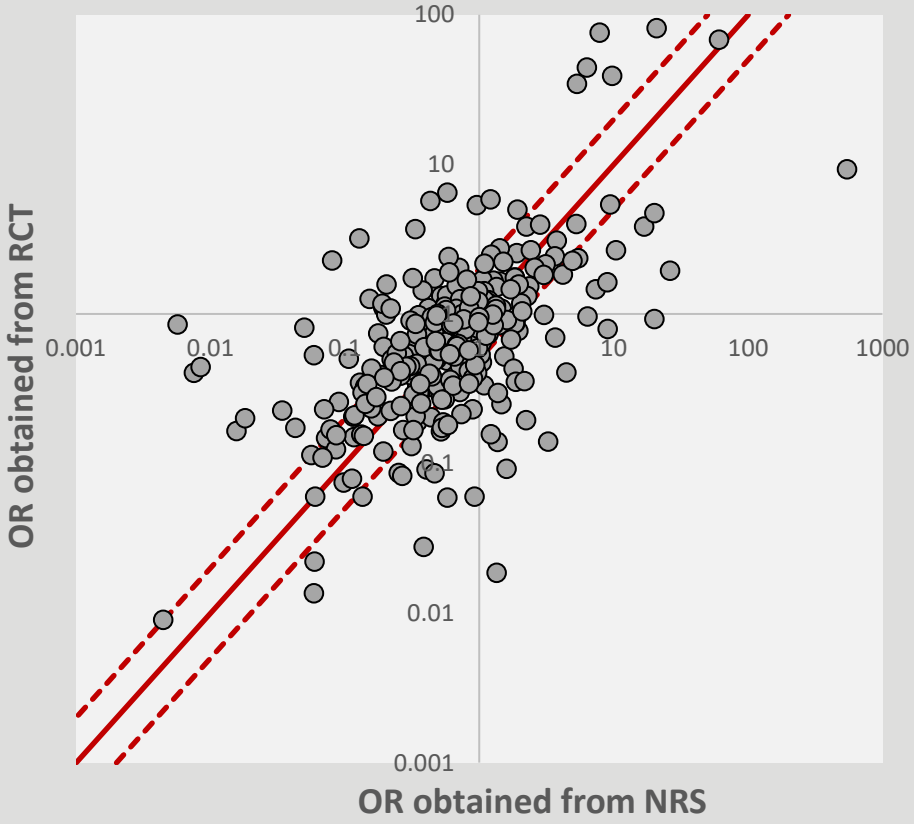
Do randomised and non-randomised studies agree about the magnitude of therapeutic benefit?

Non-randomised studies can severely **over- or underestimate** the effect obtained by randomised studies



38%

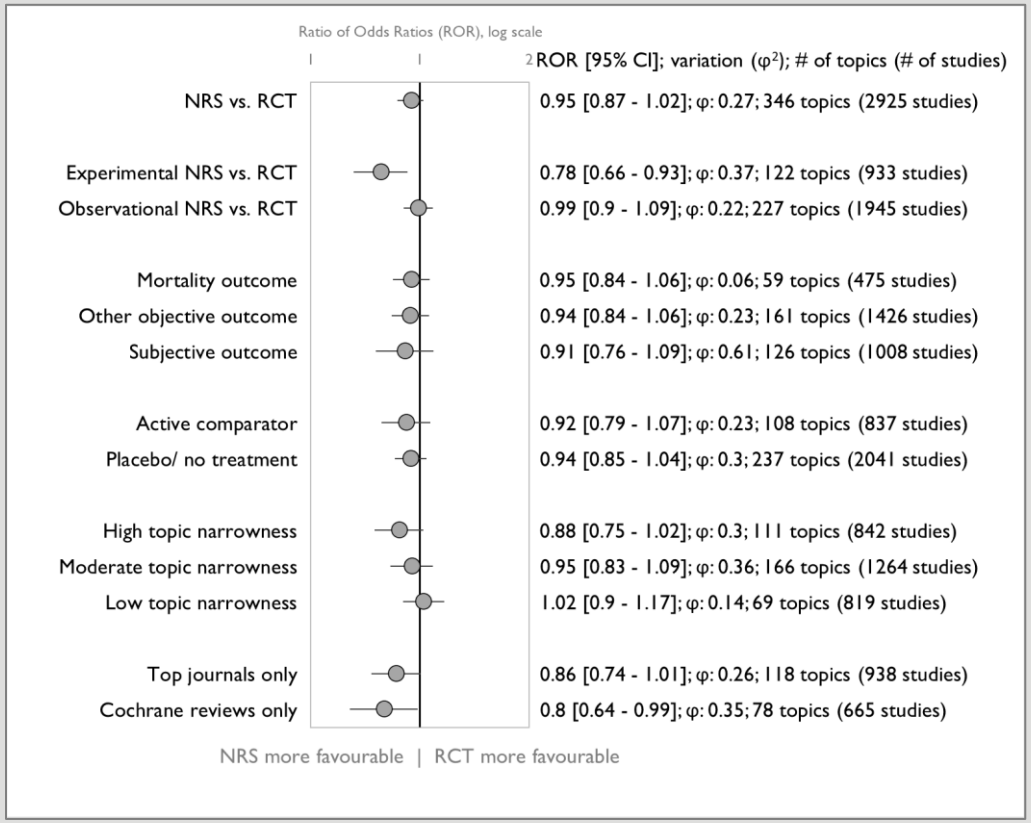
Clinical topics where the effect estimate was twice as large in one study type vs. the other

16%

Clinical topics where the difference in effect estimates between randomised and non-randomised studies was beyond chance (z-score for difference <-1.96 or >1.96)

Do randomised and non-randomised studies agree about the magnitude of therapeutic benefit?

Pooling discrepancies across all clinical questions, there was **on average no significant difference** in between randomised and non-randomised studies



0.95 (95% CI: 0.87-1.02)

Pooled ratio of treatment effects between randomised and non-randomised studies across 346 clinical topics

Substantial variation

in discrepancy of treatment effects, including over- and underestimation. Reduced variation for topics with mortality outcome.

22%

More beneficial treatment effects in experimental non-randomised studies compared to randomised trials

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Guidance	• Issue and enforce best practice guidance
Research/engagement	• Supporting future research and initiatives

Thank you!

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