



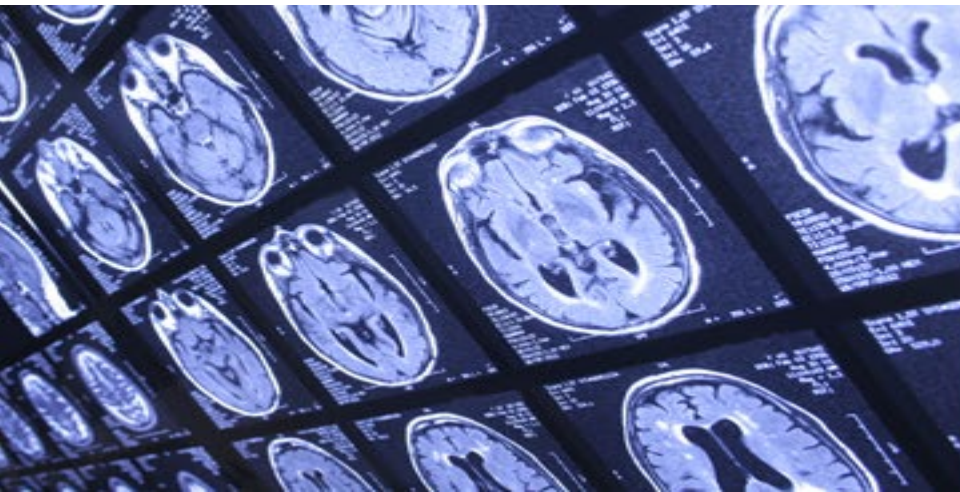
Medicines & Healthcare products
Regulatory Agency



MHRA
Regulating Medicines and Medical Devices

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

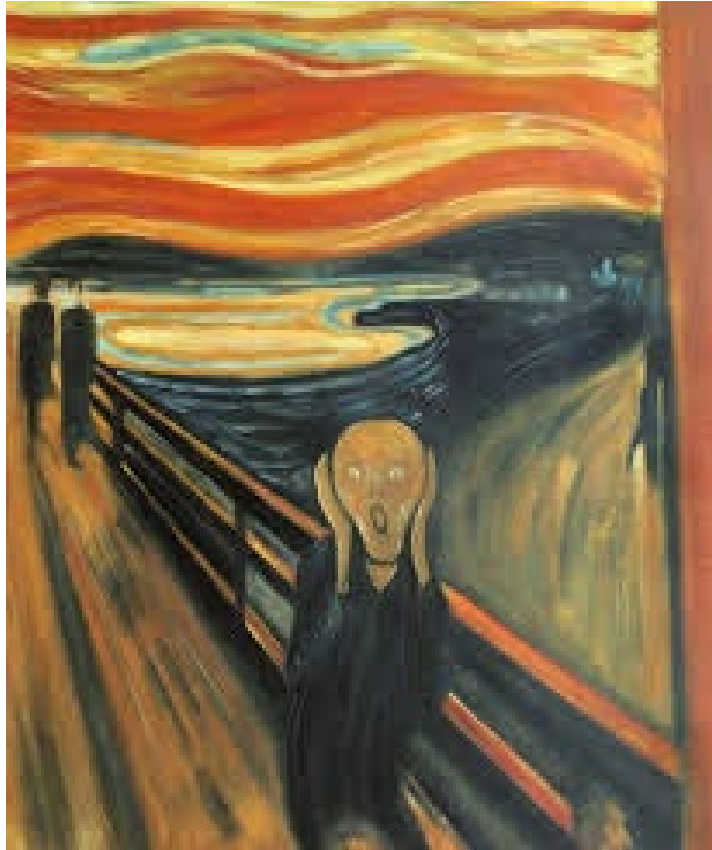
Rob Hemmings, MHRA



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?

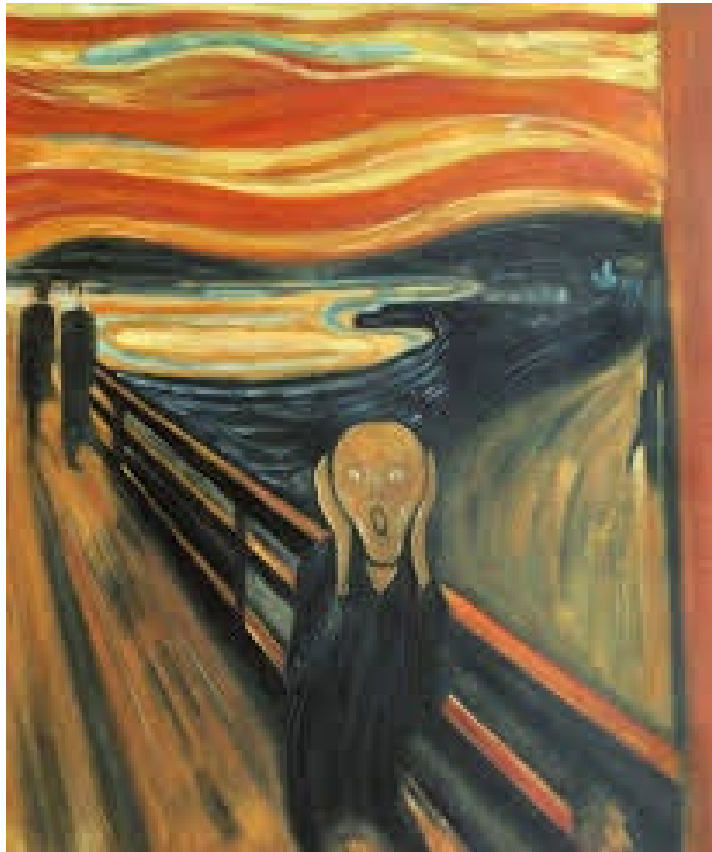
Is it acceptable to supplement RCTs with external data?



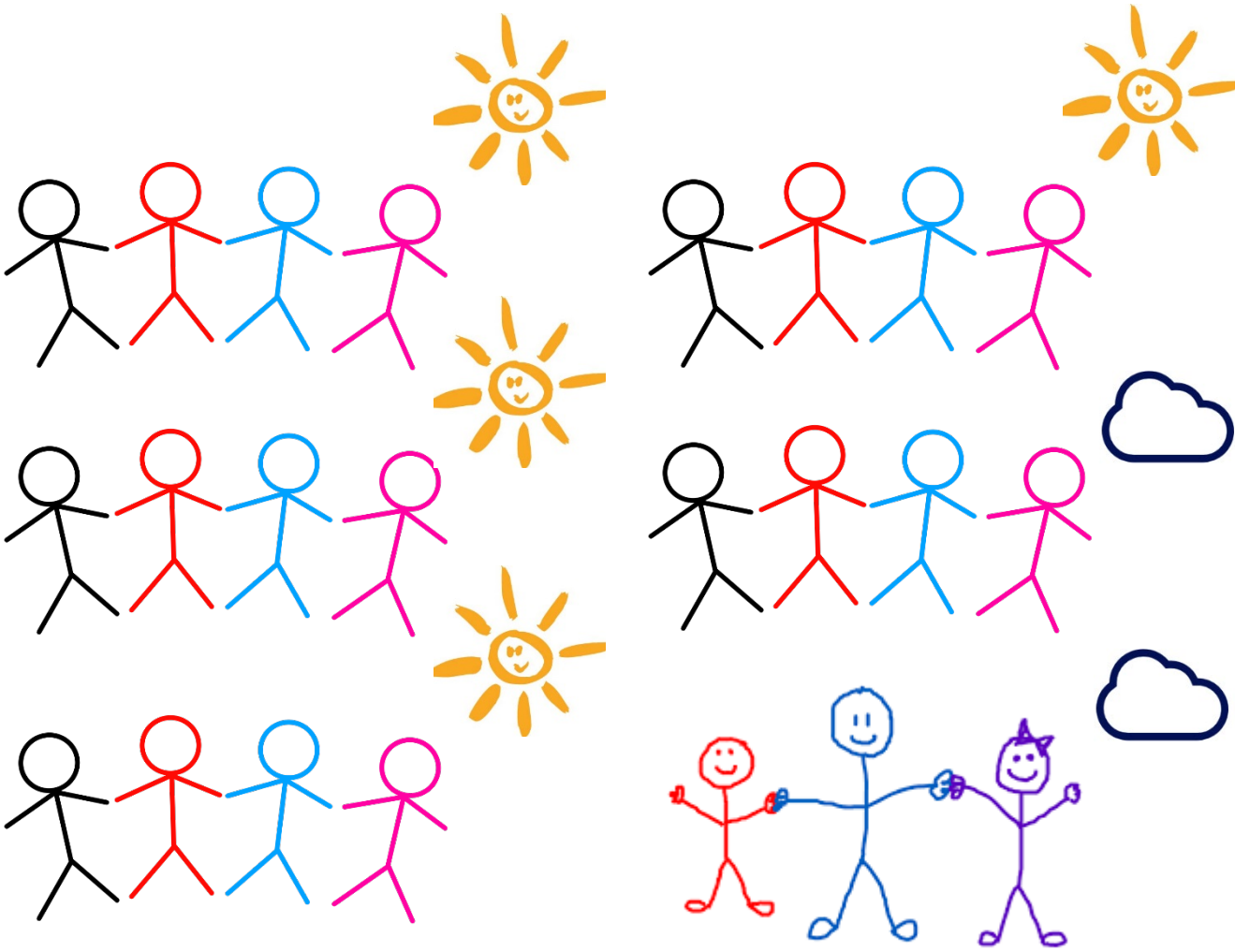
“It depends”

A lot is covered
already in E9 / E10

Is it acceptable to supplement RCTs with external data?



Is it acceptable to supplement RCTs with external data?



Why?



Why?

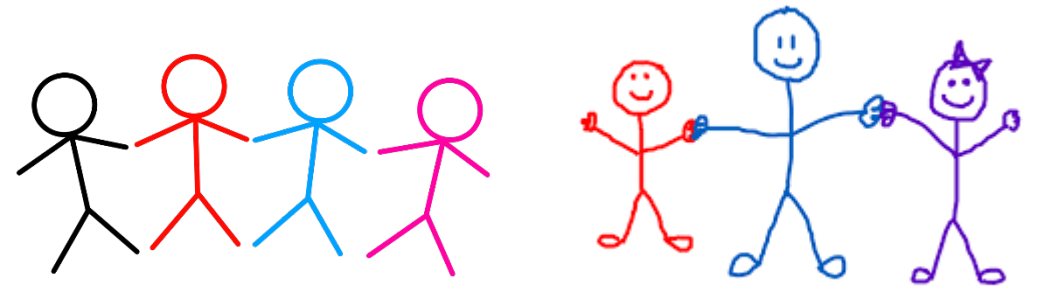


'Efficiency'



- “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 explicitly.

Methods based on similarity of observed data



Which external data source?

What would I consider?



BIAS

ICH E9(R1)
臨床試験のための統計的原則 補遺
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(案)

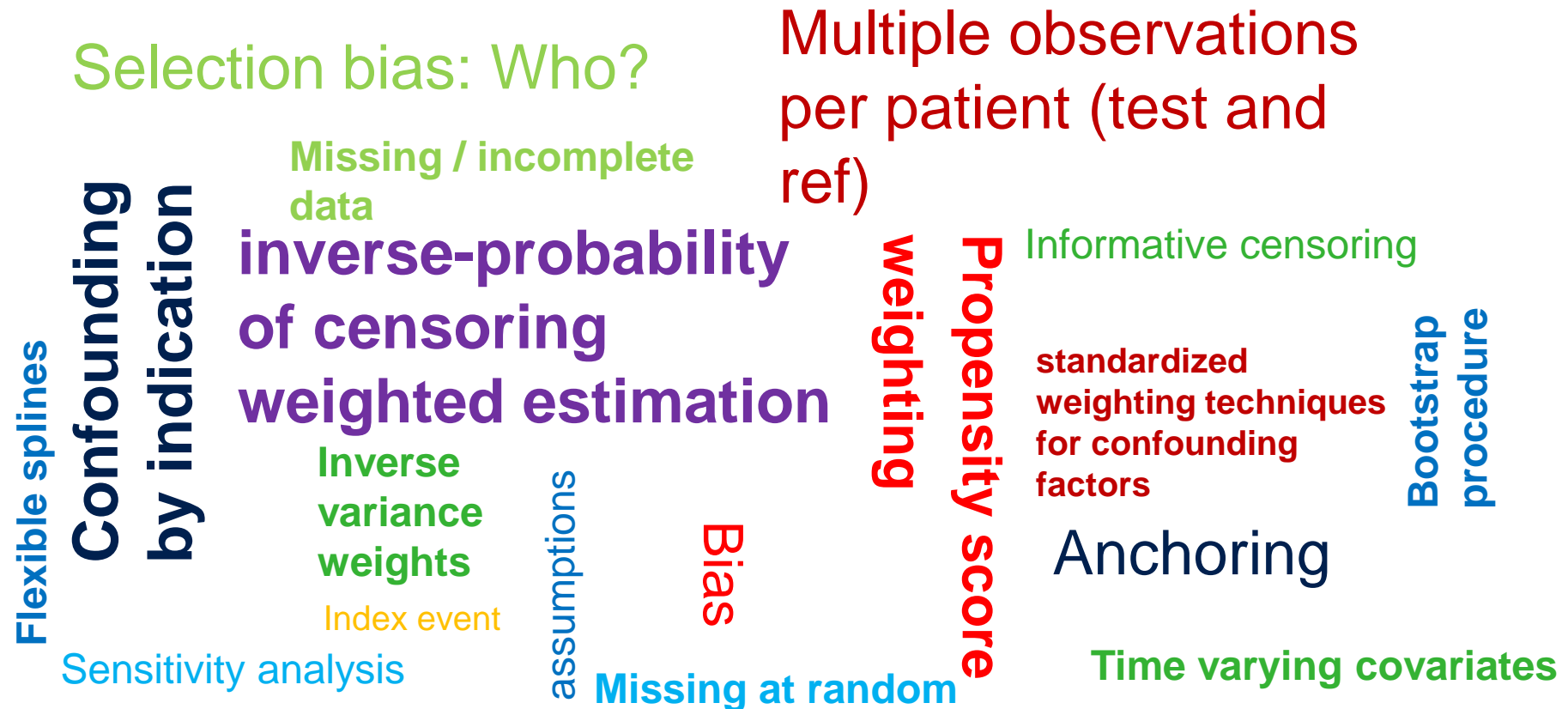


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Historical CTs

Data generated in clinical practice, RWD

Example



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.