Exploring New Frameworks for Real-World Evidence (RWE)
Best Practices in Asia Pacific: the REALISE Project
ISPOR – 15 minutes

'NICE's experience on using 'real-world evidence' to support HTA and make decisions about reimbursement'

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My comments,
as chair of an independent NICE technology appraisal committee,
are my own, and do not necessarily reflect those of NICE

International Advisory Panel for REALISE
REAL World Data In ASia for HEalth Technology Assessment in Reimbursement

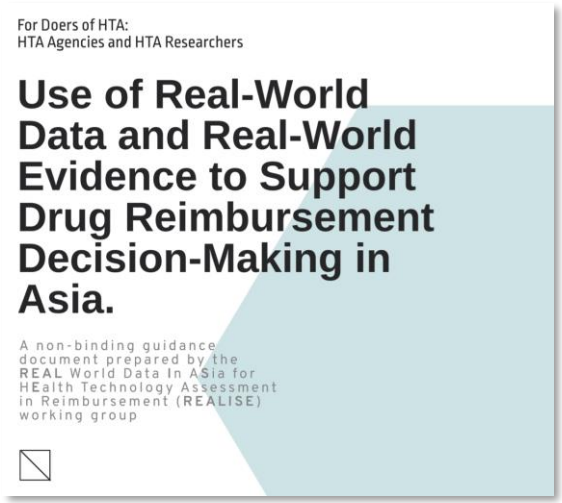


Outline



Examples of methods

- Pharmacoepidemiology
- Surrogate endpoints
- Unanchored indirect comparisons



Examples from appraisals

- Kyphoplasty for osteoporotic vertebral fractures
- Treating hyperkalaemia
- Ibrutinib for CLL chronic lymphocytic leukaemia

NICE methods on pharmacoepidemiology

Non-randomised and non-controlled evidence

3.3.4 The problems of confounding, lack of blinding, incomplete follow-up and lack of a clear denominator and end point occur more commonly in non-randomised studies and non-controlled trials than in RCTs.

3.3.5 Observational (or epidemiological) studies do not apply an intervention, but instead compare outcomes for people who use the technology under appraisal with outcomes for people who do not use the technology. These studies may be biased in that the people who use the technology may fundamentally differ in their risk of the outcome than the people who do not use the technology. Some observational studies lack a control group, and include only people who receive the technology.



Guide to the methods of technology appraisal, 2013

Committee accepted observational mortality data supporting non-confirmatory trial data

Percutaneous Vertebroplasty and Percutaneous Balloon Kyphoplasty for Osteoporotic Vertebral Fractures

No confounding or chance agreement?

Comparison	Hazard ratio (95% CI)
TRIAL Assessment Group meta-analysed 3 trials mortality at 12 months	
Intervention (9/190) vs. no intervention (13/186)	0.68 (0.30 to 1.57)
OBSERVATIONAL US Medicare Registry* 858,979 with newly diagnosed vertebral fracture 4 years follow-up	
Intervention vs. no intervention	0.63 (0.62 to 0.64)
OBSERVATIONAL German Health Insurance Fund* 3,607 with vertebral fracture	
Intervention vs. no intervention	0.57 (0.48 to 0.70)

** Edidin et al. 2011 adjusted for sex, age, race/ethnicity, patient health status, type of diagnosed fracture, site of serv physician specialty, socioeconomic status, year of diagnosis, region*

***5 Lange et al. 2012 adjusted for sex, age, patient health status and site of first diagnosis*

Committee did not accept

Drug for hyperuricaemia in people with gout

Trial new drug vs. placebo:

- Improves serum uric acid
- Does not improve:
  - Attacks (‘flares’)
  - Tophi
  - Mortality

Company presents observational data:

- exposure uric-acid lowering drugs
- outcome mortality

Claim: new drug extends life



Takes uric acid lowering therapy



Does not take uric acid lowering therapy

Noun project: Marco Fleseri Adrien Coquet
Lesinurad for treating chronic hyperuricaemia in people with gout

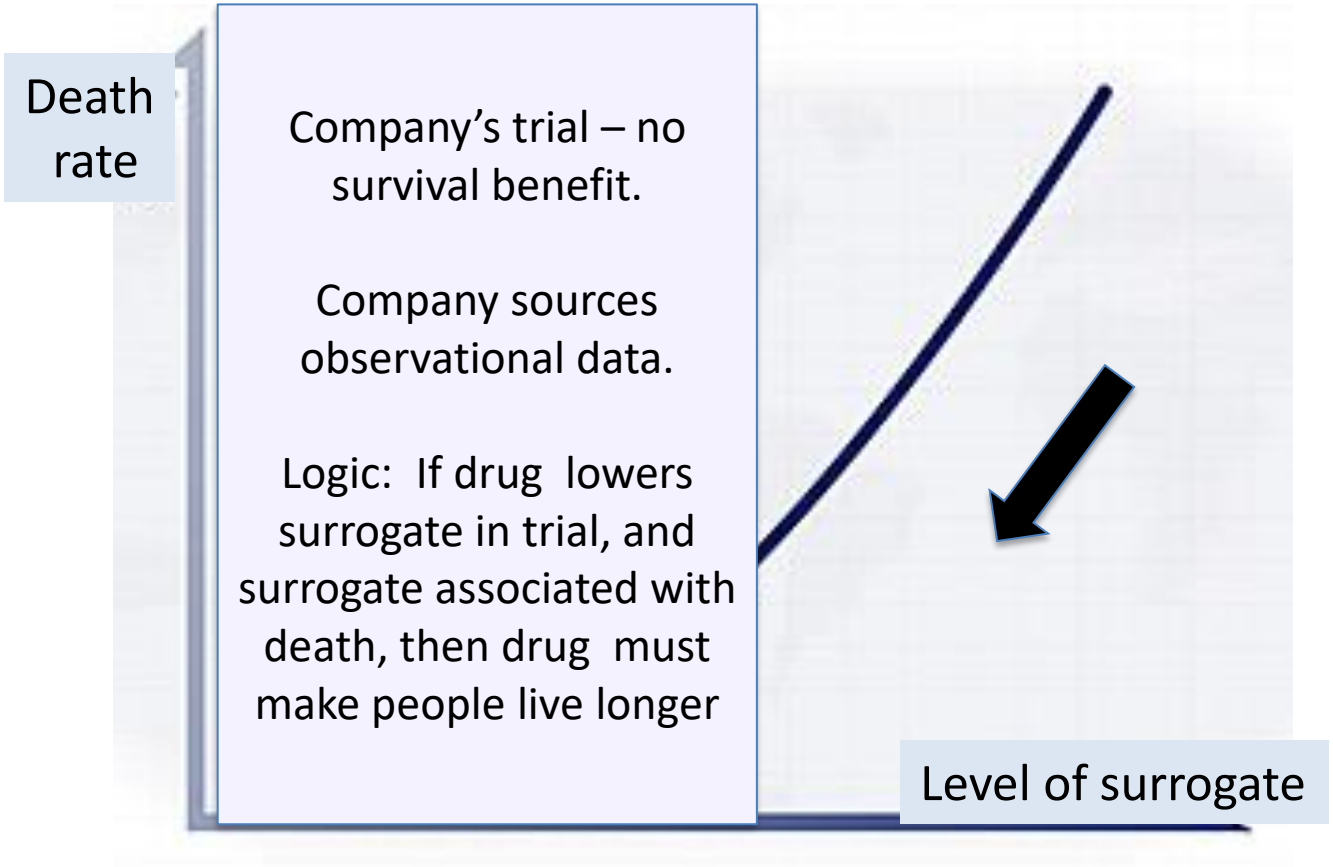
NICE methods on surrogate endpoints for length of life, quality of life

5.7.5 Clinical end points that reflect how a patient feels, functions, or how long a patient survives are regarded as more informative than surrogate end points (such as laboratory tests and imaging findings). When the use of 'final' clinical end points is not possible and 'surrogate' data on other outcomes are used to infer the effect of treatment on mortality and health-related quality of life, evidence in support of the surrogate-to-final end point outcome relationship must be provided together with an explanation of how the relationship is quantified for use in modelling. The usefulness of the surrogate end point for estimating QALYs will be greatest when there is strong evidence that it predicts health-related quality of life and/or survival. In all cases, the uncertainty associated with the relationship between the end point and health-related quality of life or survival should be explored and quantified.



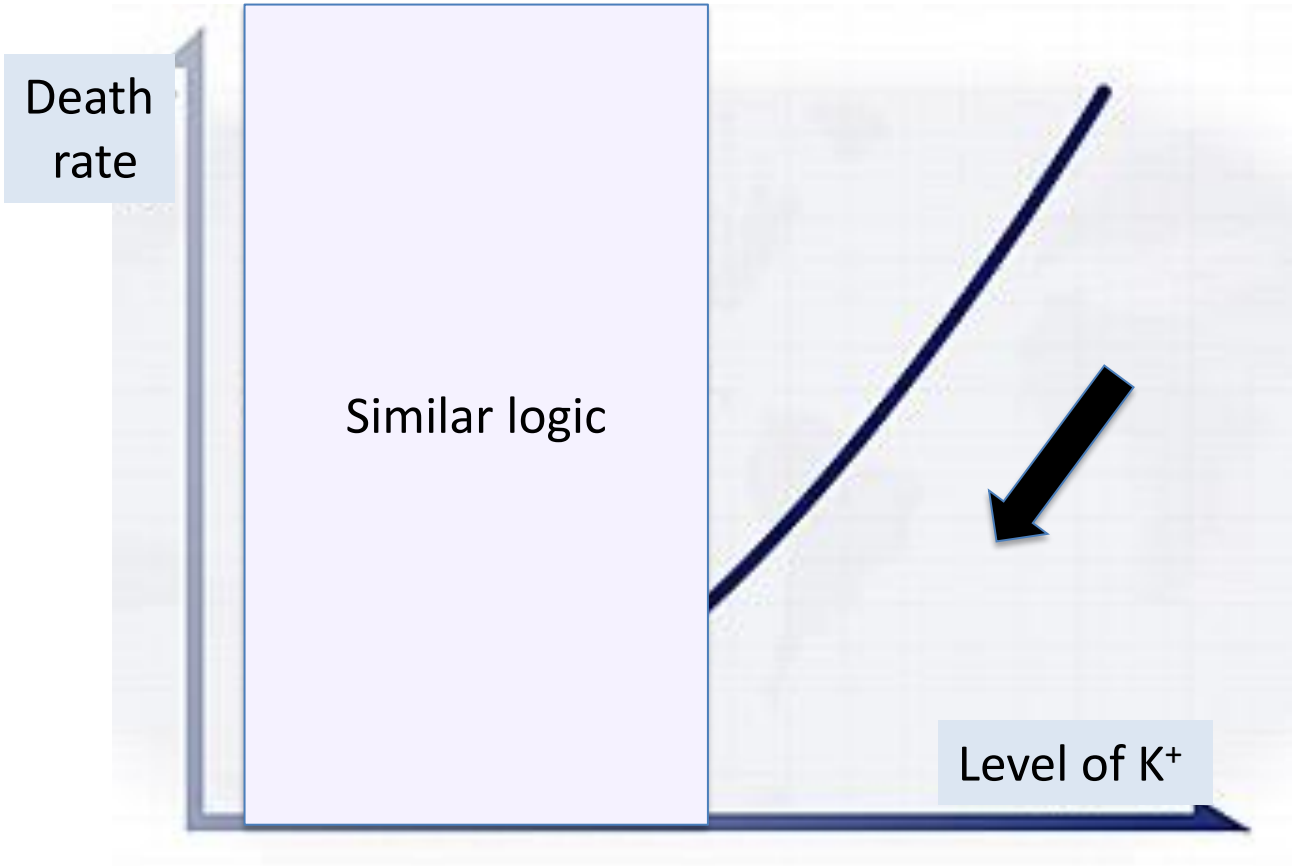
Implied causality – serum uric acid

Drug lowers surrogate endpoint, and surrogate associated with mortality



Implied causality – serum K^+

Drug lowers surrogate endpoint, and surrogate associated with mortality



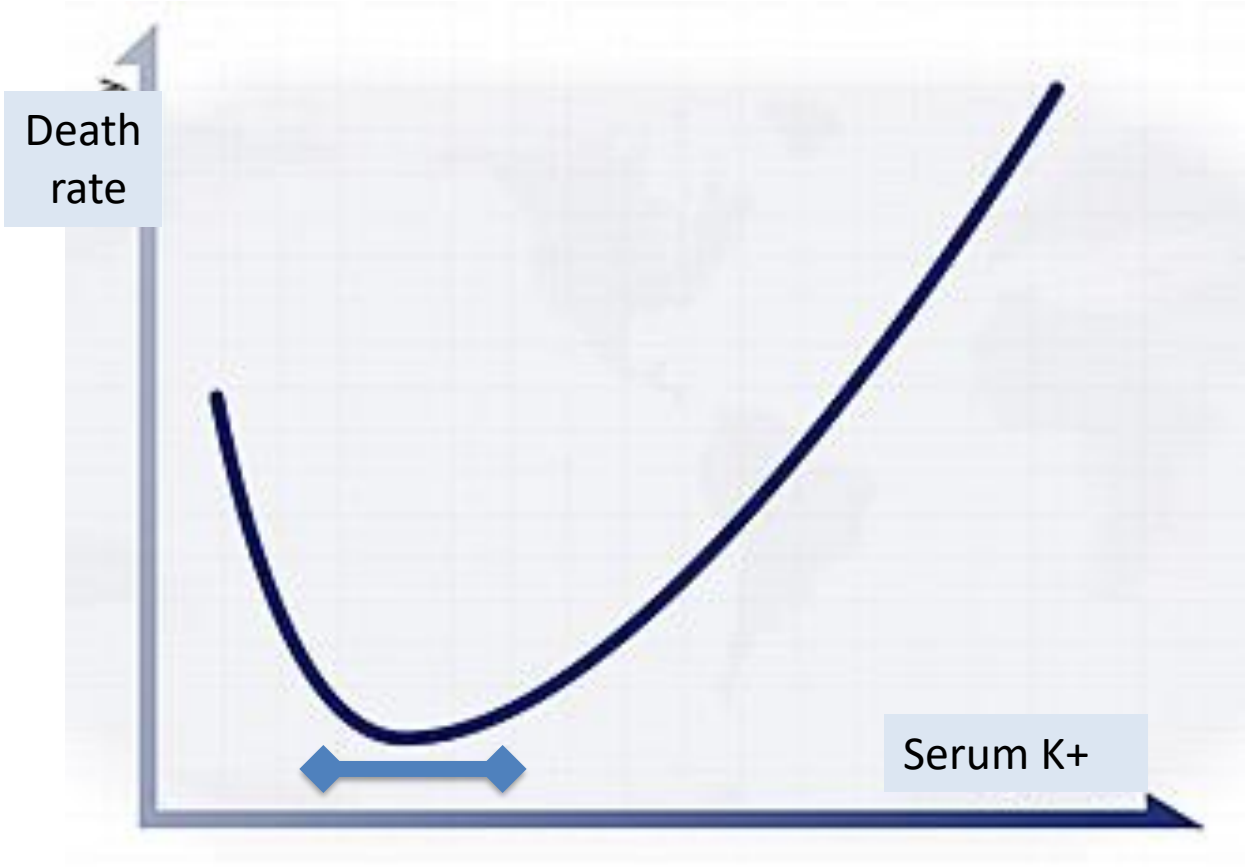
Association between serum K^+ and death

U- and J-shaped associations

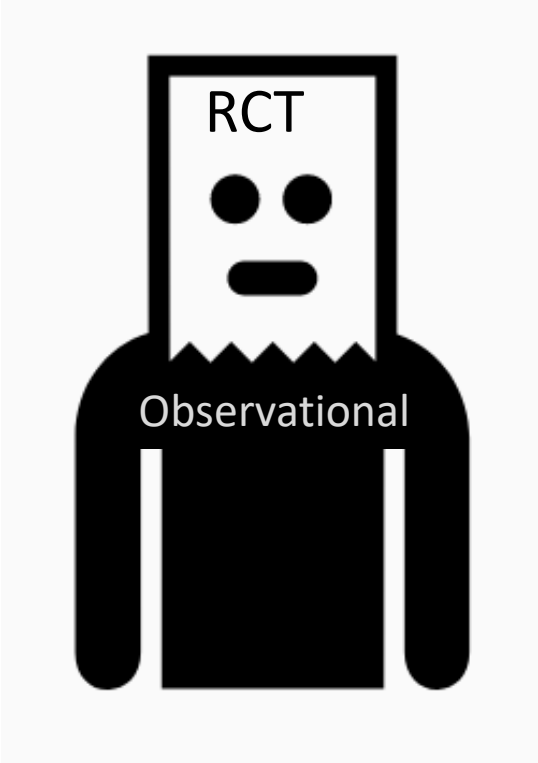
Data had been presented numerically only

Trial done in people with modestly elevated serum K+

Increase in mortality (for hypokalaemia) 'not explored'



‘Evidence from randomised controlled trials exists for the relationship between serum X and outcomes’

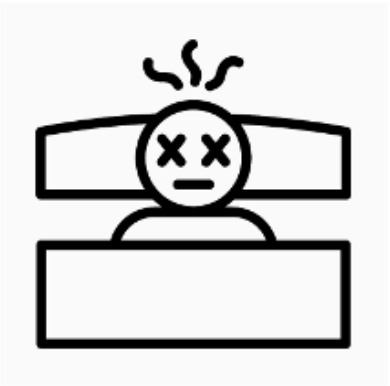


NICE methods discourages naïve ‘unadjusted’ comparison – ‘not acceptable’

5.2.16 In all cases when evidence is combined using adjusted indirect comparisons or network meta-analysis frameworks, trial randomisation must be preserved, that is, it is not acceptable to compare results from single treatment arms from different randomised trials. If this type of comparison is presented, the data will be treated as observational in nature and associated with increased uncertainty.

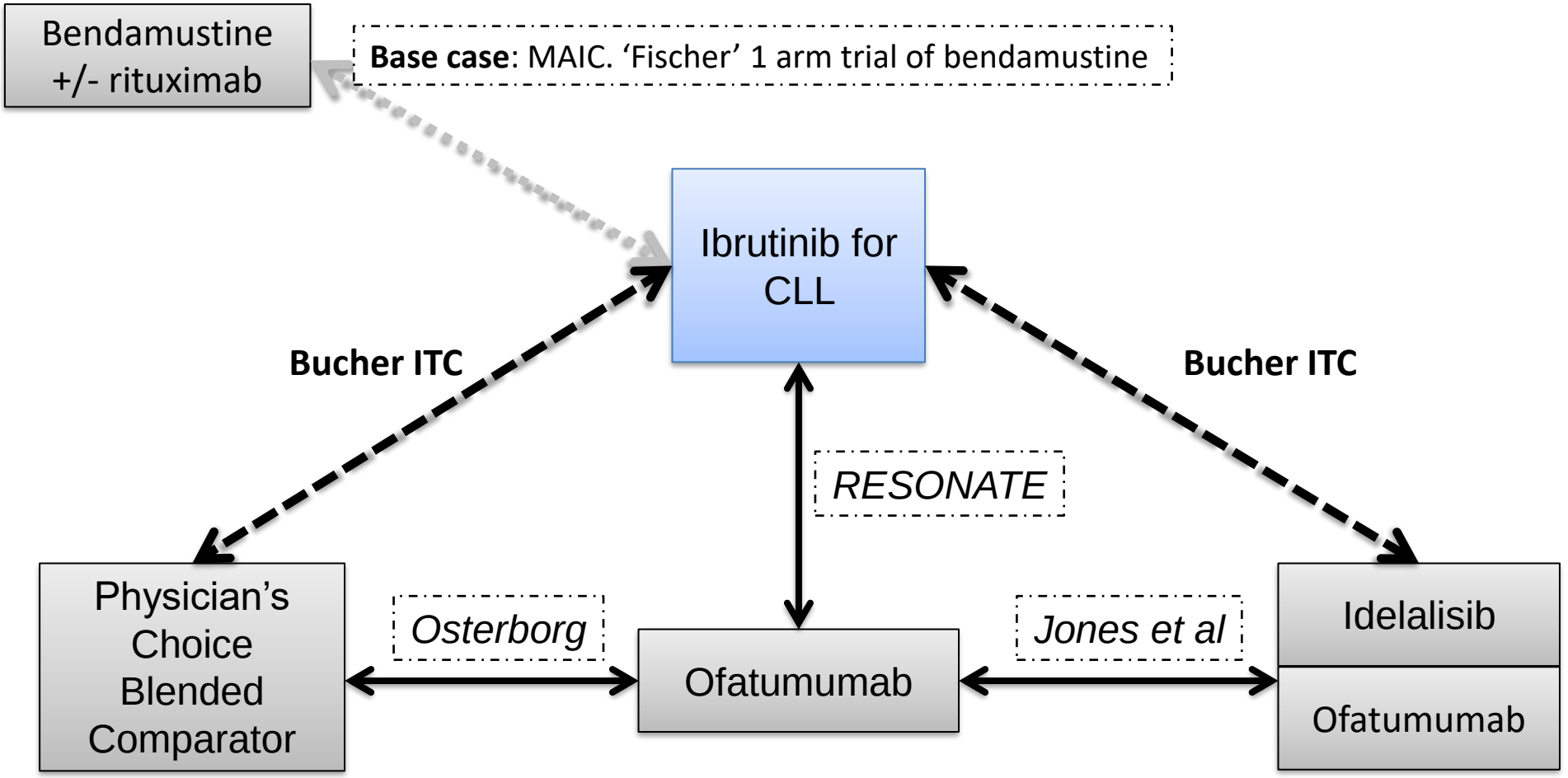


Takes new drug



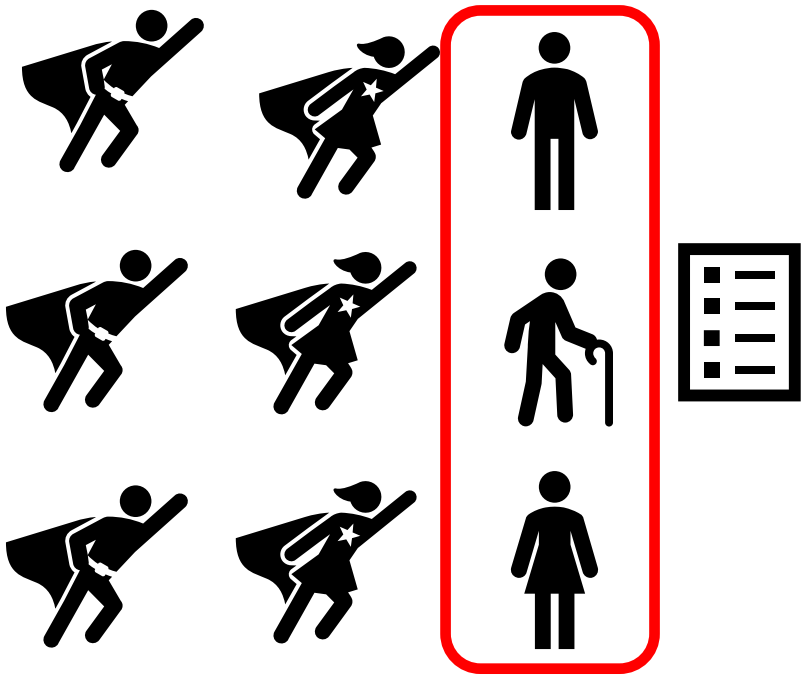
Takes old drug

Network with both 'anchored' and 'unanchored' comparisons

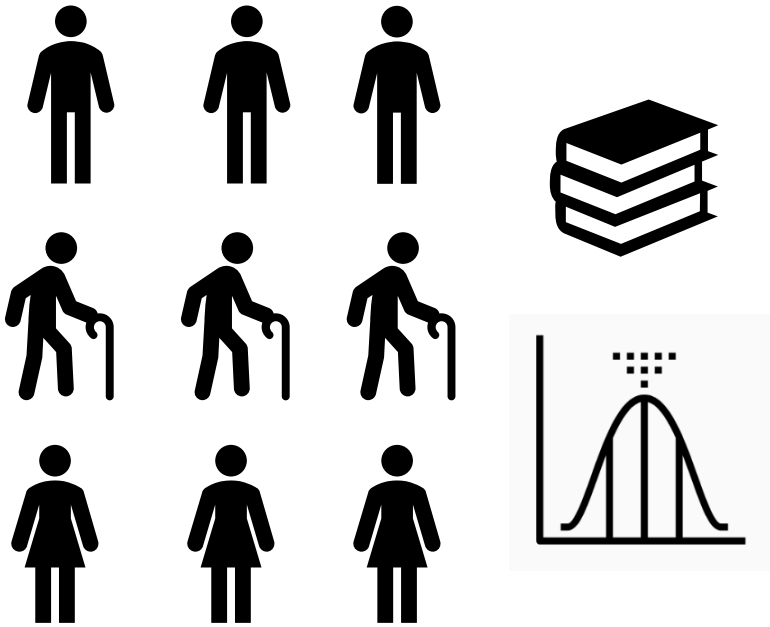


ITC = indirect treatment comparison
MAIC = Matched adjusted indirect comparison
CLL = Chronic lymphocytic leukemia

Matched adjusted indirect comparison



Intervention arm of key trial
or only arm of key trial
Individual patient level data

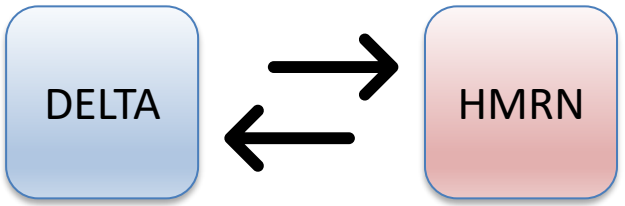


Comparator arm of a different trial
Study level data

Committee sees 2-way matched adjusted indirect comparison; asks for propensity scores

3.12 In response to the consultation, the company submitted the following matching indirect comparisons using updated data (see section 3.5 and section 3.8) from DELTA and the HMRN:

- Unanchored matching adjusted indirect comparisons with the HMRN cohort (see section 3.8) including:
  - An 'updated' matching adjusted indirect comparison: the company matched individual patient-level data from the HMRN cohort to the population-level descriptive characteristics of patients in the DELTA study. This estimated the effects of chemotherapy in a DELTA-like population.
  - A 'reverse' matching adjusted indirect comparison: the company matched individual patient-level data from the DELTA study to the population-level descriptive characteristics of patients in the HMRN cohort. This estimated the effects of idelalisib in a HMRN-like population.
- Propensity score matching analyses (see section 3.14):
  - With DELTA as the 'treated' group and the HMRN as the 'control' group: it matched individual patient-level data from the DELTA study to individual patient-level data from the HMRN cohort. This estimated the effects of chemotherapy in a DELTA-like population.
  - With the HMRN as the 'treated' group and DELTA as the 'control' group: it matched individual patient-level data from the HMRN cohort to individual patient-level data from the DELTA study. This estimated the effects of idelalisib in a HMRN-like population.



Trial

Haematological Malignancy Research Network

Definitions

Clinical Trial

'Any research study that prospectively assigns human participants or groups ..to one or more health-related interventions to evaluate the effects on health outcomes.'

World Health Organization

Observational Study

'What we do when we cannot conduct a randomized trial'

Miguel Hernan,
Professor of Biostatistics and Epidemiology, Harvard

- 'Other than baseline randomization, there are no other necessary differences between analysis of observational data…and randomized trials. That is, a randomized trial can be viewed as a follow-up study with baseline randomization and the analyses of observational longitudinal data as a follow-up study without baseline randomization.'
- '…one would expect that randomized trials and observational studies would be analysed similarly (apart from the need to adjust for baseline confounders in observational studies)'



Methods in Comparative Effectiveness Research. Gatsonis and Morton, eds. 2017

Conclusion

