Consistency of treatment effect across pre-specified subgroups – should we (and, if so, how?) adjust for biases?

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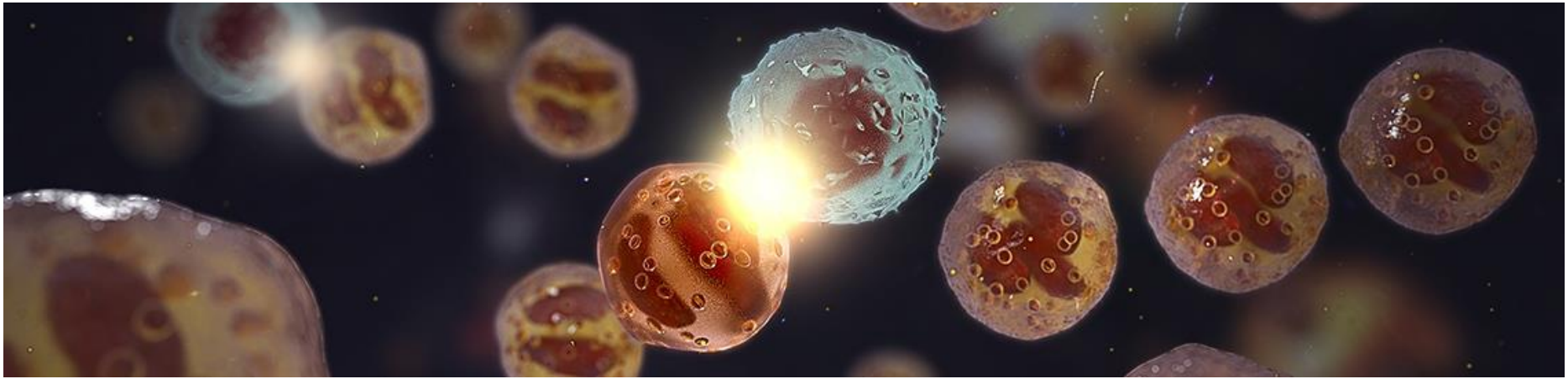

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Content & Outline

- A key step in the evaluation of any pivotal Ph III RCT is to make a risk-benefit assessment and **identify the right patient population** to treat.
- This is '**consistency of treatment effect**', a regulatory requirement (e.g., ICHE5, E9 & E17, EMA [13, 21]). A failure might lead to restricted labelling.
- Special case of interest: regions/countries in MRCTs. Overall result versus country-specific results?
- Despite the importance, no detailed regulatory guidance how to statistically demonstrate consistency. Current standard practices: **statistical issues**.
- **Alternative methods** have been proposed: some discussed here.
  - (*industry view on these*?)

Short remarks:

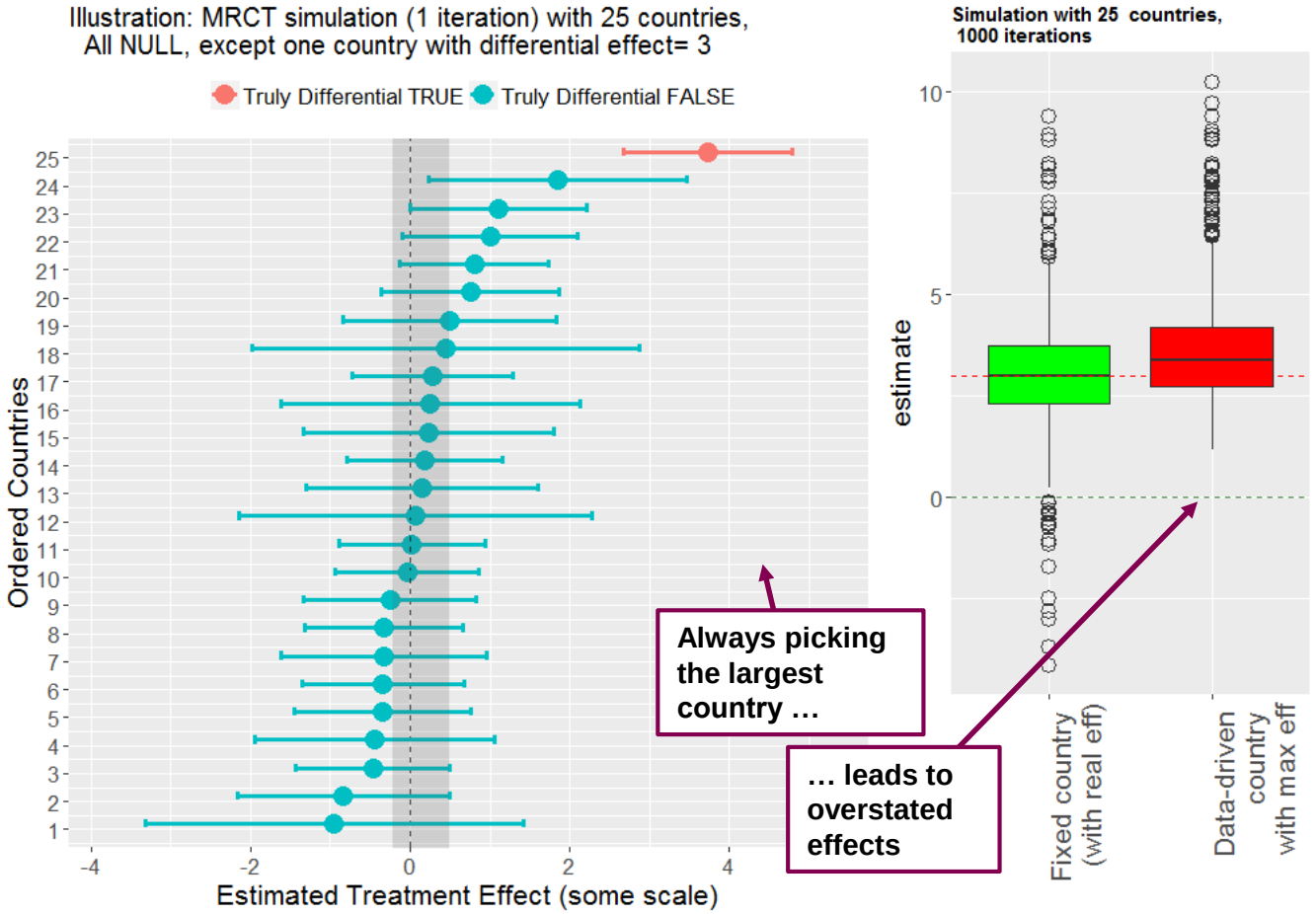
- We have (at this time) **no** strong preference regarding proposed approaches.
  - Rather: are there **any good alternatives** out there?
- But focusing mostly on **shrinkage** here (as an example of a new approach).
- (Aspects will be illustrated with simulations: **exaggarated** effects for clarity).
- Note**: Overlapping** versus **non-overlapping** subgroups:
  - Mostly non-overlapping here (= *a patient belongs to one subgroup only*).
  - E.g., ”country” in MRCT.
- The overlapping (general) case is harder for various reasons (more later).

Are the standard estimates biased?

- Not per se ..
- … unless the reason you look at it is data-driven.

Any data-driven selection: bias.
(e.g., [1])

True even if a country truly has larger expected value (simulation illustration).



Current Approach to consistency: issues …

We reckon that consistency asessement is not merely a statistical exercise, (other considerations too, complex …)

Still, **expect more attention to extremes**; i.e., biases are inherent.

Subgroup estimates = limited data = **large variability**. (Risk of false positives).

Testing sometimes done: e.g., Global Interaction Test (GIT)?

- Low power (trials not sized for it).
- Multiplicity (If a test per subgroup factor – general subgroups).
- Not a testing problem. *Absence of evidence* vs *evidence of absence* …

Well-known issues [2], [5], [29], and alternatives have been proposed …

Any more holistic approach available?

- E.g., **EMA guideline** [13]: useful to assess subgroups together (display full range) although not many details given. Recommendation:

  1. Aim to **pre-group subgroups** into categories (scientific credibility reasons),
     - (A) differential effect plausible, or (B) no differential effect expected.

  2. Use **graphical** methods (e.g., Forest plots).

- **EFSPI Subgroup WG** – White Paper [6]; compared various methods (e.g., simulations); e.g., SEAMOS [8], SIDES [24], Bootstrap Bias Reduction [33], GIT. Recommendation: as EMA, plus:

  – Consider **expected-worst under NULL** [8], to provide a context of the results.

- Jury still out on some other methods? (E.g., Bayesian shrinkage?)

Bayesian Shrinkage has been suggested, e.g.,:

- *Empirical shrinkage estimator for consistency assessment of treatment effects in multi-regional clinical trials.* [30].
- *Multi-regional clinical trial design and consistency assessment of treatment effects.* [31].
- *Treatment effect heterogeneity for univariate subgroup in clinical trials: Shrinkage, standardization, or else.* [35]
- *Exploratory Subgroup Analyses in Clinical Trials.* [32]
- *Bayesian models for subgroup analysis in clinical trials.* [23]
- *Comparing Approaches to Treatment Effects Estimation for Subgroups In Clinical Trials*. [26].
- *Bayesian Assessment ot the Influence and Interaction Conditions in Multipopulation Tailoring Clinical Trials*. [27]
- *A Bayesian Approach to Evaluating Regional Treatment Effect in a Multiregional Trial*. [3]

The idea of Shrinkage

- Well-known **classical** concept, e.g., [11, 12, 26, 36].
  - Stein's classical 'shocking' theorem:
  - *ML estimates can be (dramatically) improved (sometimes)*. [11]

- **Widely used** for high-dim data, e.g.,
  - Microarray screening [11], Pharmacovigilance FDA Signal Detection [19].

- **The Core Idea**: seems to be:
  - *True effects less spread out than observed ones…*
  - *Some shared information across subgroups.*
  - *Self-tuning smoothing towards overall estimate...*

- Borrowing information might help with sparse subgroups (e.g., few events)?

Shrinkage, basic model

i = countries: standard est. $\hat{\delta}_i \sim N(\delta_i, s_i^2)$

Prior for (true) country effects:

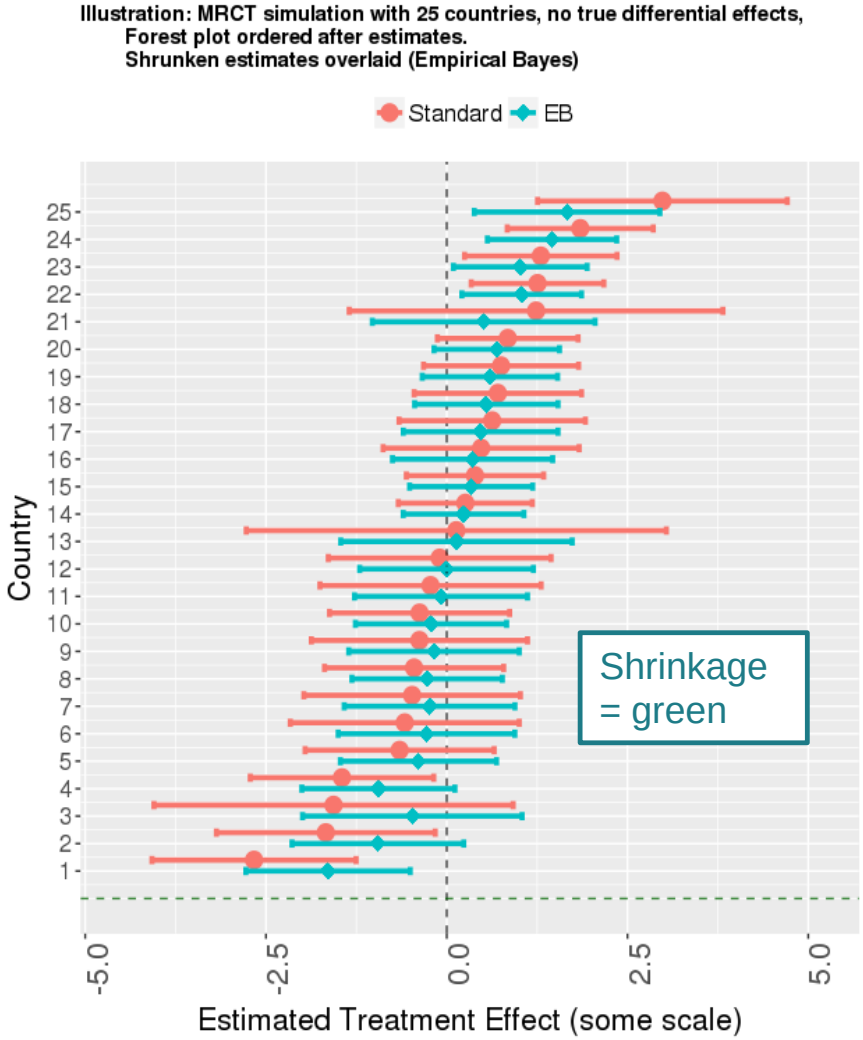
$$\delta_i \sim N(\delta, \tau^2)$$

Gives posterior 'estimate' (MAP):

$$\tilde{\delta}_i = w_i \cdot \hat{\delta}_i + (1 - w_i) \cdot \tilde{\delta}$$

with $\tilde{\delta}$=overall (RE) estimate, and weights: $w = \tau^2/(\tau^2 + s_i^2)$

Model fit? MCMC (Full Bayesian [16]), or **Empirical Bayes** (ML fit of prior to data [26, 35]).



Drivers of amount of Shrinkage? (How much modified):

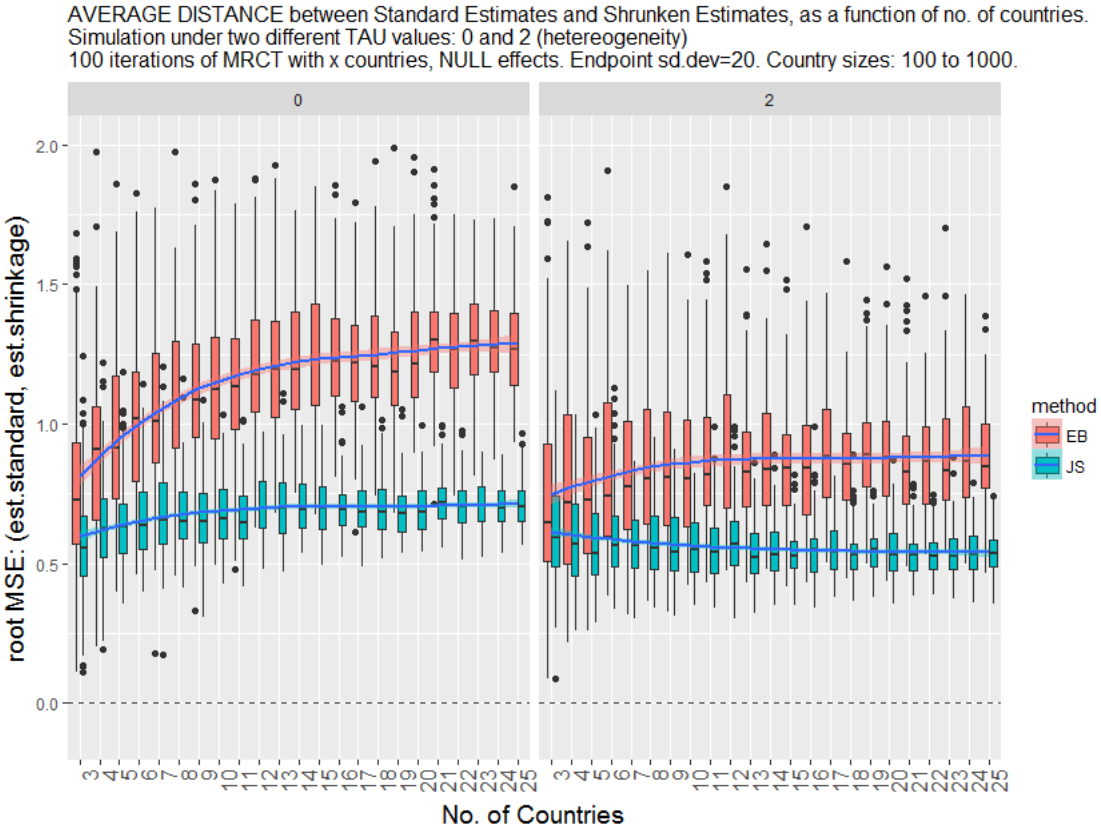
- **Between $\hat{\tau}$ vs within s_i^2**

$$s_i^2 \approx 0 \;\Rightarrow\; \tilde{\delta}_i \approx \hat{\delta}_i$$

$$s_i^2 \; large \;\Rightarrow\; \tilde{\delta}_i \approx \tilde{\delta}$$

- **No. of countries**
  (=x-axis in graph)

- Shrinkage **method** choice
  (several exist –more later).



Some remarks on Emp Bayes estimates

- Remark 1: They are **unbiased** (despite shrinkage towards overall – any confusion?). [under the correct model]

- Remark 2: They also do **bias-adjustments** of 'random-highs':
  – The max.EB (and min) is still biased, but less so.

- Remark 3: Modified ('Improved' or 'manipulated'?) estimates: **controversial**?
  – Assumes 'exchangability' ($\delta_i \sim N(\delta, \tau^2)$: unrealistic?).
  – (Note: an assumption re. the *unobservable*, *true* country effects).

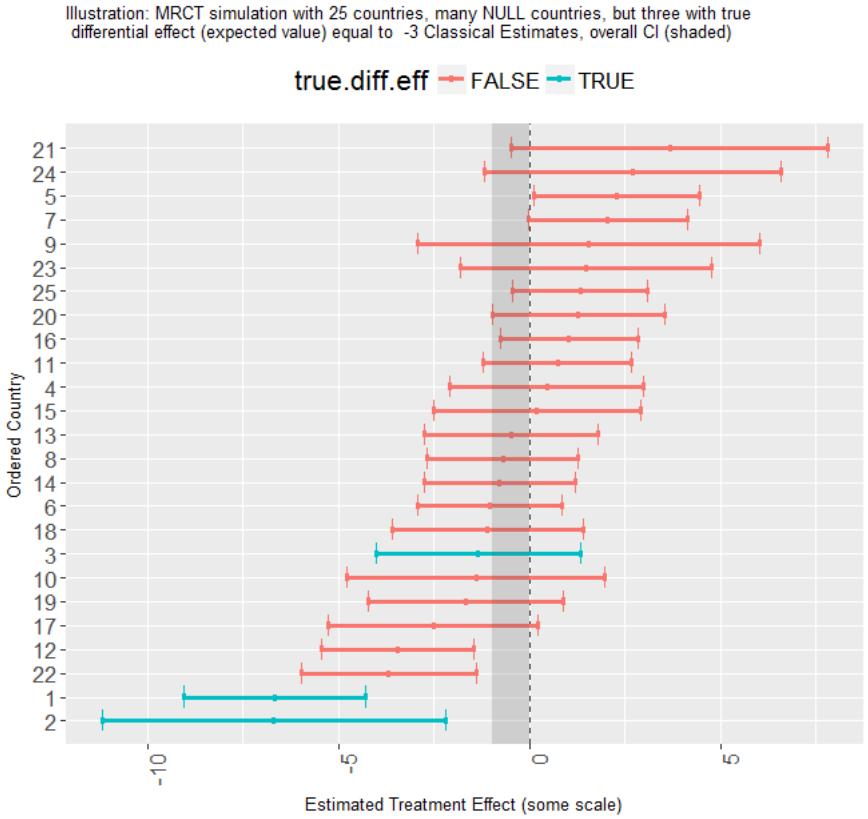
Real differential effects will be shrunken - but recall, noise shrunken too.
  – Does it make it ***easier* or *harder*** to detect truly differential subgroups?

Question: *shrinkage useful as a kind of secondary 'sensitivity analysis*'?

Simulation illustration, under broken assumtion:

What if exchangability is violated?!

- Iterations of simulation of
  - MRCT with 25 countries.
  - 22 with **NULL** effects, δ_i=0.
  - 3 **DIFF** countries with δ_i=x. (-3 in graph)
- **QUESTION**: our ability to detect this, with/without shrinkage?
- Tracking MSE & BIAS & Interval Coverage.
- (Also overlaps: country-specific intervals relative to the overall interval).



Some results, broken assumption (highlights only):

(Full results in Back-Up section)

Considerably **lower MSE for** Emp.Bayes, overall seen.

- (but not uniformly so)..

EmpBay **estimates biased**:

- differential countries were under-estimated.
- The null countries (zero effect) were slightly over-estimated.

But what does it mean, in terms of ability to detect differential countries?

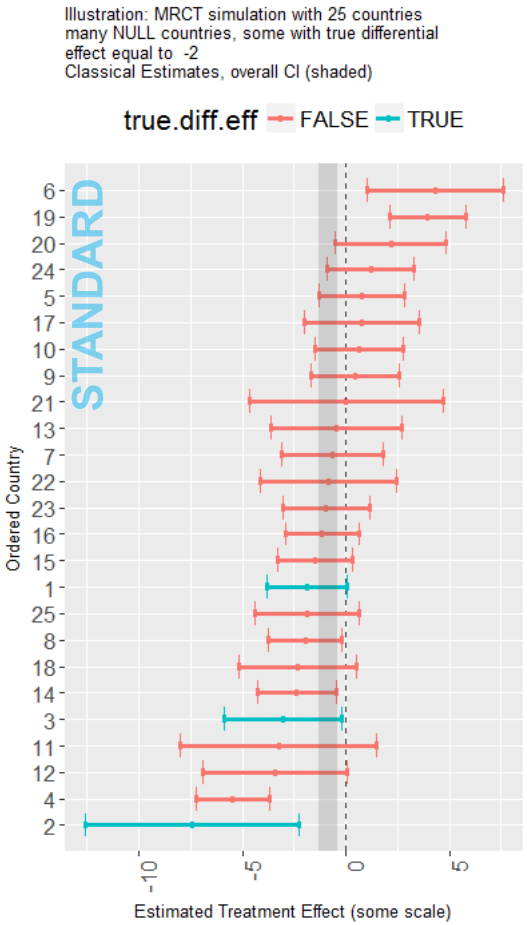
CI overlaps? (under broken assumption).

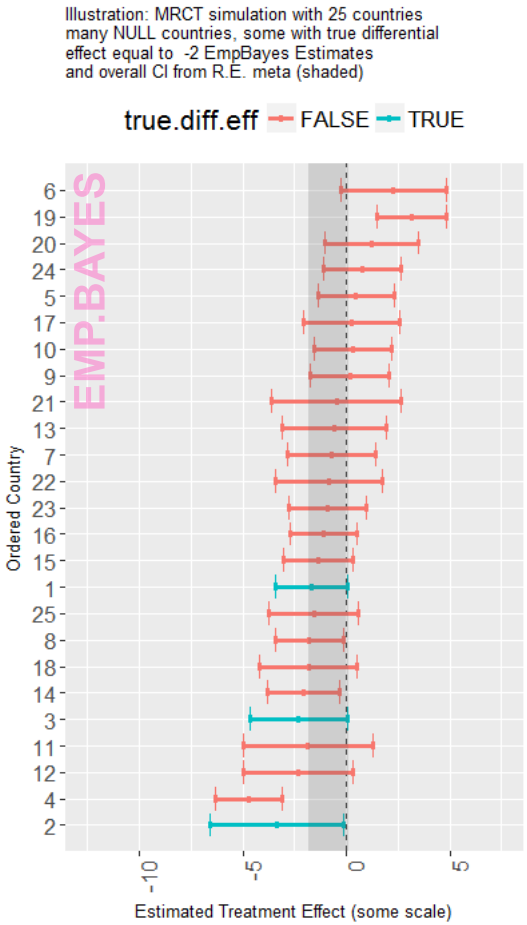
What if **CI overlap** was the key aspect? (Discovery Rates).

- **QUESTION**: ability to detect differential countries via 'non-overlaps', BEFORE/AFTER shrinkage?

1. $\hat{\delta}_j^{EB} \rightarrow$ center (estimates moving).
2. $\|CI_{ac}^{EB}\| \geq \|CI_{ac}\|$ (width, allcomer).
3. $\|CI_j^{EB}\| \leq \|CI_j\|$ (width, countries j).

How will it play out? (1,2 vs 3)



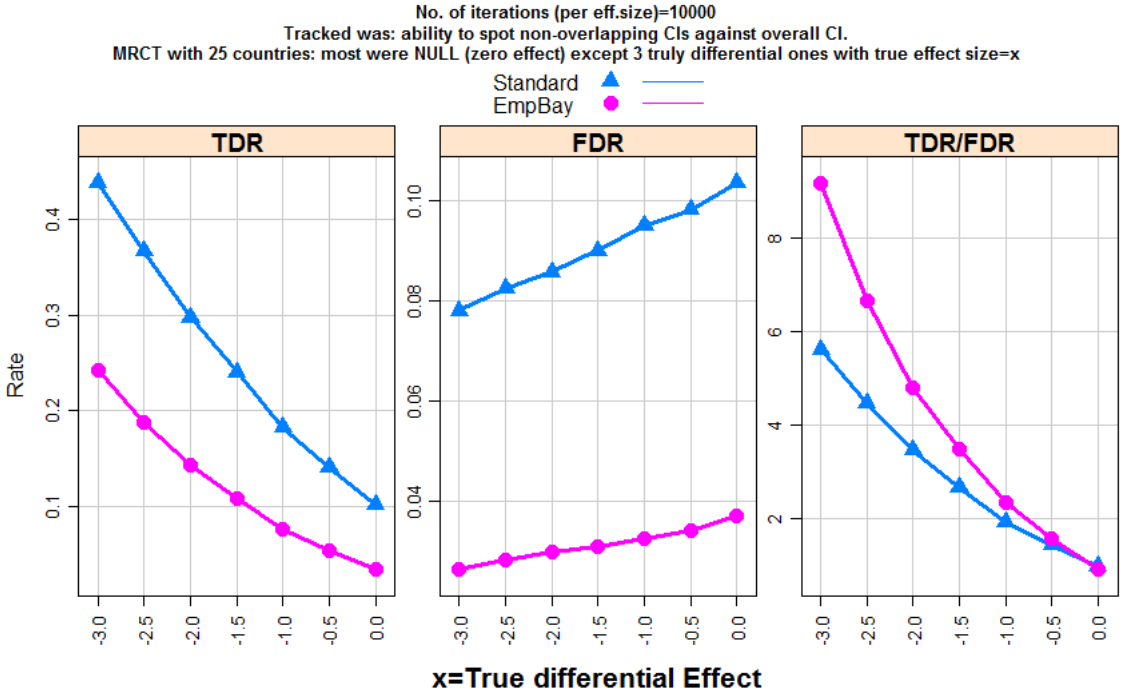


Easier or harder: preliminary results:

Many iterations,
each set with true
differential effect δ_i= x.

Tracked (for both methods):

- **T**rue **D**iscovery **R**ate:
  - (true countries detected?)
- **F**alse **D**iscovery **R**ate:
  - (NULL countries detected?)



Conclusion:
Ratio better ”after shrinkage”, but driven by lower FDR.

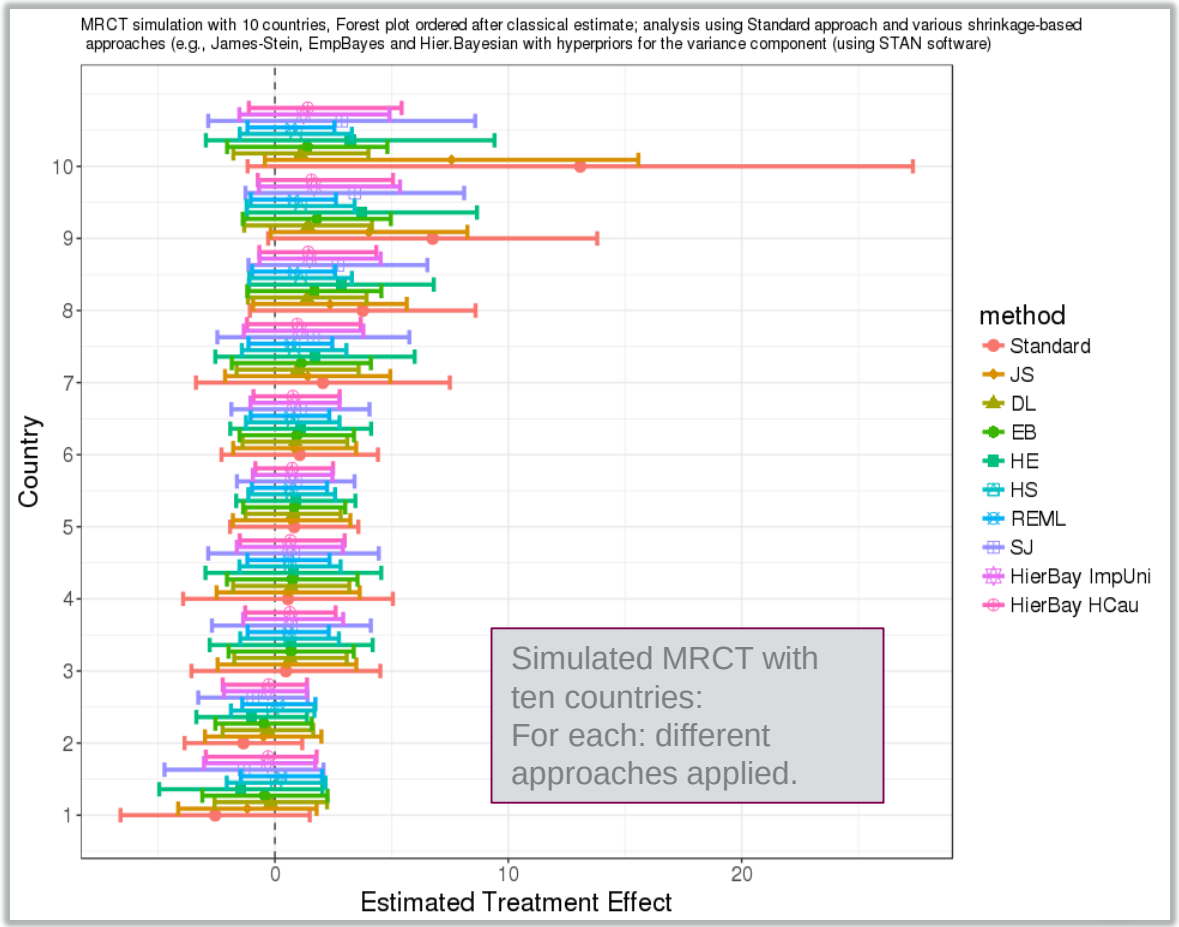
Shrinkage: not just Emp.Bayes; there is more …

- Empirical Bayes is only one of the possible forms of Shrinkage.
- **Meta Analysis** approaches (same model, but different 'τ^2 approaches' [28,37])
- Other well-known instances: **James-Stein** (frequentist approach) [30].
- **Full Bayesian Hierarchical** Model [16]:
  - Don't fit the prior to the data (as EB did): instead, 'let the data speak'.
  - But requires hyperpriors for variance component
  - Computational intensive fitting (e.g., STAN, hamiltonian chains [18]).
- (One motivation: EB ignores uncertainty in prior estimation, FB doesn't).

Shrinkage: many flavours, different results...

(RE approach, various options [37, 27], Hier. Bayes [16,17], Emp.Bayes [37], James-Stein [30]).

- Which is 'Vanilla'?
- Sponsor cherry-picking?
- Note:
- Amount of shrinkage.
- Interval width.

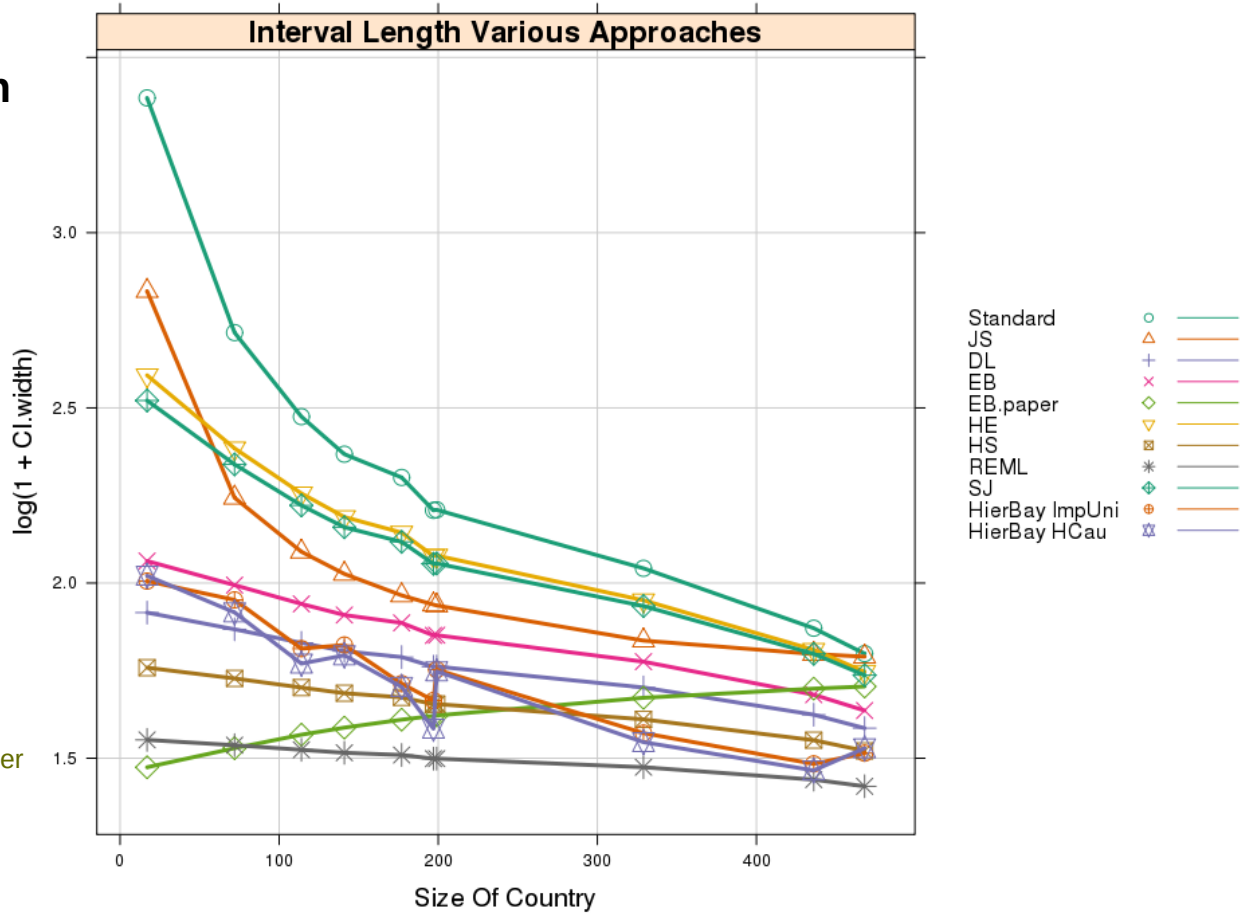


Shrinkage flavours; operating char. differ …

- Interval Length as a **function of subgroup size** – across different shrinkage flavours.

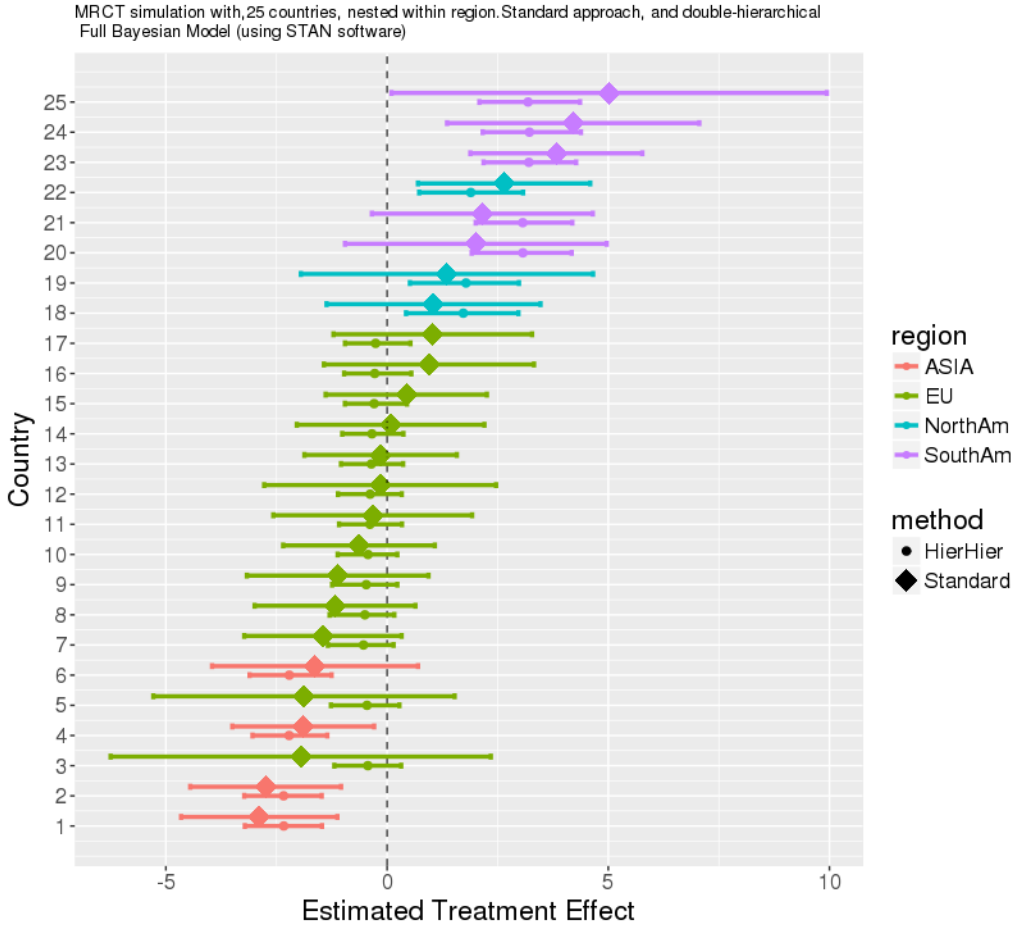
(RE approach, various options [37, 27], Hier. Bayes [16,17], Emp.Bayes [37, 30], James-Stein [30]).

(EmpBayes Variance formula wrong in [30]: smaller regions got more precise CIs …)



Multi-level hierarchical (e.g., country within region?).

- In the spirit of the EMA guideline recommendation [13, 7]; **shrinkage within pre-specified stratas** useful?
  - Could be 'region'.
  - Or, other cathegories:
    - Cat1: differential eff. not expected
    - Cat2: differential eff. plausible
- Possible using a Full Bayesian model.
- Assumptions:
  - Relaxed assumption re. country exchangability.
  - Prior for Regional eff.,
  - Prior for country-eff. within Regions,
  - Hyper-priors for variance components.
  - Unknown operating characteristics?



Shrinkage; overlapping subgroups:

The general (overlapping) case (e.g., `Disease Status, Conc.Med, Gender`):

- Hierarchical Bayesian models after splitting patients into **mututally exclusive** (disjoint) subgroups (e.g,. [9, 26, 38]).
  - Sometimes model fitting instability due to 'sparse cells'?
- Special case of Model selection: **Model averaging** of subgroup-specific models; [1]. Primarily developed for bias-reduction of *selected* subgroups.
  - But does shrinkage for all subgroups (via BIC model uncertainty).
  - Technically different: ensemble of models instead of a single model (such as e.g., with the EB)

Shrinkage; some question marks:

- Shrinkage **assumes what we want to demonstrate?**
-
  - e.g., FDA [34] – ”*apriori assuming exchangability”.*
  - *(”Perhaps this can be helpful in limiting […] random highs*”).

(Stratified assumption/mixture more realistic?).

- **Normality** assumption of the true effects:? Some **skewness** and/or heavier tails more realistic?

- Full Bayes **requires hyper-prior**:
  - No non-informative exists (variance component). [17]. So, which is it?
  - Diagnostics – **operator dependent**?

Conclusions:

- The current approach has **flaws**, and novel approaches have question marks too.
  - Which flavour of Shrinkage?
  - Hierarchical model fitting issues with overlapping subgroups?
  - Exchangeability assumption unrealistic?
  - Unclear trade-offs by shrinkage when true differential effects are present.
  - Stratified (pre-specified?) approach might be worth considering?
  - Technical model fitting issues sometimes with overlapping subgroups?

- Several **other approaches** suggested ([1], [32, 33], [4]):
  - Some only for selected subgroup? some only for non-overlapping subgroups?
  - Some further head-to-head comparisons of operating characteristics needed?
  - Some question marks on the handling of prognostic factors for some permutation approaches [15]?

Regulator's & other sponsor's view on this entire topic? **What do you think**?

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In the event of errors or false claims, the main author takes the full responsibility for it.

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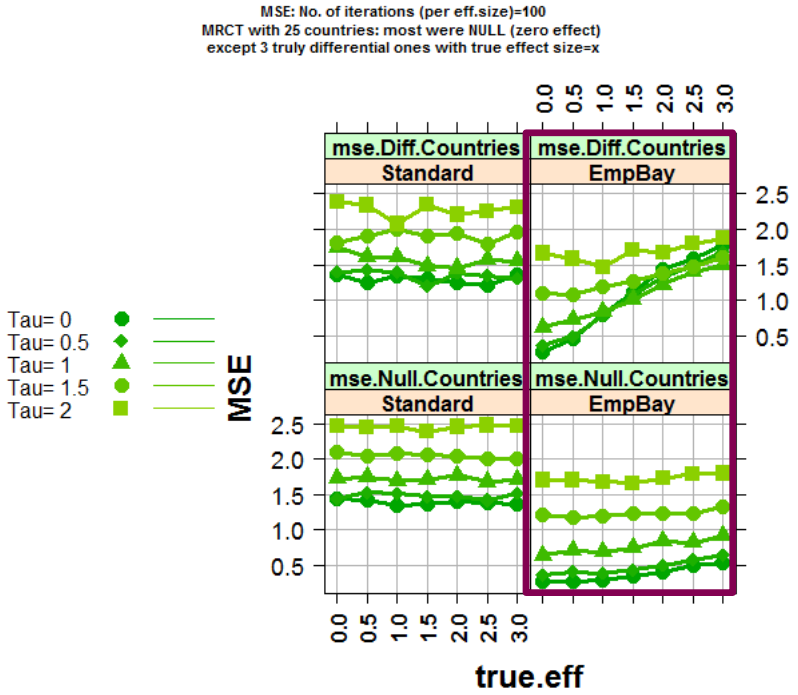
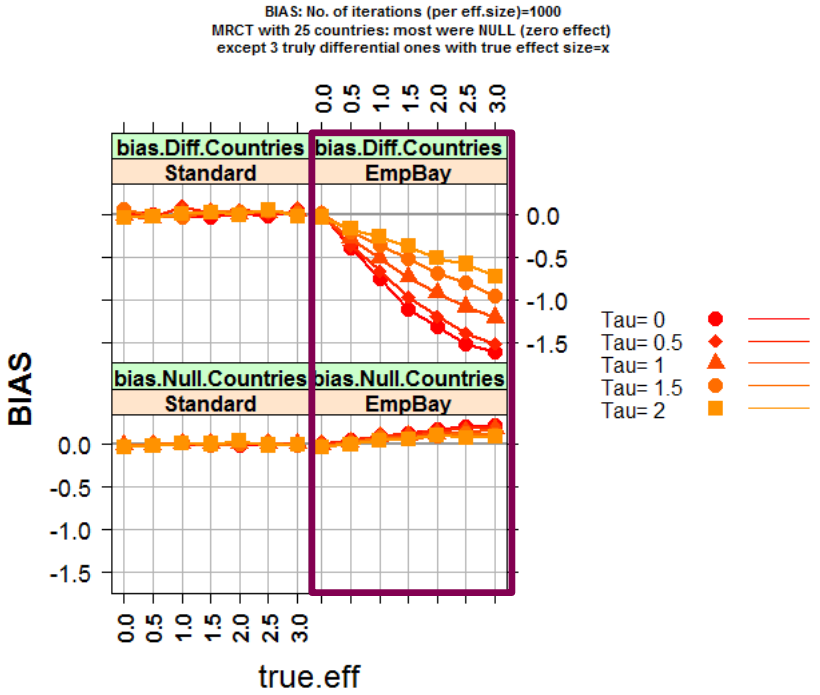
Back-Up Slides:

MSE & Bias (exchangability violated).

X-axis= True Effect (x) in the differential countries.





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