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
Is it acceptable to supplement RCTs with external data?
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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)

I haven’t seen these addressed explicity.
Methods based on similarity of observed data
Which external data source?

What would I consider?

Historical CTs

Data generated in clinical practice, RWD
Example

Selection bias: Who?

Missing / incomplete data

Confounding by indication

Inverse-probability of censoring

Weighted estimation

inverse-variance weights

Index event

Bias

Sensitivity analysis

Propensity score

Informative censoring

Bootstrap procedure

Anchoring

Multiple observations per patient (test and ref)

standardized weighting techniques for confounding factors

Flexible splines

Inverse variance weights

Missing at random

Time varying covariates

Missing data

Bias

Sensitivity analysis

Bootstrap procedure
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.