Review of Methods Used to Estimate Treatment Effects Against Relevant Comparators

Using Evidence from Single-Arm Studies in NICE Single Technology Appraisals

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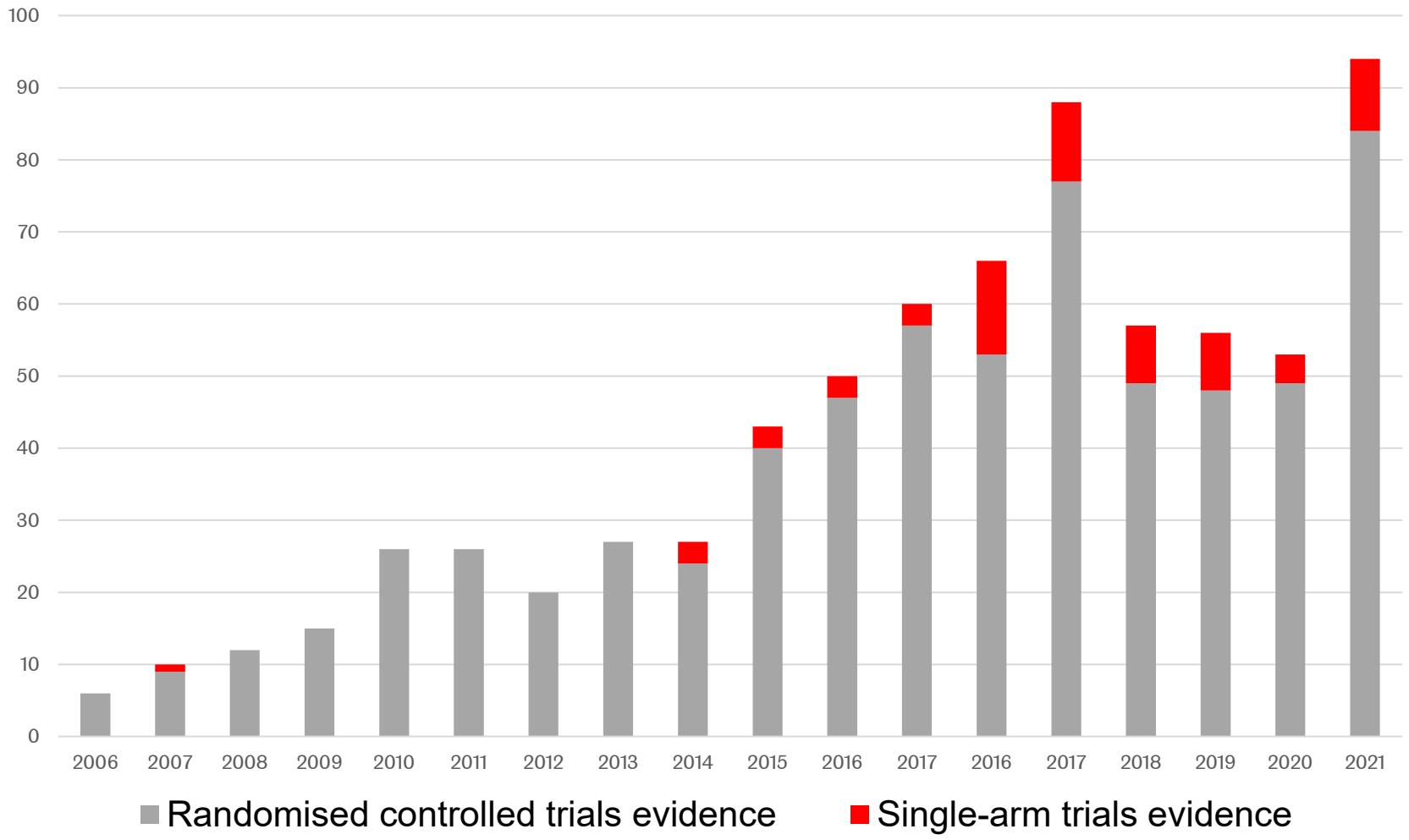
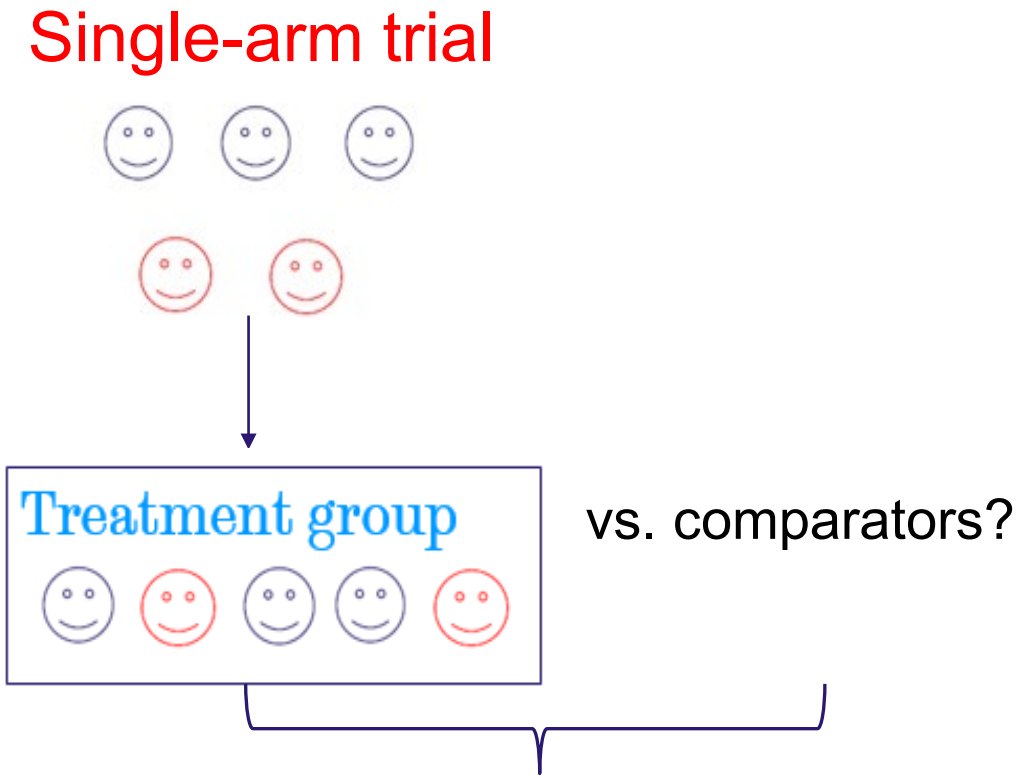
NICE Single Technology Appraisals



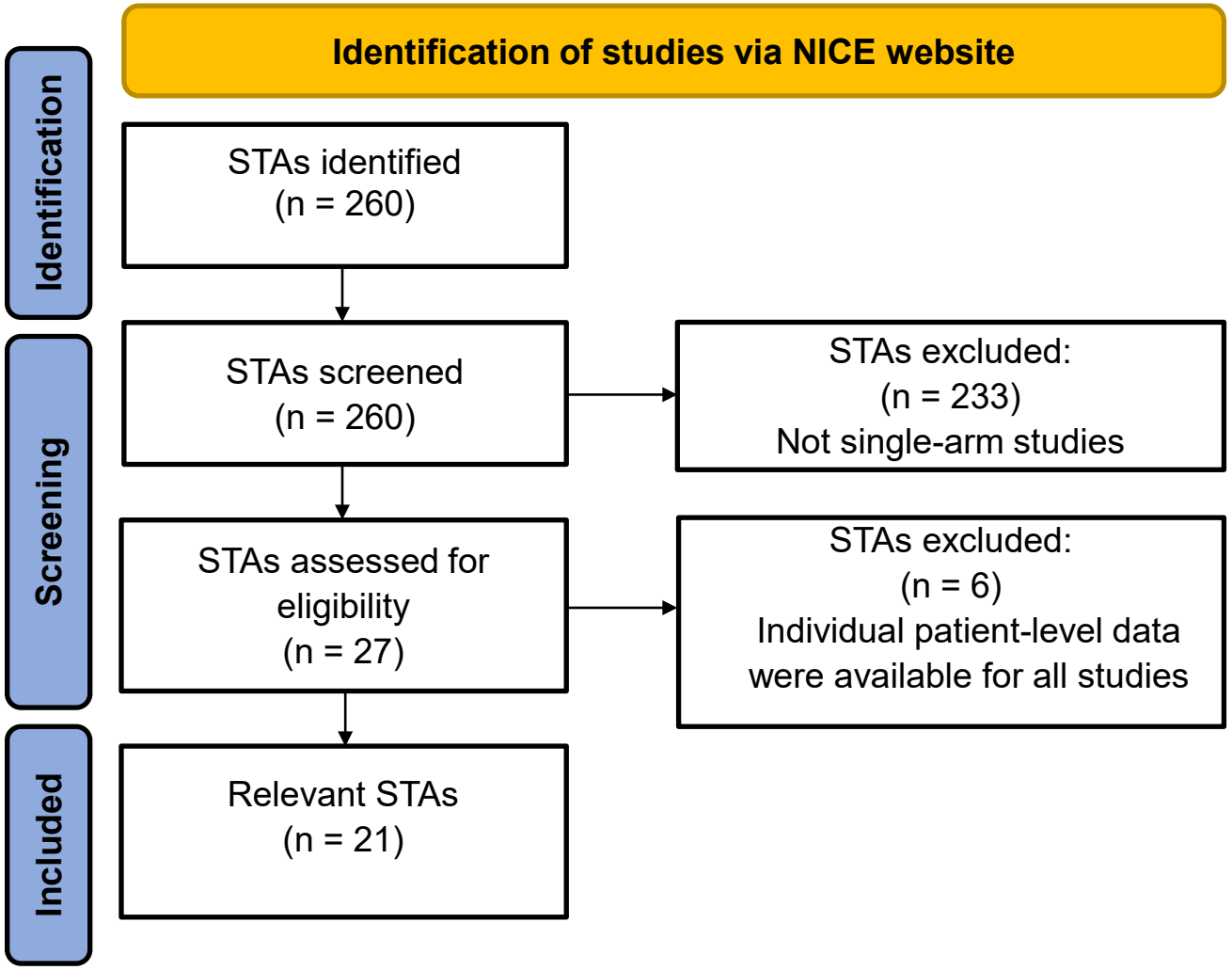
Using single-arm trial data to inform estimates of treatment effect increases risk of bias



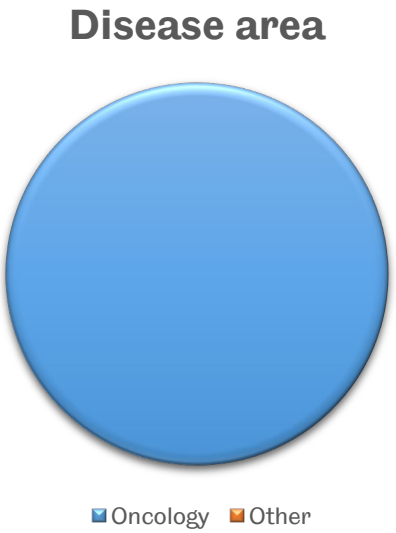
Review of NICE STA

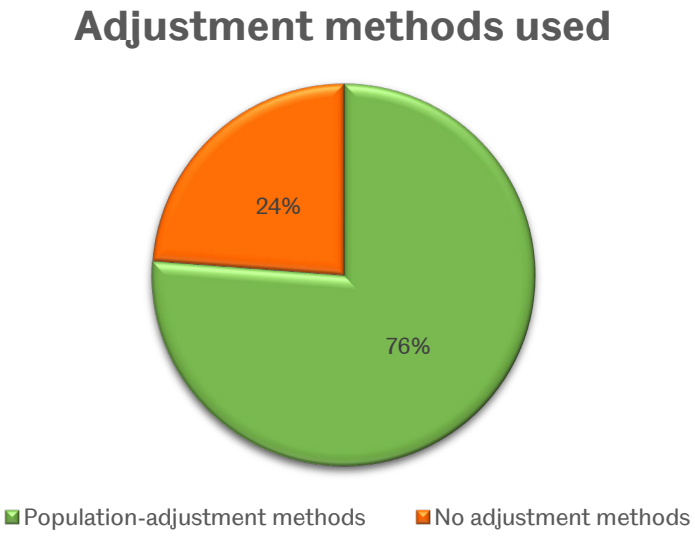
- Aim
  - Identify the methods used when only single-arm trial data were used to inform treatment effect
- Methods
  - Period: from January 2018 to December 2021
  - Study screening: TAs involving single-arm trials
  - Data extraction
    - Methods used to estimate treatment effect
    - How prognostic factors and effect modifiers were identified
    - How survival extrapolation has been conducted

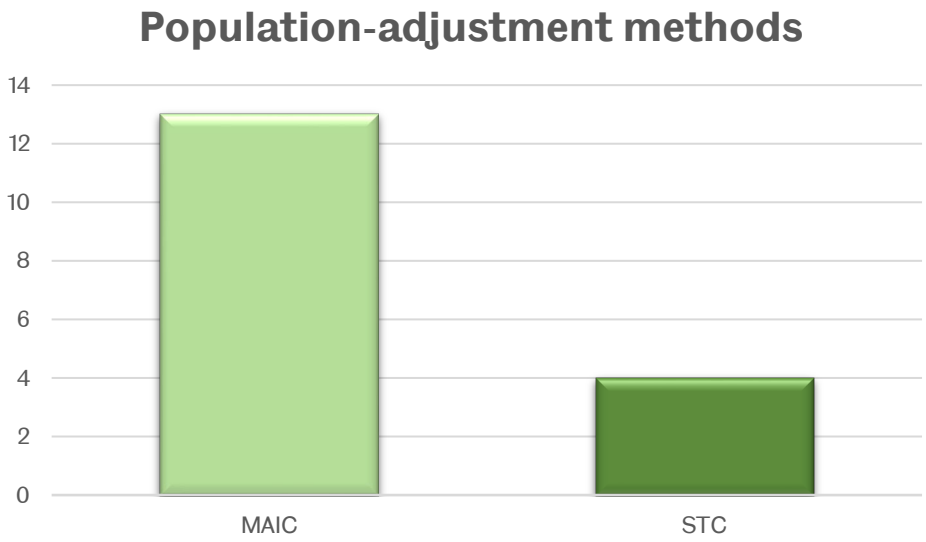
PRISMA diagram



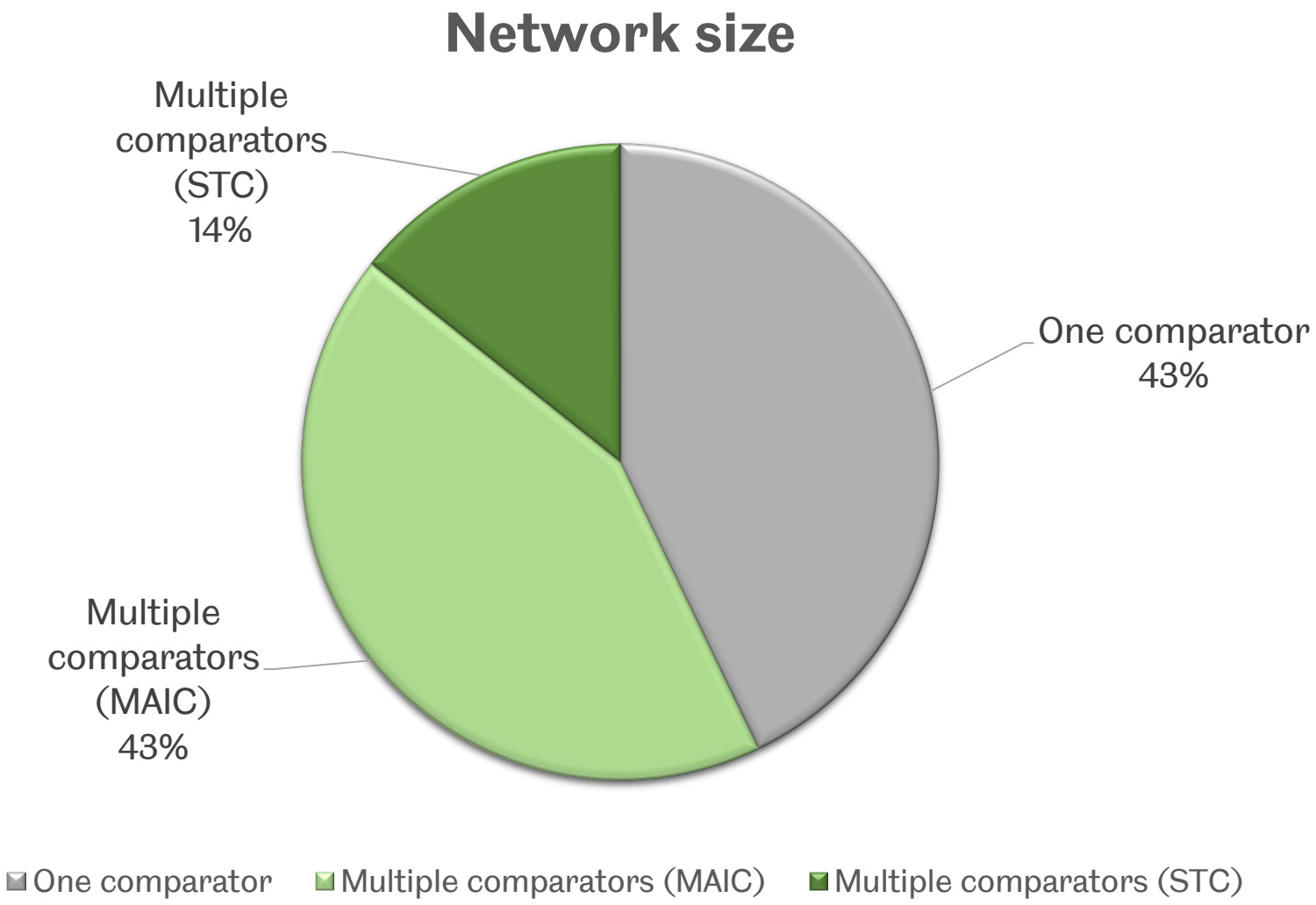
Review results







Review results



Review results

- Survival extrapolation
  - The target population was not clearly defined
  - Majority TAs extrapolated the unadjusted survival data for the intervention group
  - One TA applied a two-stage approach
    - Digitised adjusted Kaplan-Meier function and created pseudo individual patient-level data (IPD) for the intervention group
    - Extrapolate using the pseudo IPD

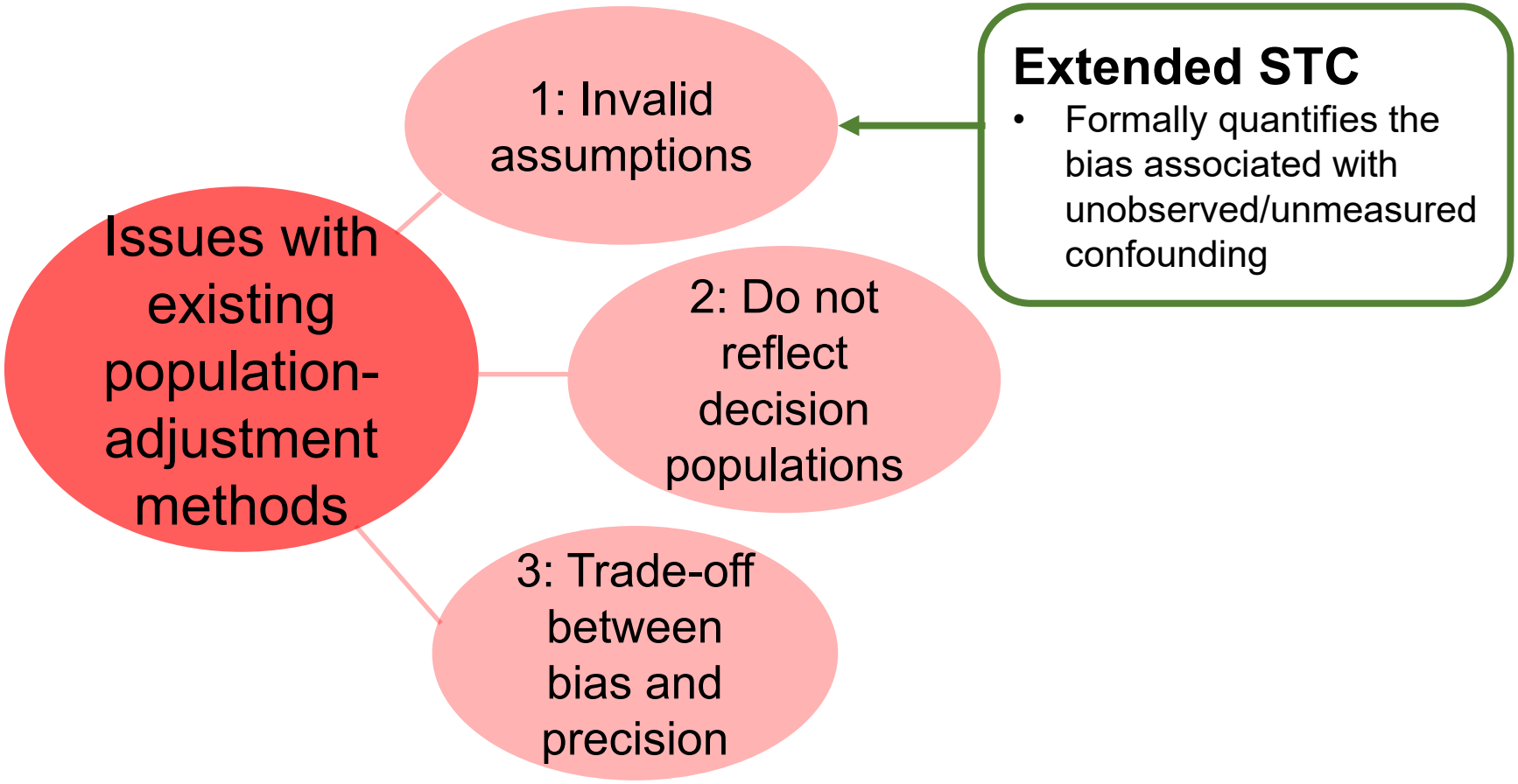
Review results

- Identification and inclusion of covariates
  - Unanchored ITC: include all prognostic factors and treatment effect modifiers
  - Availability of baseline characteristics
  - 10/21 TAs: the strategy were literature search, or clinical opinion, or combination of both
  - Most TAs did not discuss whether the identified variables were prognostic factor or treatment effect modifier

Review results

- TA592: "**None** of the indirect comparisons provide a **reliable estimate** of relative effectiveness"
- TA567: "the results seemed **implausible**"
- TA540: "**neither** method to be **robust**"
- TA530: "… the concerns about the **robustness** of the simulated treatment comparison"
- TA478: "…**uncertainty** about the **robustness** of the results"
- TA380: "…was **not consistent** with the population in the marketing authorisation"
- …

Improve the reliability of using single-arm trials data in decision-making



Extended STC

- Take into account of unobserved confounding in the indirect treatment comparison

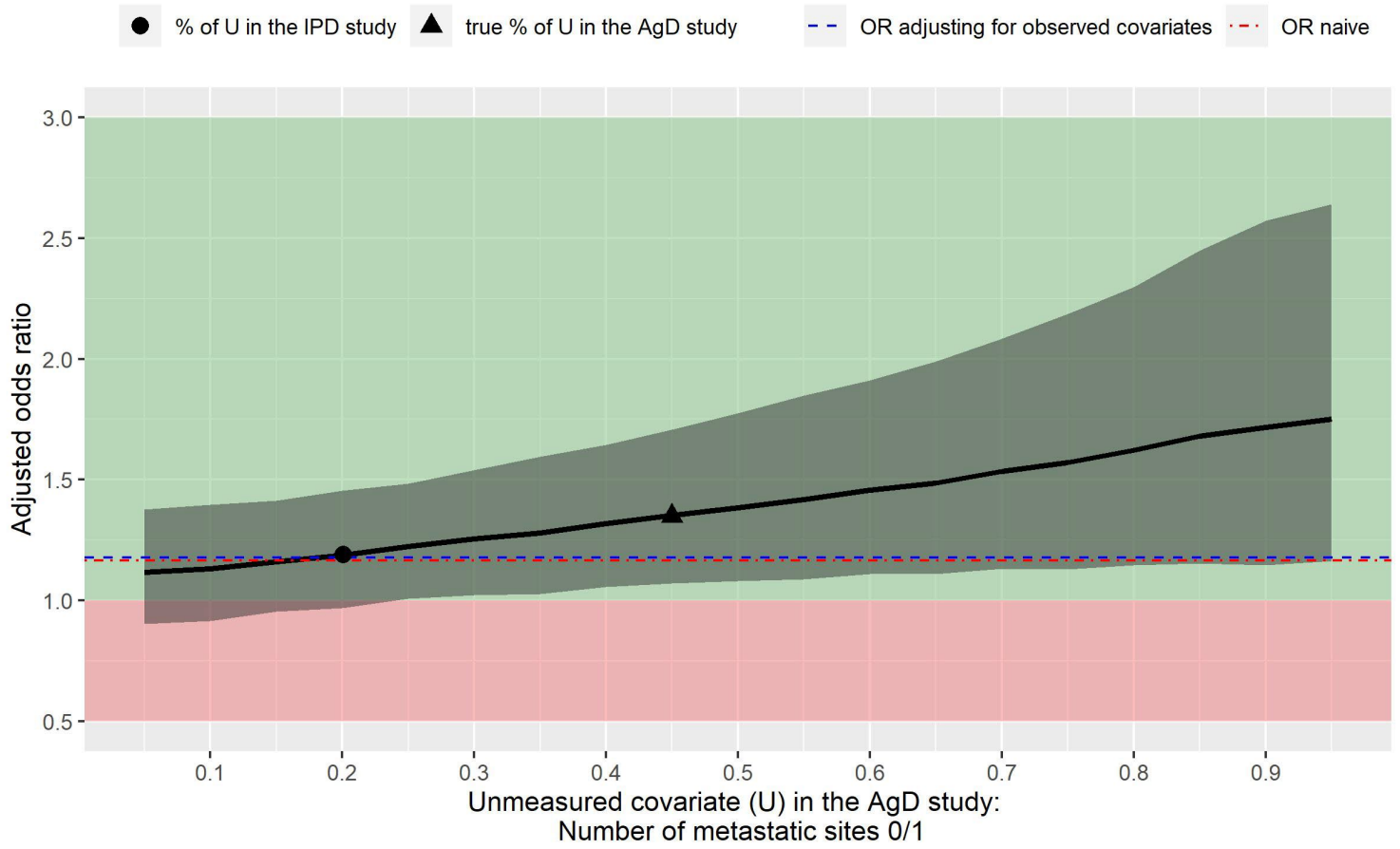
		Standard STC	Extended STC
Regression model	**Covariates**	Observed PFs and EMs only	Both observed and unobserved/unmeasured PFs and EMs
	Data	IPD for Study A and AgD for the Study B	IPD for Study A and AgD for the Study B; Assume AgD for unobserved/unmeasured covariates for Study B
Prediction	**Continuous outcome**	Plug in mean of covariates	Plug in mean of covariates
	Other types of outcome	Simulate covariates for other types of outcomes	Simulate covariates for other types of outcomes using Copula; G-estimation
Obtain treatment effect		Assume all PFs and EMs are adjusted for in the analysis	Sensitivity analysis for the impact of unobserved/unmeasured PFs and EMs

- Simulation
  - Asymptotically unbiased for binary outcome

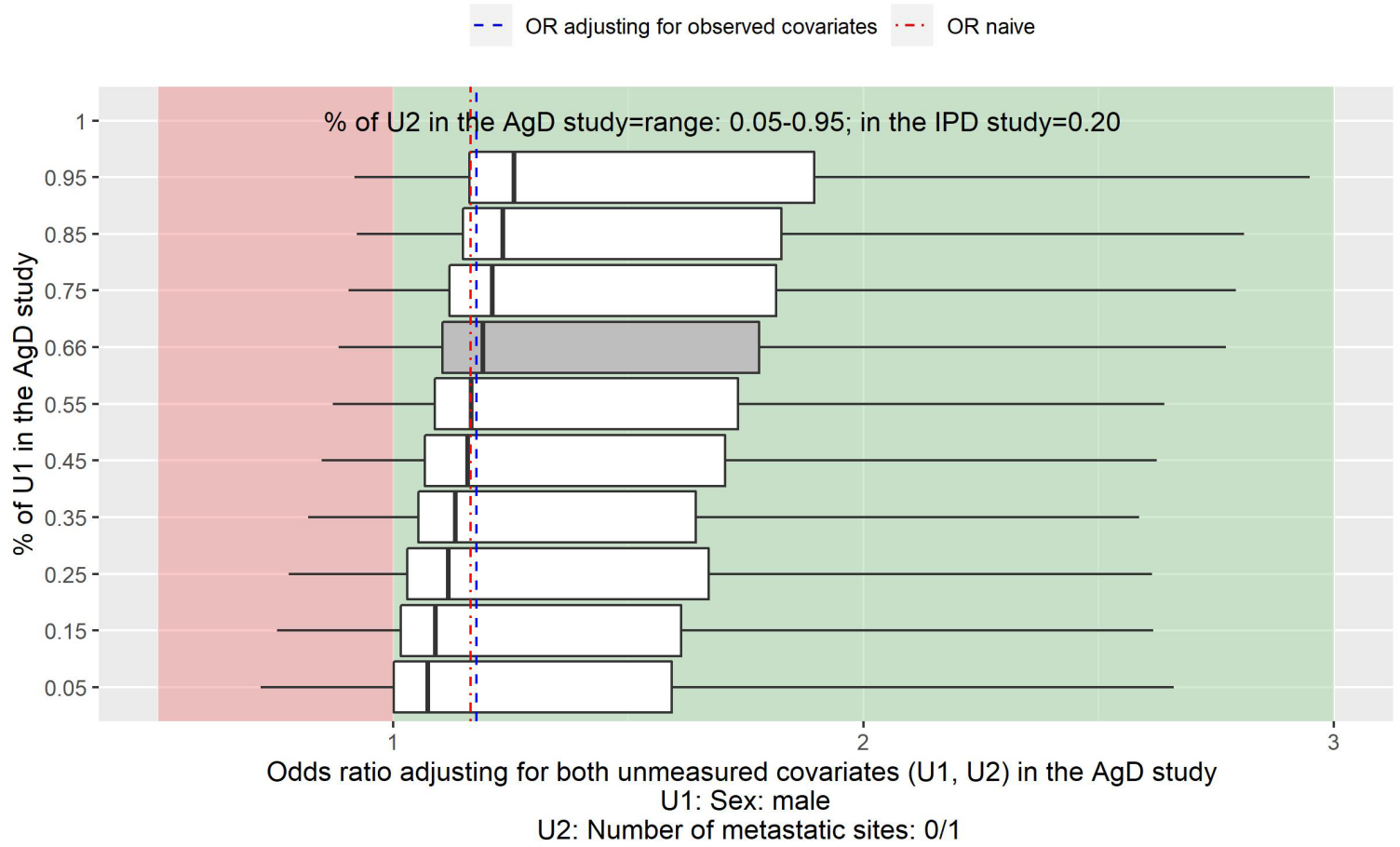
Case study

- Re-analyse data from the PRIME study
  - A Phase III RCT of panitumumab with FOLFOX4 vs. FOLFOX4 alone in patients with previously untreated metastatic colorectal cancer
  - Obtain anonymous IPD for the PRIME study from the Project Data Sphere® platform
  - Drop the FOLFOX4 arm and treat the data in the panitumumab with FOLFOX4 arm as a single-arm trial
  - Obtain summary statistics for the FOLFOX4 arm from an external source (Cunningham et al. 2009)
  - Apply ESTC method for objective response rate

Sensitivity analysis assuming the number of metastatic sites (U) is not reported in Cunningham et al. (2009)



Sensitivity analysis assuming sex (U1) and number of metastatic sites (U2) are not reported in Cunningham et al. (2009)



Summary

- Unanchored MAIC and STC are heavily criticised for it's strong assumptions
- The ESTC approach formally quantifies the bias associated with unobserved/unmeasured confounding
  - It provides a quantitative assessment of the impact of this bias
  - It increases the robustness of the treatment indirect comparison approach for single-arm trials

Thank you.