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Hype, not Hope –
Using Bayesian Methods in Drug Development

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Introduction

- Recent publications advocated the use of Bayesian statistics in drug development (Ruberg et al., 2023):

  - conceptual arguments
  - recommendations for Bayesian models
  - examples of empirical studies
- Position papers used similar arguments in the past but have not impacted the adoption of Bayesian methods as much as desired
- Issues in the arguments used (Igl & Constant, 2023)

Key Issues

- Overstatements: Bayesian statistics is not fundamentally distinct with enormous consequences (cf Gill, 2011)
- Miscommunication to target audience: Regulators' priority is to be conservative and consistent and not innovative, creating reluctance (cf Campbell, 2020)
- Inappropriate Bayesian methods: Bayesian methods may show massive inflation of risk for false positive conclusion (cf Berry et al., 2013; Chu & Yuan, 2018)
- Poor empirical examples: questionable assumptions, no added value (cf Senn, 2022)

Conceptual Arguments

Fundamental differences and enormous consequences

- Differences are overstated, because Bayesian and frequentist approaches will give the same results:
  - if a non-informative prior distribution is used
  - if more data are collected
- Argument will scare away regulators, because the priority for regulators is more on being conservative and consistent and less on being innovative.

Use of existing empirical data

- Against principle of "Design trumps analysis!"
- Prospective Randomized Controlled Trials (RCTs) are still the reference standard
- High complexity will raise concerns by regulators by adding hard-to-understand Bayesian methods to hard-to-understand data

Conceptual Arguments (cont.)

Use of existing knowledge

- Subjective belief in the validity of a prior distribution needs to be agreed upon with regulators
- Bayesian statistics does not solve the problem of subjectivity but moves it to other stages in the decision process

Costs and complexity

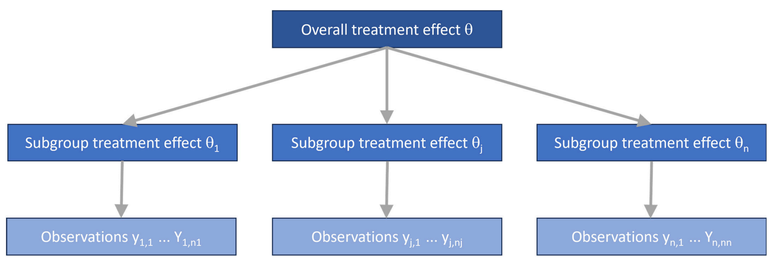
- Bayesian analysis may make a study smaller, but more complex and expensive, while creating efficiencies in the entire clinical development program
- Vague incentive for drug developers
- Safety data may be cost driver, not efficacy data

Recommended Methods

Bayesian hierarchical models (BHM)

- assumes an overall treatment effect
- allows "borrowing information" between subgroups
- appropriate if subgroups are similar ("exchangeable")

Figure 1. Hierarchical Model (Chu & Yuan, 2018)



Equation 1. Bayesian Hierarchical Model (Chu & Yuan, 2018)

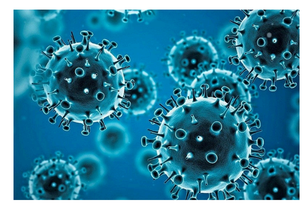
$$y_j|p_j \sim Bin(p_j)$$
$$\theta_j = \log\left(\frac{p_j}{1-p_j}\right)$$
$$\theta_j|\theta,\sigma^2 \sim N(\theta,\sigma^2)$$
$$\theta \sim N(\alpha_0,\omega_0^2)$$

- Issues:
  - If objective is to detect differential treatment effects assumption of an overall treatment effect not plausible
  - original BHM proposed by Berry et al. (2013) can show an inflation of the nominal risk of false positive conclusions of 10% to over 50% (cf Chu & Yuan, 2018)
- Solution:
  - Bayesian predictive cross-validation models (Dias et al, 2011) predict treatment effect in subgroup of interest based on overall treatment effect of all other (!) subgroups, i.e., without this questionable assumption

Empirical Studies

Pfizer/BioNTech COVID-19 vaccine study

- Pfizer/BioNTech evaluated the vaccine efficacy of the BNT162b2 ("Comirnaty") mRNA vaccine using Bayesian statistics



- Questionable assumptions, e.g., prior distribution for vaccine efficacy centered around 30% labelled as "pessimistic" and "minimally informative"
- Bayesian statistics did not add value because of very strong effects (Polack et al., 2020; Senn et al., 2022)

Pediatric Cardiac Arrest Trial (THAPCA-OH)

- Primary Frequentist analysis: Therapeutic hypothermia did not reach the standard statistical significance threshold of 5% to demonstrate superiority over therapeutic normothermia → ineffective treatment

- Secondary Bayesian analysis: Therapeutic hypothermia had a 94% probability of any benefit over therapeutic normothermia → effective treatment (Harhay et al., 2022)

Key Solutions

Rethink the line of argumentation (cf McElreath, 2020):

- Balance the presentation of differences and (!) similarities

- Target communication to audience, esp. regulators
- Evaluate operating characteristics based on regulatory standards, esp. risk for false positive conclusions
- Promote Bayesian studies which show added value, especially for patients

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