Practical Bayesian Design for Rare Disease Drug Development

Satrajit Roychoudhury, Pfizer Inc
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There is a scientist who wants to compare a new treatment in rare disease

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Can this new drug prolong the survival of patients with rare disease X?

• How to do a reasonably well controlled trial in this rare population?
• How to design this trial properly to address the scientific question of interest?
• Can this be done with available resource and timeline?
Borrowing external information for control arm can make the traditional design efficient

Question: Can we bring this information in trial design and analysis?
A single arm trial can also be informative with indirect comparisons

Patients in a disease area

Treatment arm (EXP)

Trial external information (SOC, Real World Data or Comparator Drug)

Question: Can we still do a comparative analysis?
Master Protocol can use all available resources efficiently

However, such designs are not common, which leads to concerns

- Relevance of external data
- Interpretation of result
- Communication to key stakeholders

Shall we??
However, such designs are not common, which leads to concerns

- Heterogeneity for data source
- Degree of borrowing
- Complexity of estimand in interest

- Relevance of external data
- Interpretation of result
- Communication to key stakeholders
World is seeking new treatment in rare disease

RARE DISEASES BIG IMPACT

IN TOTAL, RARE DISEASE IMPACT
30 MILLION
1 in 10 AMERICANS

Source: National Institutes of Health

Source: PhRMA 2013 report on Rare Diseases
Current landscape demands innovation in development

There are 7,000+ rare diseases worldwide.

Of these, 80% are genetic diseases, which affect

an estimated 320 million people worldwide.

https://www.pfizer.com/science/rare-diseases
Recent healthcare and regulatory changes are supportive of such innovative designs.

Upfront discussion with regulators is highly encouraged.
Careful consideration of study design is the key to success

- **Design considerations**
  - Endpoint: asking the right question
  - Replace or augment control arm with available information in standard of care
  - Extrapolation to other demographic subgroups
  - Modeling disease from natural history data
  - Master protocol
  - Use of real world data (RWD)

- **Other considerations**
  - collaboration and data sharing
  - registry development
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There are different approaches of borrowing external data

The main approaches include

1. Test and pool (Viele et. al. 2014)
2. Bias model (Pocock 1976)
3. Commensurate prior (Hobbs and Carlin 2011)
6. Propensity score approaches (Lim et. al. 2018)

Approach 2-5 are similar: discounting of external information due to between-trial heterogeneity
External control data augmentation design can be helpful to save resources

- **Use of available information in the design**
  - Use information for control worth n* patients and allocate n- n* patients to saves sample size
  - Bayesian methods provide a natural way to incorporate external data in the form of prior

- **Choice of relevant external control data**
  - Requires judgment about similarity of external and current trial setting (e.g., Inclusion/exclusion criteria, endpoint, time-trends)
  - Requires interaction with non-statistician

- **n* is often referred as prior effective sample size (pESS)**
  - Quantifies amount of information borrowed from external control

End of Study

SS=n

SS=n – n*

E

C

HC

pESS=n*

Screen

Breakthroughs that change patients’ lives
Meta-analytic approach uses Bayesian hierarchical model to bridge between external control and study data

- Uses a model for all quantities, which involves a parameter model
- Infers the parameter of interest $\theta^*$: **dynamical borrowing**
We use a meta-analytic predictive approach to borrow external data in the control group

Meta-Analytic Predictive (MAP)

Meta-Analytic Combined (MAC)

MAP and MAC are equivalent: “exchangeability” is the key assumption

• MAP priors not analytically available: approximated by mixtures

• MAC requires one combined analysis: based on posterior or “shrinkage” estimate
One main criticism of using external data is the possibility of prior-data conflict.

Prior-data conflict means: actually observed $Y^*$ is in the tail of the prior predictive distribution.

Requires robustness.

*De Groot always carried an $\varepsilon$ of probability for surprises in his pocket!*
Meta-analytic framework can handle the possibility of prior-data conflict by using mixture priors.

Robustness and more rapid adaptation to prior-data conflicts by adding extra weakly-informative mixture component.

MAC framework can also handle prior-data model with mixture model.
Example: Use of external control in a phase II design of Progressive Supranuclear Palsy (PSP)

- Progressive supranuclear palsy (PSP) is a degenerative neurologic disease due to damage to nerve cells in the brain
- 20,000 PSP patients have been diagnosed with the disease (6.5 cases per 100,000 individuals)
- No effective drug halting the progression of the disease
A traditional design will require 160 patients for a reasonably powered study

- **Disease**
  - PSP

- **Experimental treatment**
  - Monoclonal antibody (E)

- **Endpoint**
  - PSPRS (A clinical rating scale) change from baseline assessed at week 52

- **Traditional clinical trial design**
  - New treatment (n=80) vs. Placebo (n=80)
  - Z test

Can external placebo information be used?

Golbe and Ohman-Strickland 2007
Using meta-analytic framework we can improve the design

- Double-blind, randomized, placebo-controlled study for experimental drug

- **Primary endpoint**: Change from baseline in PSPRS at 52 weeks
  - 4 points from placebo clinically meaningful

- **Planned sample size 120**
  - 2:1 in favor of E
  - Z test: 73% power for $\delta = 4$

- 2 historical trial data for placebo (n=144))
  - Tideglusib vs. placebo (Tolosa et. al. 2014)
  - Davunetide vs. placebo (Boxer et. al. 2014)

<table>
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<th>Study</th>
<th>N</th>
<th>Y</th>
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<tr>
<td>Boxer14</td>
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Informative prior for placebo arm considers the heterogeneity between different data sources

- External data for placebo is homogeneous in two studies
  - Sample size varies: poses uncertainty
- MAP prior reflects this uncertainties
  - \textit{apriori} placebo effect varies 7.8-13.3
  - prior worth 52 subject information for placebo
  - non-informative prior for E
- New trial is successful if
  - \( P(\delta < 0 \mid \text{data}) > 97.5\% \)
Robust MAP prior reflects the degree of confidence on external control data

A mixture of MAP and weakly informative prior becomes a heavy-tailed version of the prior derived from external placebo data

- Mixture prior - 75% informative, 25% non-informative

MAP prior
(100%-0%)

Robust MAP prior
(75%-25%)
Robust MAP prior can handle prior data conflict

Scenario: No Conflict

Weights
- aprior informative 75% weak 25%
- posterior informative 90% weak 10%

Scenario: Conflict

Weights
- aprior informative 75% weak 25%
- posterior informative 1% weak 99%

Note: Weights are fix apriori but posterior weights get updated using standard Bayesian calculus (Schmidli et. al 2014)
Robust MAP prior provides good design operating characteristics

- Robust prior provides a nice balance between Type-I error and power
  - Type-I error: well controlled when prior and data are aligned
  - Type-I error: max 8% under prior-data conflict
  - Power = 87% for $\delta = 4$: considerable gain over traditional frequentist design
- Type-I error inflation is much higher with informative prior only under prior-data conflict
Meta-analytic framework can be extended for extrapolating information from adult to children

- Meta-Analytic framework: a powerful tool for extrapolation
  - flexible structure of borrowing from different cohorts (adults, adolescents, and younger children)
  - extrapolation from adult population to pediatric refers to borrowing “treatment effect” information
- However validation of extrapolation concept is key
  - use of predictive check to ensure data or model adequacy for extrapolation

Predictive Evidence Framework: provides a measure of adequacy of information for regulatory purposes (Neuenschwander, Roychoudhury, and Branson 2017)
Meta-analytic framework is useful to borrow external control in platform trial

- Two sources of external control data in a platform trial with
  - data generated outside the platform trial in multiple trials
  - non-contemporaneous data generated on the control arm within the platform trial itself
  - one can’t *just pool*: need to consider heterogeneity among different sources
  - possible conflict with different sources

- Borrowing of the contemporaneous and non-contemporaneous control requires careful consideration
  - consideration of time-lag in data collection
  - less controversial: experimental arm is only compared to the control arm data generated contemporaneously

Meta-analytic approach provides robust way to incorporate both historical and non-contemporaneous control arm data in platform trial
There are examples of using history data in regulatory submission now

- **Brineura** for Batten Disease
- **APTIOM** as monotherapy for Seizures
- **Venetoclax** in Relapsed / Refractory Chronic Lymphocytic Leukemia (CLL)
- **Eteplirsen** in Duchenne Muscular Dystrophy (DMD)
Patients with rare diseases are in desperate need of innovation
- Requires a shift in thinking from 2 studies p<0.025 to continual learning via Bayesian approach

Need to leverage ALL sources of information
- Meta-analytic approach provides great flexibility for borrowing in different set-up and framework

Statisticians have a lot to add!
- “Fresh” perspective to study design
- Perform “statistical engineering” for real life implementation
- Train and influence non-statisticians

An open-minded and collaborative attitude has been (and still is) the most important factor
References


5. RBesT: R Bayesian evidence synthesis tools. 2019. R package version 1.5-0.  
https://cran.r-project.org/web/packages/RBesT/index.html

"Those that fail to learn from history, are doomed to repeat it."

- Winston Churchill