Discussion

Bayesian methods in the development and assessment of new therapies

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Bayesian applications for many different purposes in drug development: “continuous learning”, used, e.g., for
- decision making on project and trial level (e.g. stop or continue)
  - phase I toxicity
  - phase II proof of concept
- analysis in early phases used as explorative/supportive
- missing data imputation
- non-linear models e.g. for dose-time-response / pharmacometrics
- subgroup analysis
  - borrowing strength between subpopulations
- evidence synthesis
  - use of historical data
- extrapolation

Heinz Schmidli: Bayesian applications in drug development
Ralf Bender: Applications of Bayesian methods in health technology assessment

- IQWIG policy to allow for Bayesian methods in specific settings
  - some potential room for Bayesian methods
    (when “necessary”, when frequentist methods are difficult / not available)
  - sensitivity analyses
- Bayesian meta-analyses with few trials
  - may be a compromise between FE and “hard core” RE analysis
  - FE with limitations, especially if large heterogeneity cannot be excluded
  - often heterogeneity cannot reliably be assessed
  - which prior to be used needs further scientific agreement
  - Bayesian approach require the decision on the “right” prior
Sibylle Sturtz: Meta-analysis using Bayesian methods

- overview of different methods for meta-analysis
- fixed (common) effect model may be too liberal, random effect too conservative
- between-study variance $\tau^2$ difficult to assess with few studies
  - “support” estimation of $\tau$ by Bayesian priors
  - could be a compromise between FE and “hard core” RE analysis
  - but may also be more conservative
- few studies: results could be highly divergent between methods/priors
  - 2 studies: posterior $\tau$ similar to prior
- elicitation of prior on $\tau$ may be difficult but could be based e.g. on Cochrane database
- estimation of the treatment effect less influenced by priors
- pre-specification important
Why should/may we apply Bayesian methods?

- best use of all evidence
  - “learning” principle
- synthesis of different kinds of evidence
  - that are difficult to combine in a frequentist framework
- informed study design
- optimal decision making in drug development
  - stop, continue, accelerate, etc.
- “common scientific efforts (of all stakeholders) to generate best evidence”
- and some say: frequentist results are difficult to convey
Why (and when) should we be frequentists (in drug regulation)?

• epistemological background (theory of falsification, K. Popper, etc.)
• *Hitchen’s razor*
  • **burden of proof** lies with the one who makes the **claim** (the applicant) “What can be asserted without evidence can be dismissed without evidence”
  • there are (commercial and other) interests!
• independent (impartial) confirmation required in a pivotal trial to claim efficacy of a new drug
  • no influence of prior prejudice: *be agnostic - be impartial*
• regulators (law makers) need to control the long-term properties of the rule (the law)
  • how often do I wrongly approve a drug?
When may these principles (to use frequentist methods) not apply?

- studies that are at “sponsor’s risk”
  - e.g. proof-of-concept
- interim decisions
  - that do not influence frequentist properties
- in all cases that are not related to a claim (on drug’s efficacy) of a stakeholder with a give interest
When are these principles debatable?

- paediatric applications
  - efficacy confirmed in adults
  - extrapolate this efficacy to children
  - learn from adults to minimize the paediatric study participants
  - full vs partial vs no extrapolation
- different kinds of extrapolation
  - “enhancing” external validity
  - combined evidence vs new independent confirmation in new population
- use of historical controls / “real world data”
  - compromise between “no use” and “full use” of historical data
Specific application: Meta-analysis

- estimation of between-study variance not robust
  - due to the low number of studies
- robust estimation of a nuisance parameter $\tau$ to be supported by a given prior
  - reasonable (sensitivity) analysis to support more liberal FE analysis
  - put the FE (or common effect) assumption under stress
  - other settings using prior information on a nuisance parameter would be interesting to explore
- however: parameter $\tau$ may be important on its own terms
  - large $\tau$ may indicate different populations hampering interpretation
- low number of studies may also just lead to acknowledging that a proper conclusion cannot be made or based on a meta-analysis

RE and Bayesian MA assumption on “sampled studies” questionable
Bayesian meta-analysis: specific issues

• prior on $\tau$ affects the contribution from smaller trials
  • informative $\tau$ prior close to 0: low weight of small studies
  • informative $\tau$ prior far from 0: small and large studies almost equally weighted

• influence of the normality assumption of study effects (as in RE)

• pre-specification/elicitation of priors
  • less of an issue if different priors used as sensitivity analyses
    • sort of tipping-point analysis possible?

• frequentist operating characteristics still useful to know
  • to be evaluated for different $\tau$s
  • to be based on study sampling (may be difficult (to justify))
Bayesian meta-analysis on historical controls and extrapolation

- use of a robust prior
  - compromise between full use and no use of historical data
  - partially independent confirmation
  - but how to decide on scepticism factor $\varepsilon$?
  - only those settings are relevant in which a positive decision depends on the unjustifiable choice of $\varepsilon$
- potential lack of full pre-specification
  - planning a paediatric trial using Bayesian methods when adult data are known may already be an issue
  - retrospective evidence synthesis even more
(further) issues to be discussed

some agreement on accepting Bayesian methods on decision that are fully at sponsor's risk
• PoC, go/no go decisions, etc.
but if not
• frequentist properties / type-1 error: whether and how to evaluate?
  • a Bayesian design that respects frequentist properties is not fully Bayesian

Bayesian meta-analysis
• how to deal with divergent results depending on prior?
  • a significant result based on which prior should convince me?
• how to elicitate and agree upon the prior on $\tau$?
• Bayesian methods used in extrapolation or to include historical controls
  • again: how to decide if results depend on the scepticism/down-weighing?
• what about Bayesian meta-analysis on safety (with reversed burden of proof)?