Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Regulatory considerations when supplementing *confirmatory* RCTs with ~~non-randomised~~ *external* data

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Take as read that **optimal planning** of an RCT must **leverage knowledge** of the whereabouts, the demographics, the prognosis, the participation rates, the adherence etc etc of the target population **from past trials or from epidemiology**.

Can I use external data to reduce the amount of patients / information to be collected in my prospective, confirmatory RCT?

Is it acceptable to supplement RCTs with external data?

"It depends"

A lot is covered already in E9 / E10

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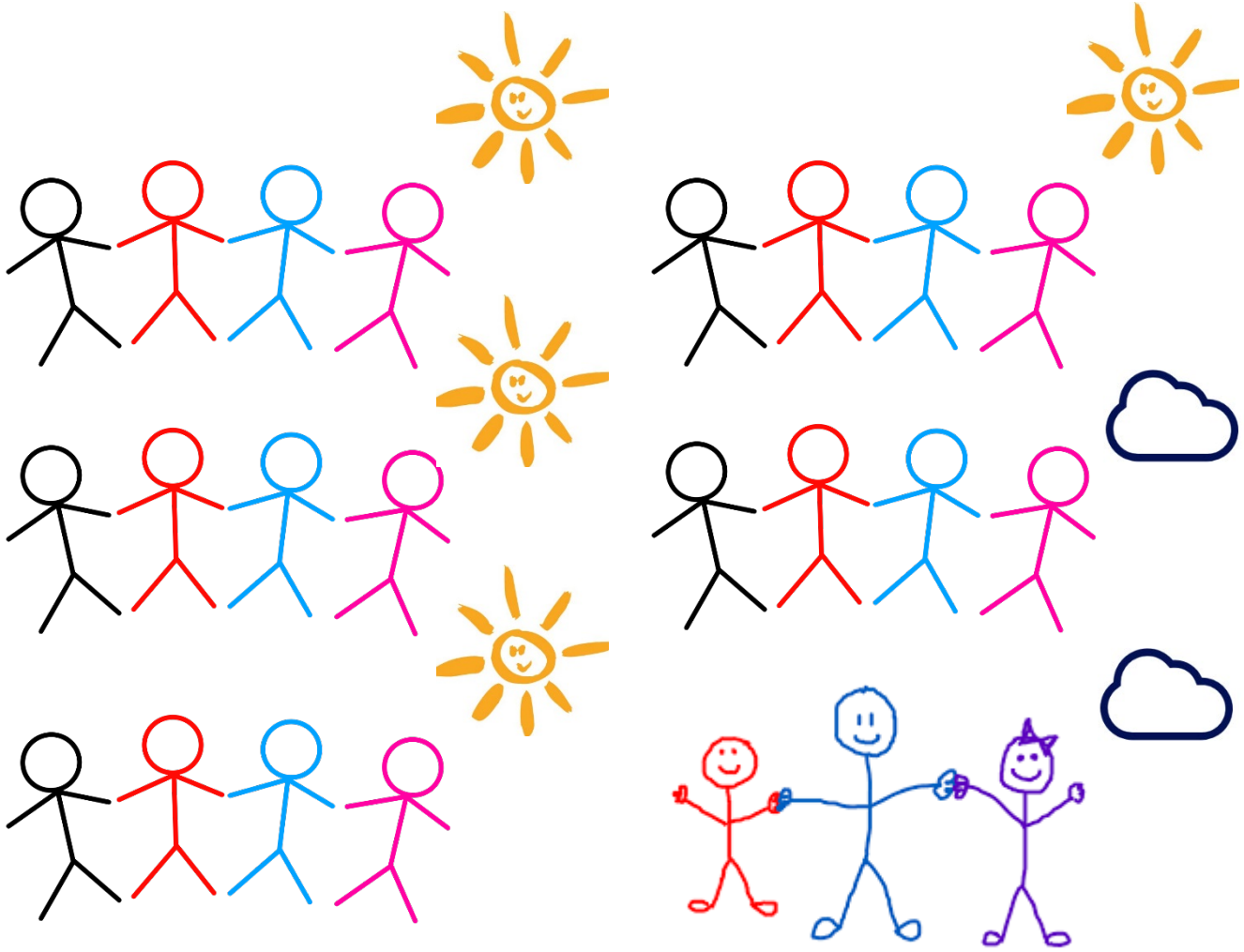


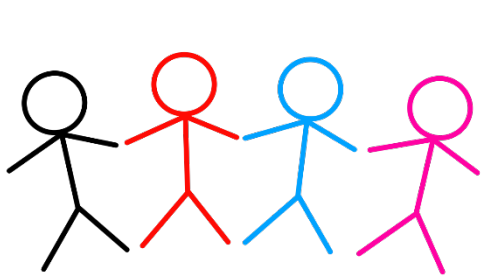
Why?

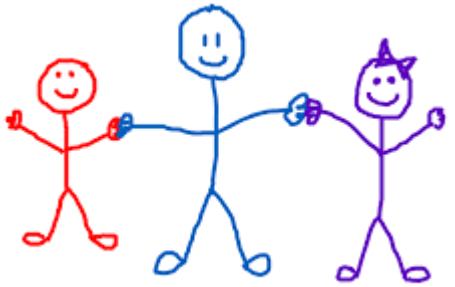
Why?

‘Efficiency’

- “Doing the same with less effort / resource.”
- Is the quality of our evidence ‘the same’?
- Quality of evidence is paramount: limited scope for trade off in ‘quality’ vs ‘cost’.

What would I consider?





BIAS

Methods based on covariates

- Matching
- Covariate adjustment
- Inverse probability weighting
- …

- None are guaranteed to work…
- How many covariates?

What would I consider?

ICH E9(R1)

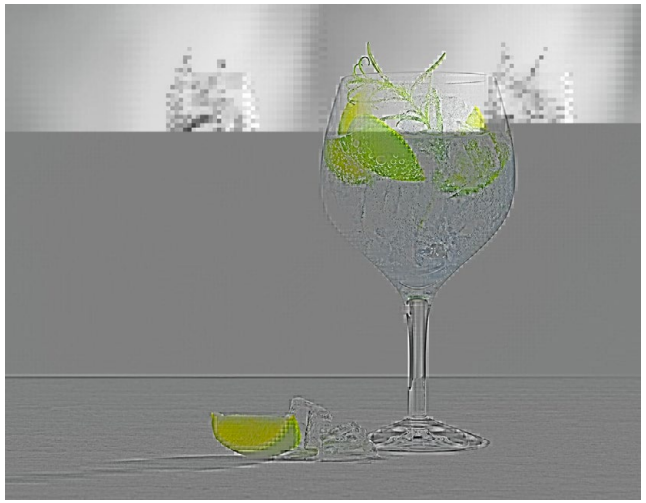
臨床試験のための統計的原則　補遺

臨床試験における estimand と感度分析

（案）

I haven’t seen these addressed explicity.

Methods based on similarity of observed data

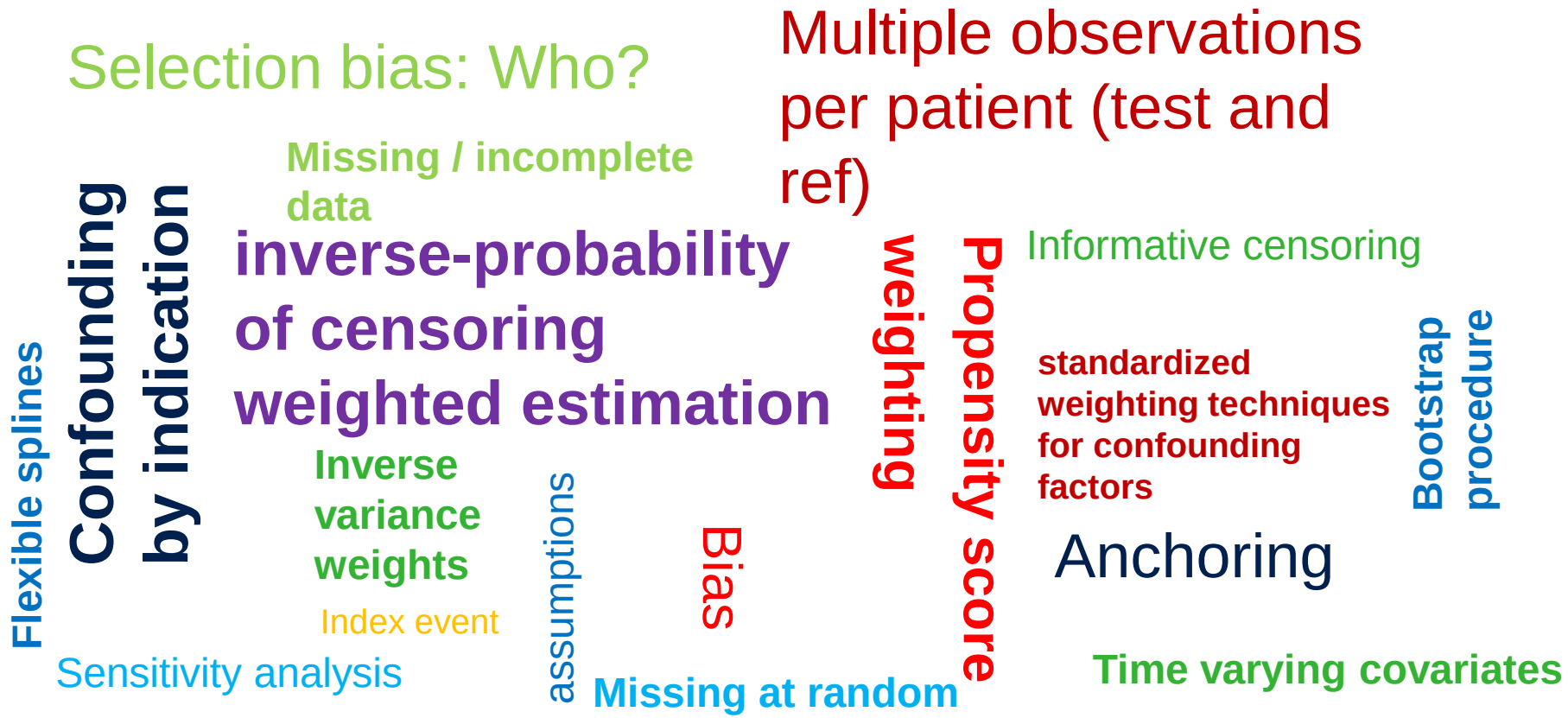


Which external data source?

Historical CTs

Data generated in clinical practice, RWD

Example


Selection bias: Who?
Multiple observations per patient (test and ref)
Missing / incomplete data
Confounding by indication
inverse-probability of censoring weighted estimation
weighting
Propensity score
Informative censoring
standardized weighting techniques for confounding factors
Bootstrap procedure
Flexible splines
Inverse variance weights
assumptions
Bias
Anchoring
Index event
Sensitivity analysis
Missing at random
Time varying covariates

Validation: what ‘variables’ are important for constancy?

Conclusions

- Randomisation is (really, really) important, isn’t it? Did something change?

- Is supplementing with external data conceivable? Perhaps.
- Commonly? No.

- Unless ‘validated’, stand-alone data from the randomised comparison should always be summarised, probably as “primary”.

- The ‘case-by-case’ regulatory consideration has to be based on a transparent discussion of sources of bias and the primary and sensitivity analyses that will address these.