Practical Bayesian Design for Rare Disease Drug Development

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Breakthroughs that change patients' lives

Pfizer

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There is a scientist who wants to compare a new treatment in rare disease

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

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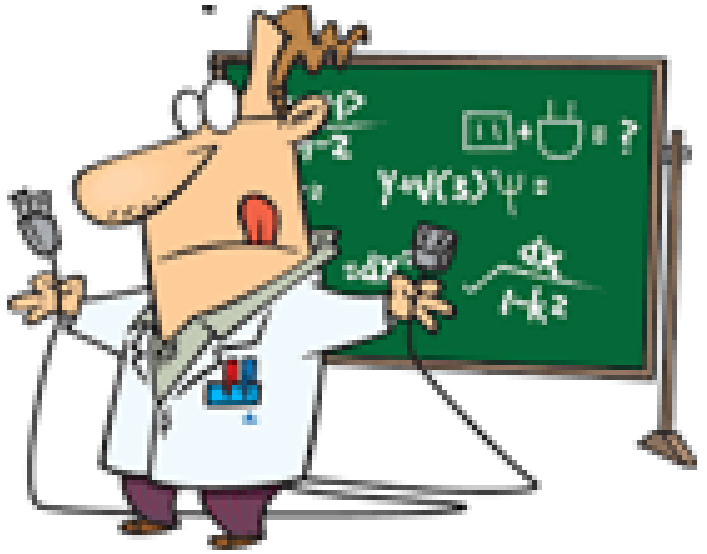
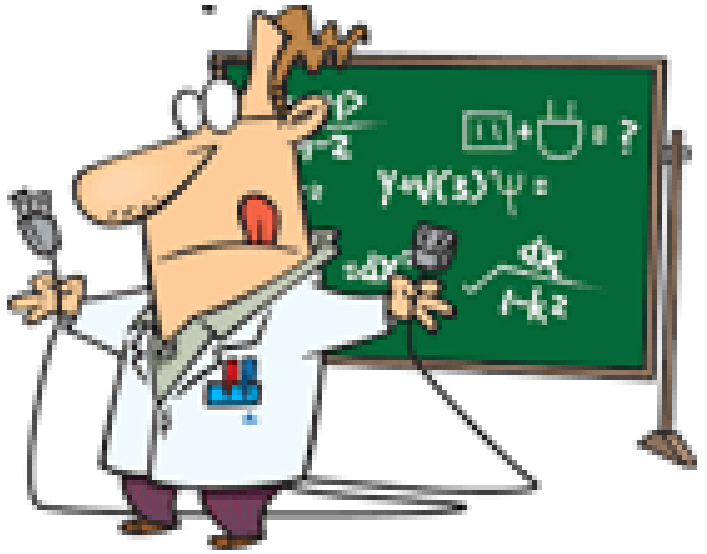


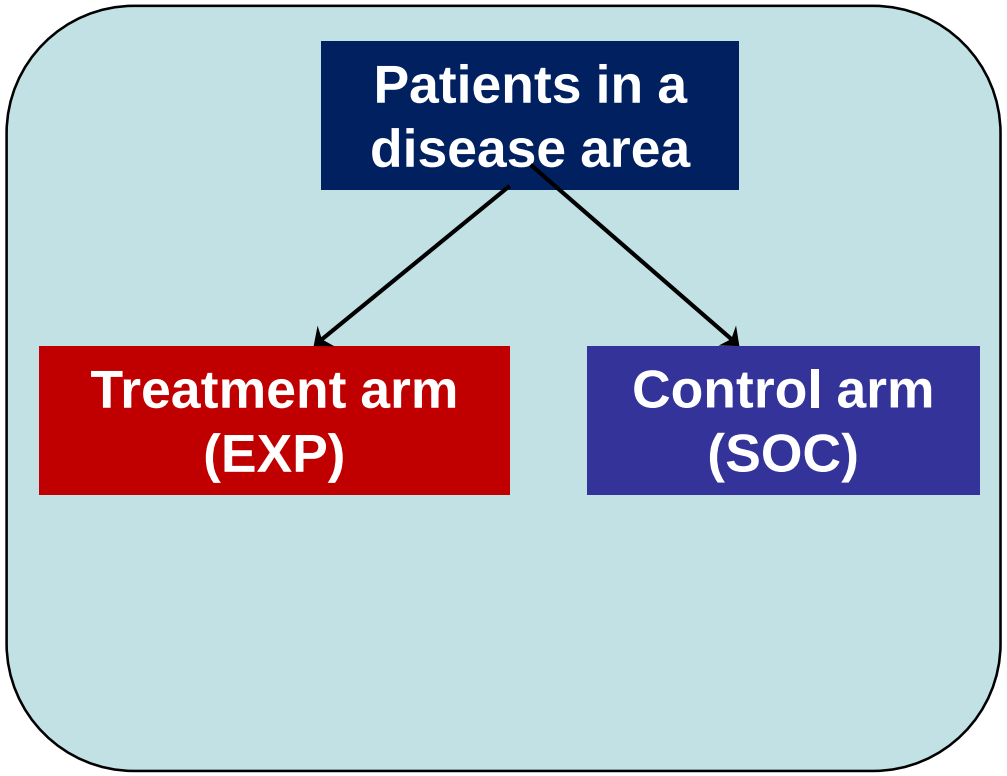
There is a scientist who wants to compare a new treatment in rare disease

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

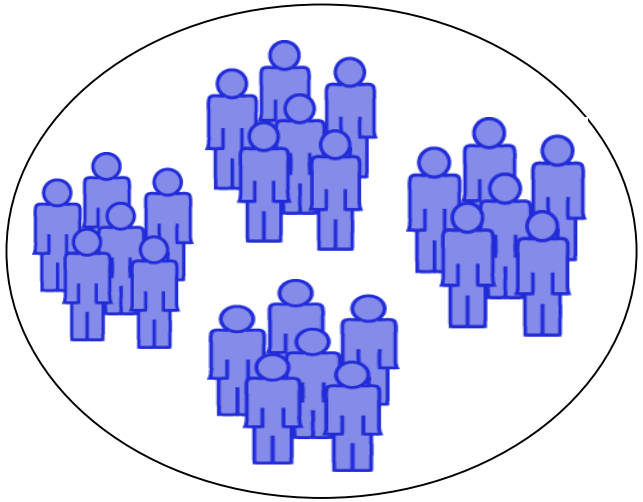


- **How to do a reasonably well controlled trial in this rare population?**
- **How to design this trial properly to address the scientific question of interest?**
- **Can this be done with available resource and timeline?**

Borrowing external information for control arm can make the traditional design efficient

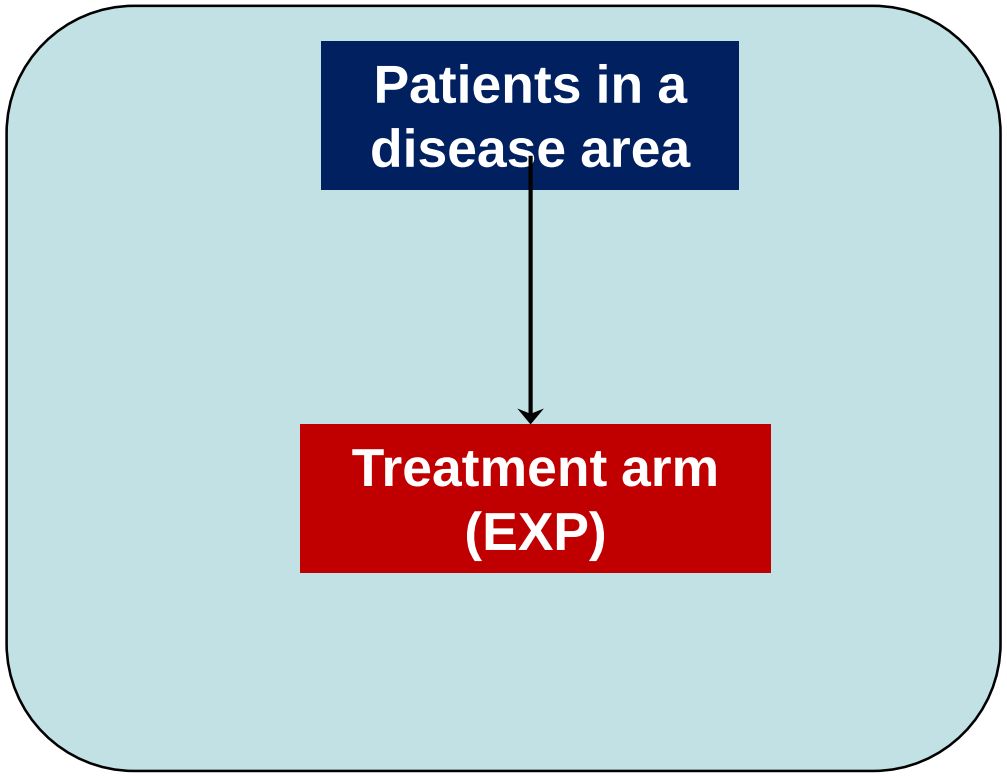


Trial external information (SOC)

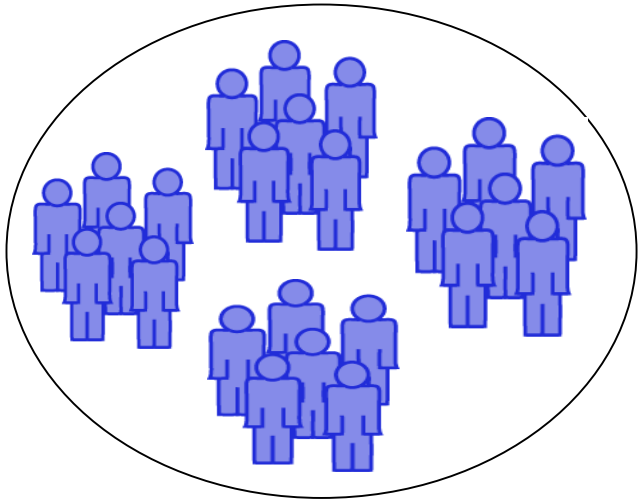


Question: Can we bring this information in trial design and analysis?

A single arm trial can also be informative with indirect comparisons

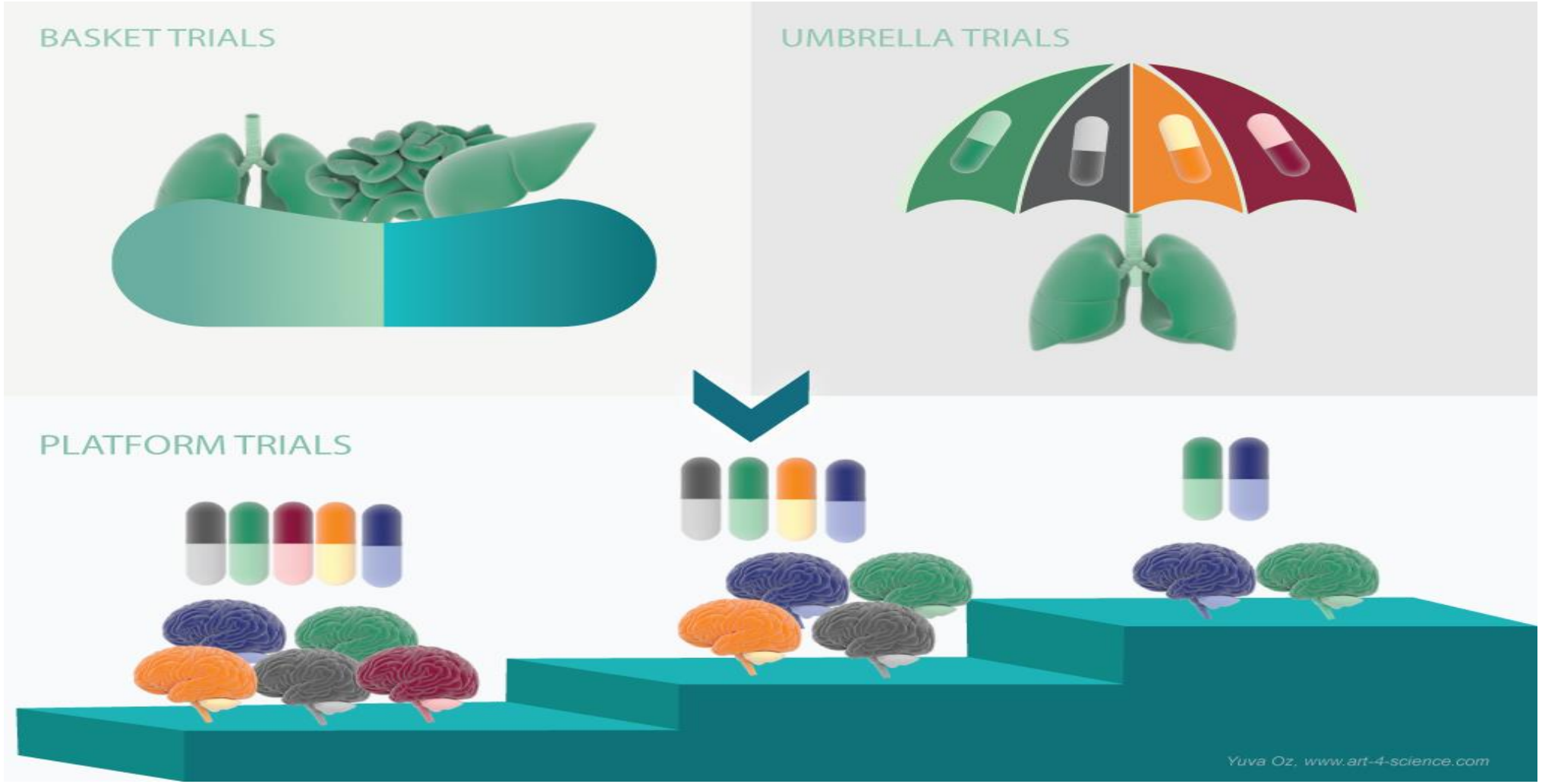


Trial external information (SOC, Real World Data or Comparator Drug)



Question: Can we still do a comparative analysis?

Master Protocol can use all available resources efficiently



https://sms-oncology.com/news/blog/the-changing-landscape-of-oncology-clinical-trials-aacr-2017/

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

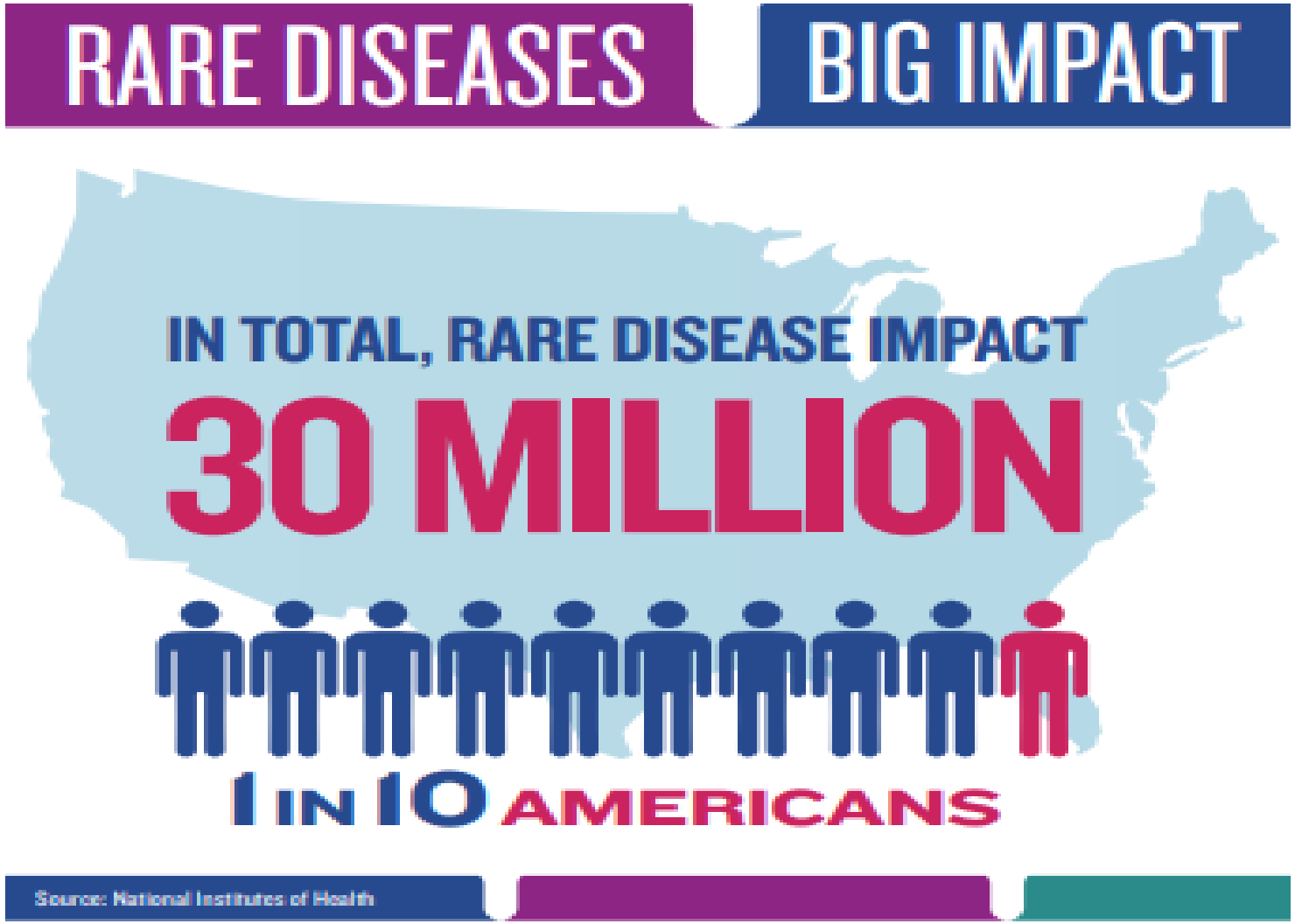
- **Relevance of external data**
- **Interpretation of result**
- **Communication to key stake-holders**

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 stake-holders

World is seeking new treatment in rare disease



Breakthroughs that change patients' lives

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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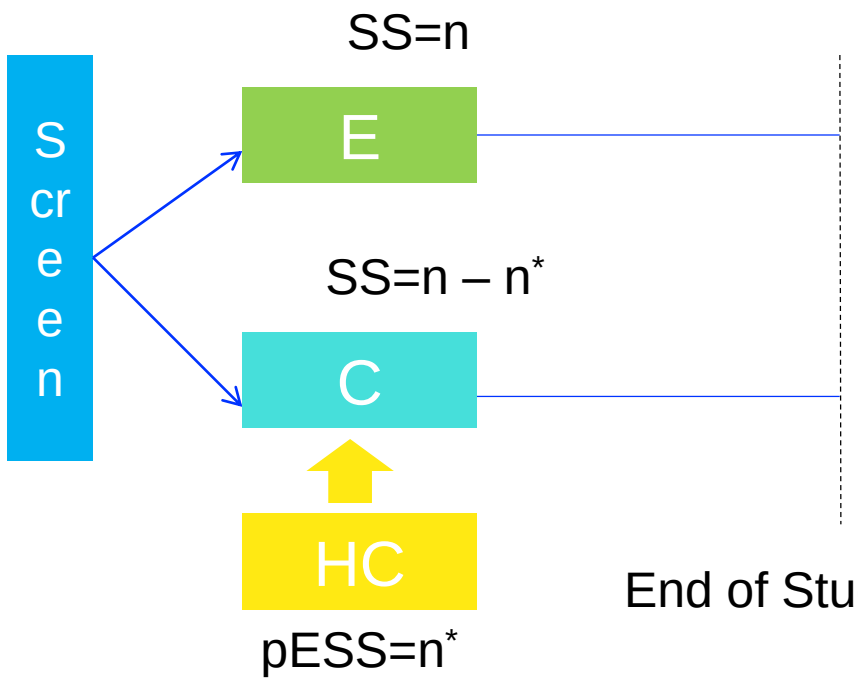
There are different approaches of borrowing external data

The main approaches include

1. Test and pool (Viele et. al. 2014)
2. Bias model (Pocock 1976)
3. Commensurate prior (Hobbs and Carlin 2011)
4. Power prior (Chen 2000, Duan 2006, Neuenschwander et al 2009)
5. Meta-analytic approaches (Spiegelhalter 2004, Neuenschwander 2010)
6. Propensity score approaches (Lim et. al. 2018)

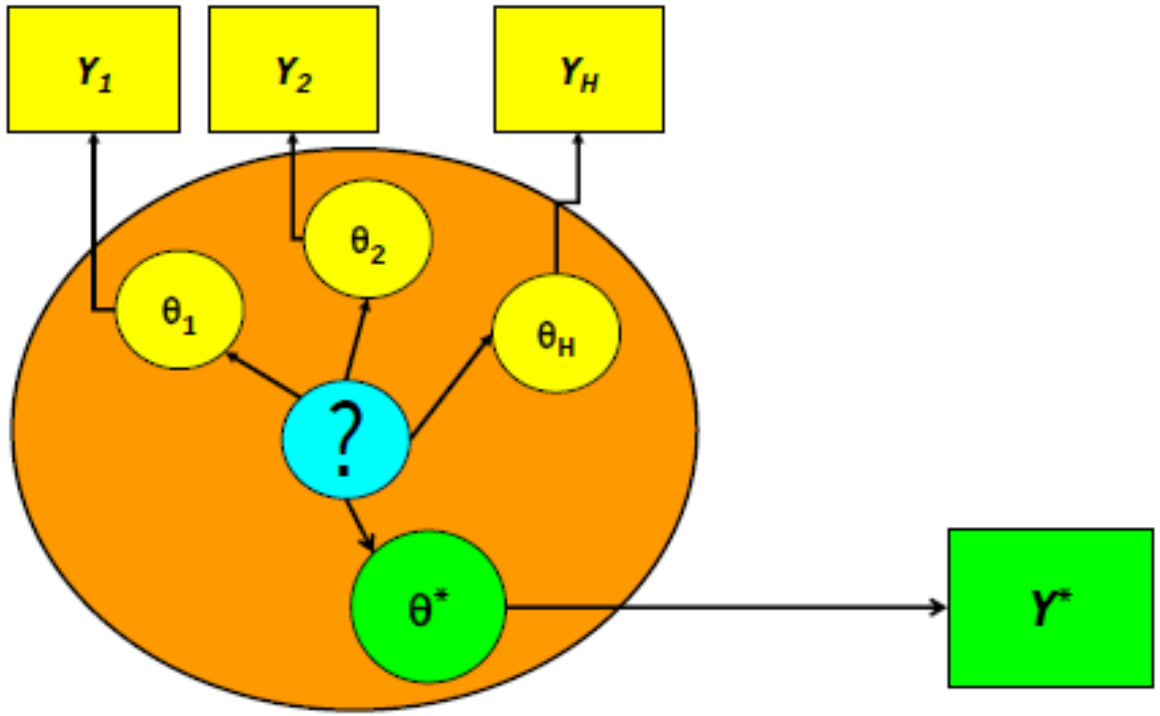
Approach 2-5 are similar: discounting of external information due to between-trial heterogeneity

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

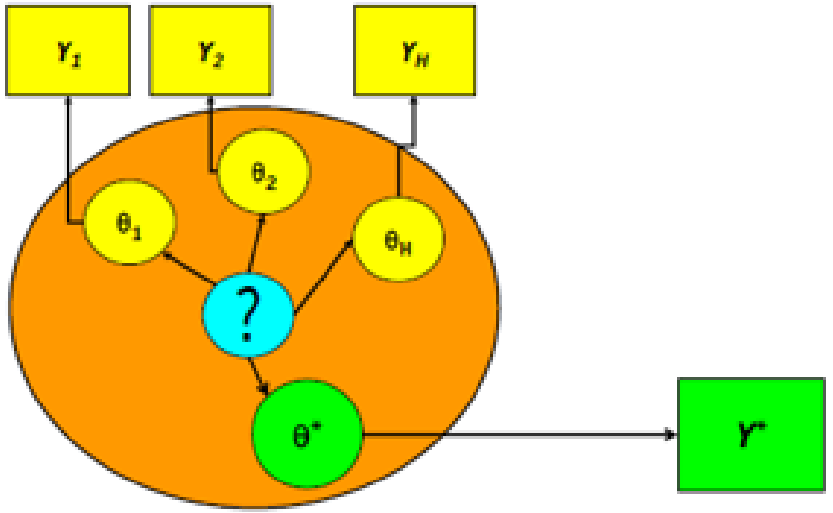
Meta-analytic approach uses Bayesian hierarchical model to bridge between external control and study data



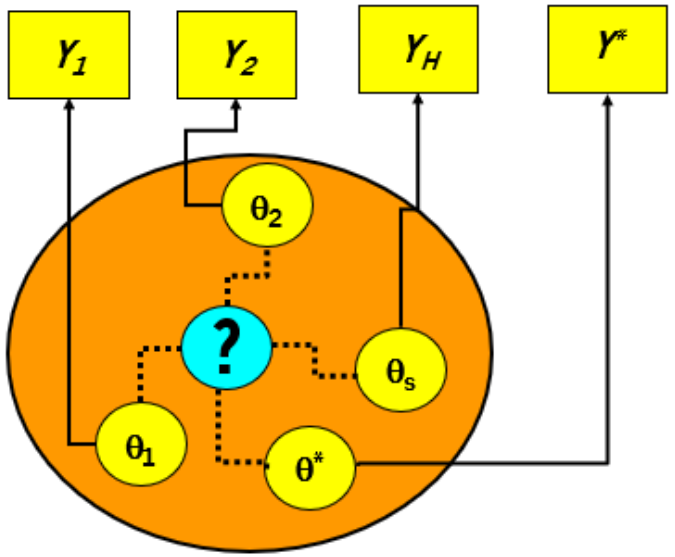
- Uses a model for all quantities, which involves a parameter model
  - infers the parameter of interest θ_* : **dynamical borrowing**

We use a meta-analytic predictive approach to borrow external data in the control group

Meta-Analytic Predictive(MAP)



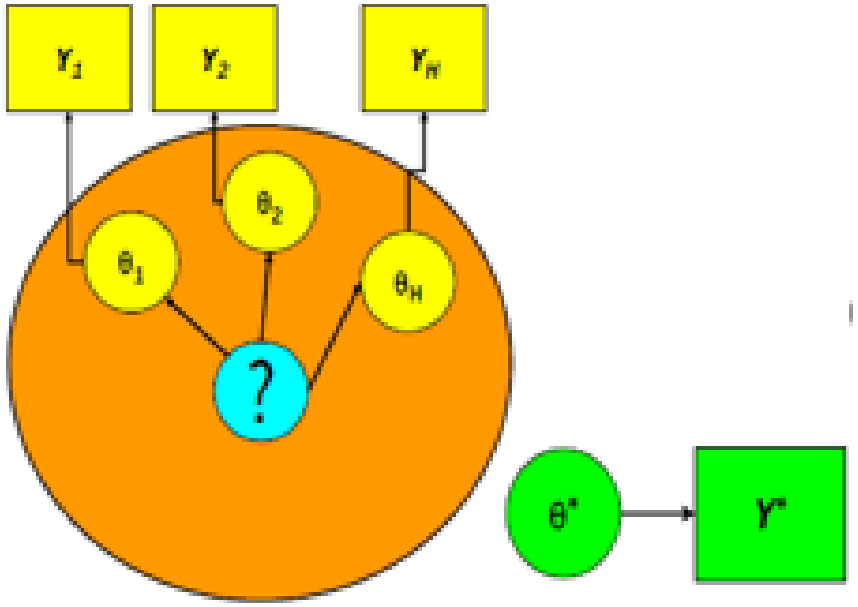
Meta-Analytic Combined (MAC)



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

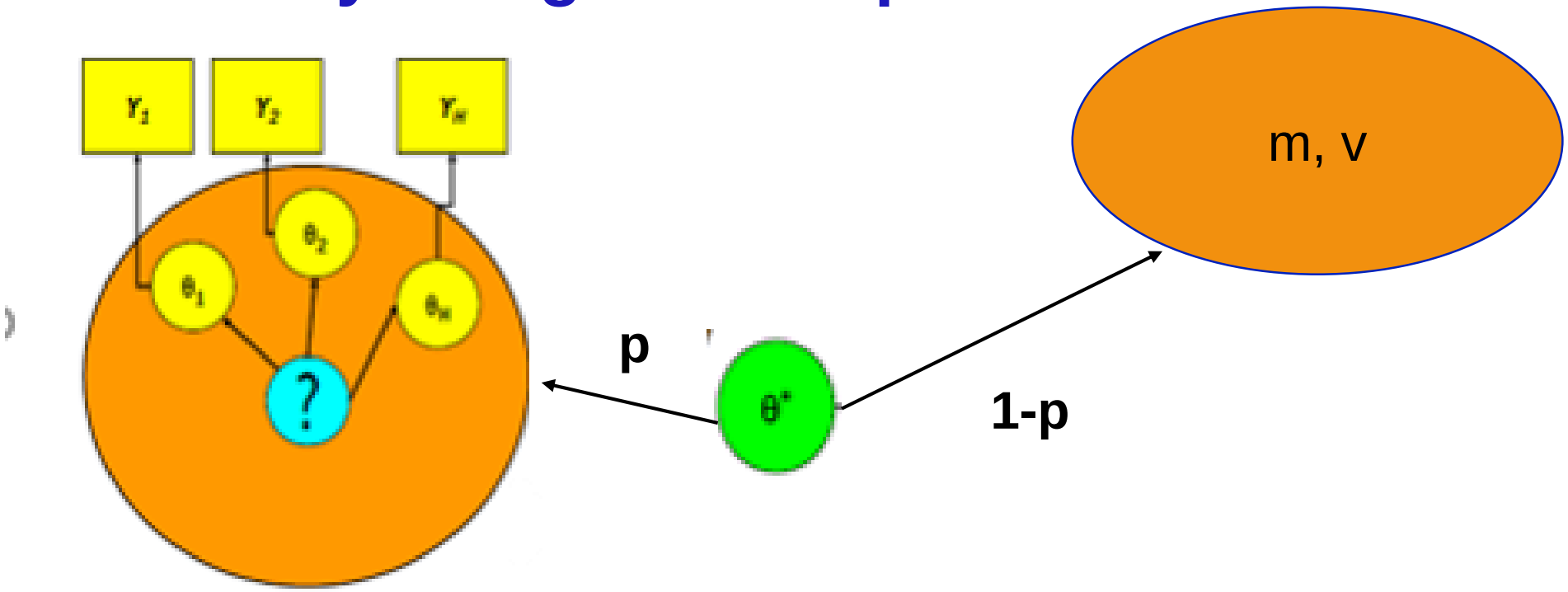


Prior-data conflict means: actually observed Y* is in the tail of the prior predictive distribution

Requires robustness

De Groot always carried an ε of probability for surprises in his pocket!

Meta-analytic framework can handle the possibility of prior-data conflict by using mixture priors

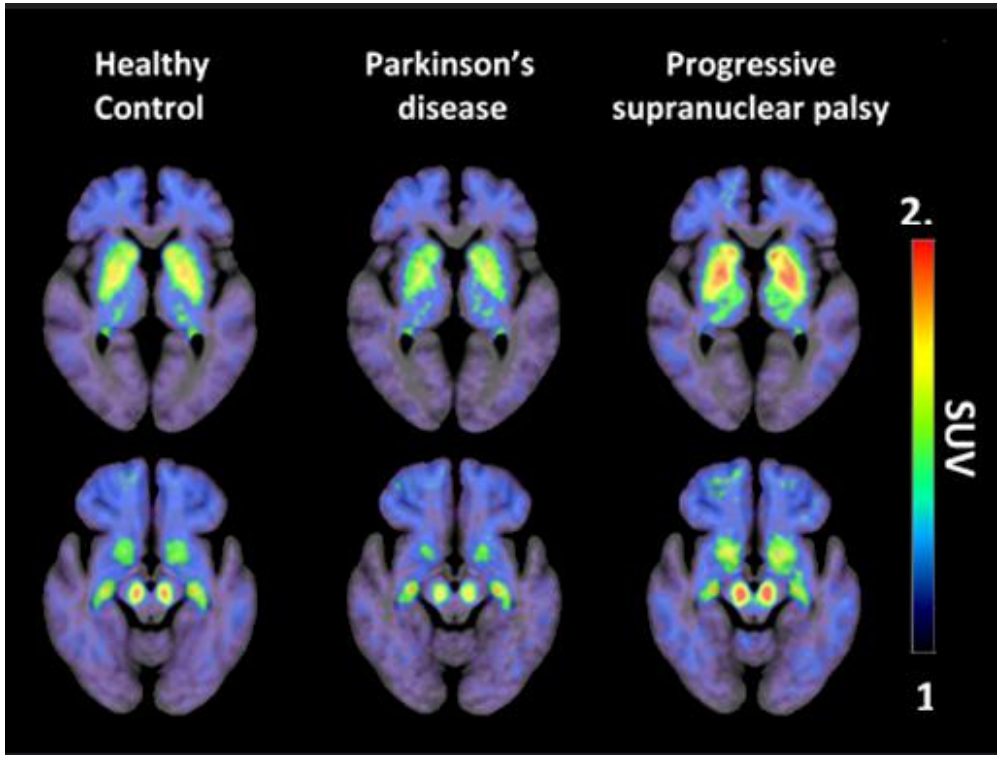


Robustness and more rapid adaptation to prior-data conflicts by adding **extra weakly-informative mixture component**

MAC framework can also handle prior-data model with mixture model

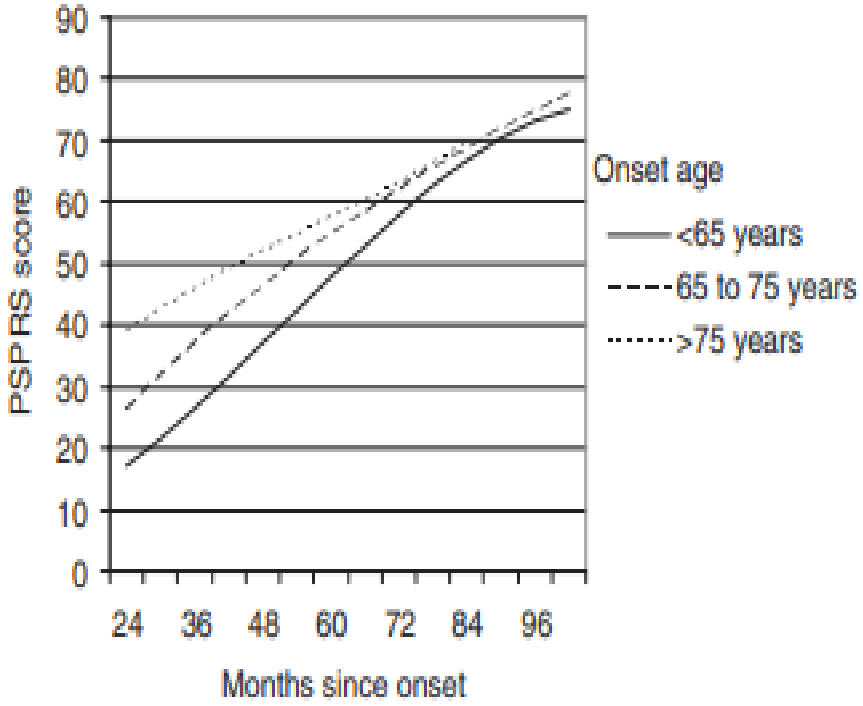
Example: Use of external control in a phase II design of Progressive Supranuclear Palsy (PSP)

- 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 tradition design will require 160 patients for a reasonablv 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



Golbe and Ohman-Strickland 2007

Can external placebo information be used?

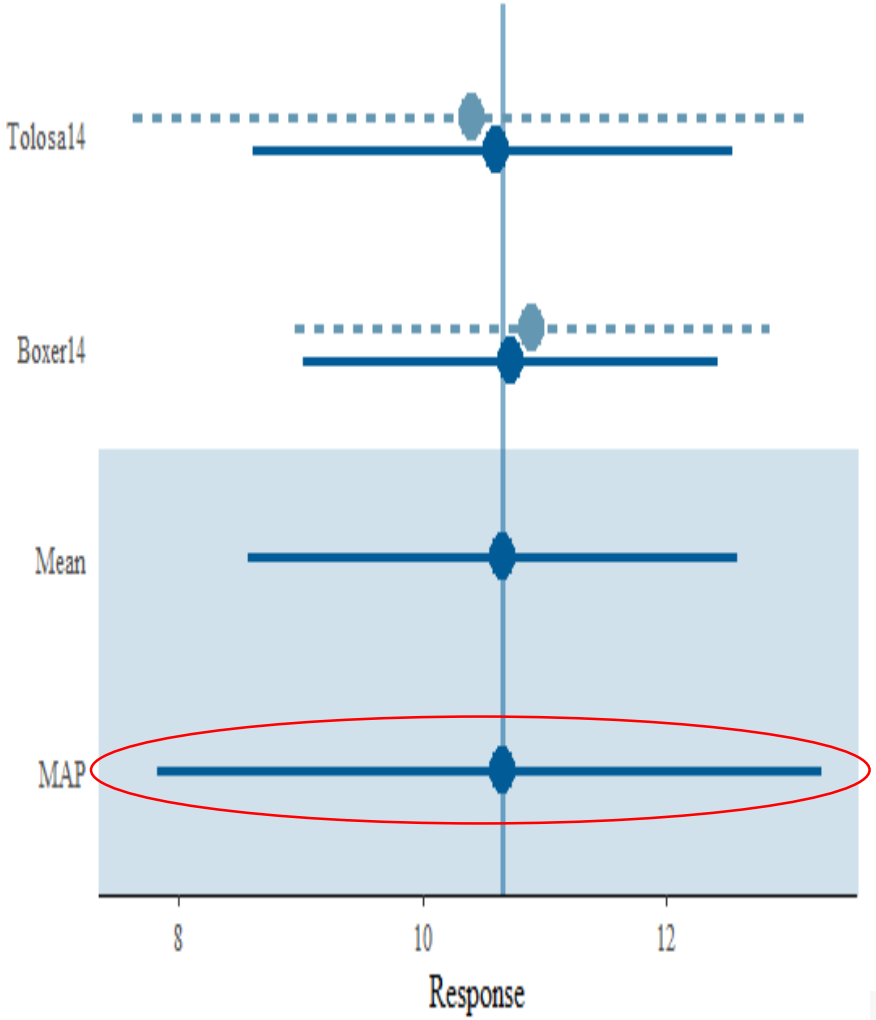
Using meta-analytic framework we can improve the design

- **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 δ= 4
- **2 historical trial data for placebo (n=144))**
  - Tideglusib vs. placebo (Tolosa et. al. 2014)
  - Davunetide vs. placebo (Boxer et. al. 2014)

Study	N	Y	se
Tolosa14	21	10.4	6.5
Boxer14	123	10.9	11.0

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**
  - *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(δ < 0 | data) > 97.5%

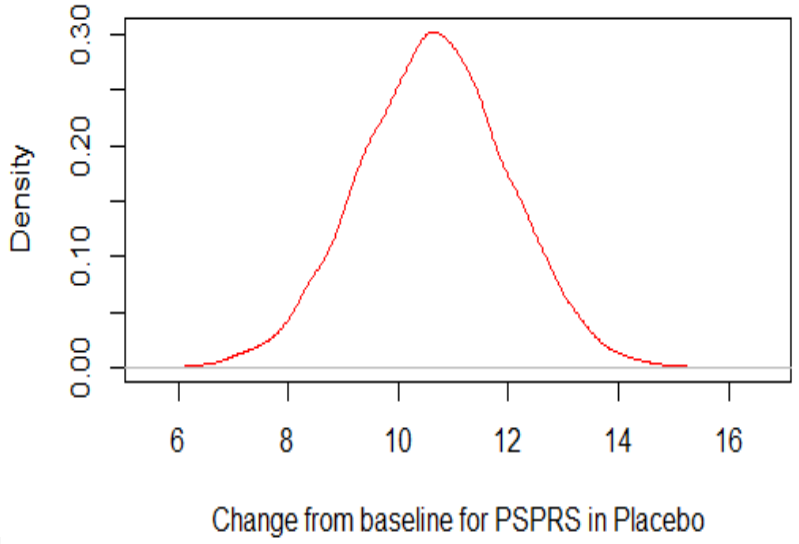


Robust MAP prior reflects the degree of confidence on external control data

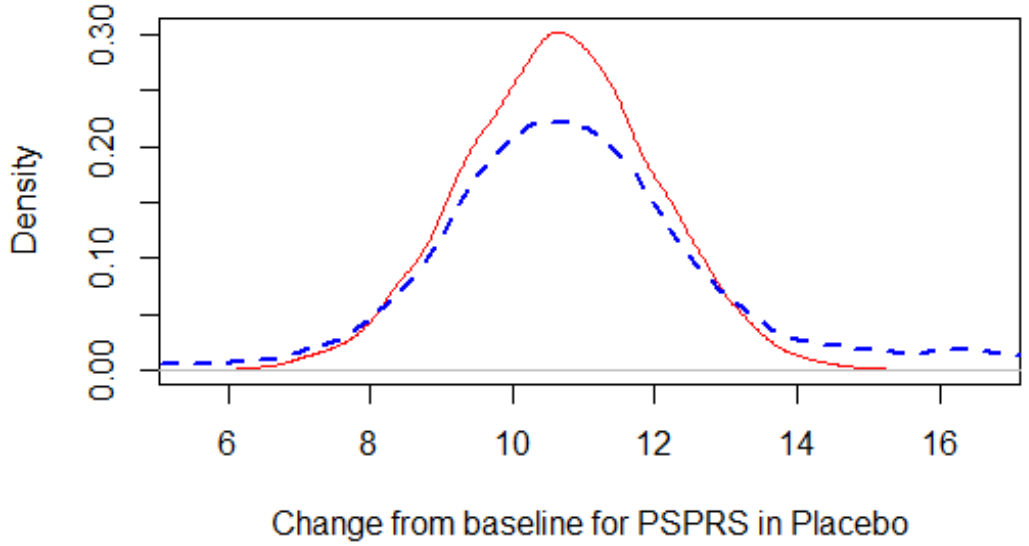
A mixture of MAP and weakly informative prior becomes a heavy-tailed version of the prior derived from external placebo data

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

MAP prior (100%-0%)

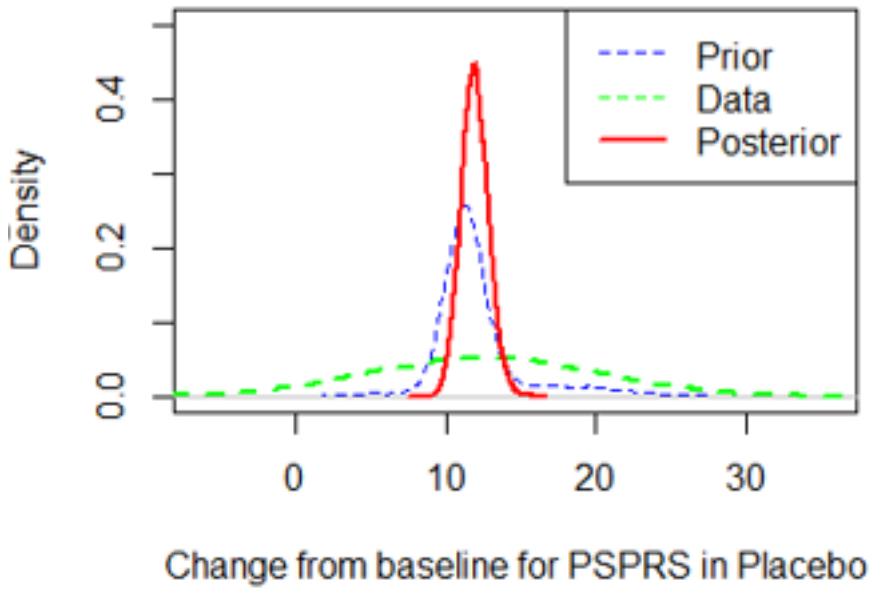


Robust MAP prior (75%-25%)



Robust MAP prior can handle prior data conflict

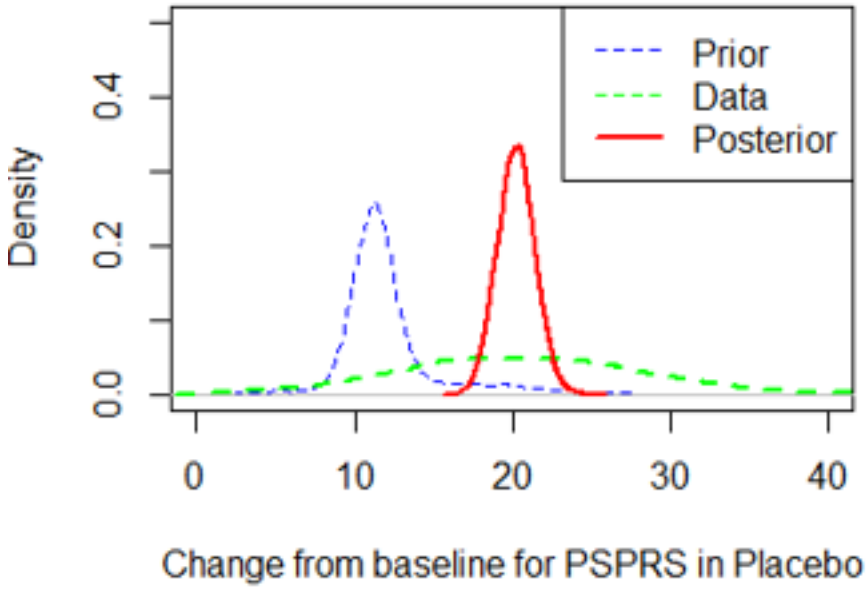
Scenario: No Conflict



Weights

- **aprior** informative **75%** weak **25%**
- **postrior** informative **90%** ↑ weak **10%**

Scenario: Conflict



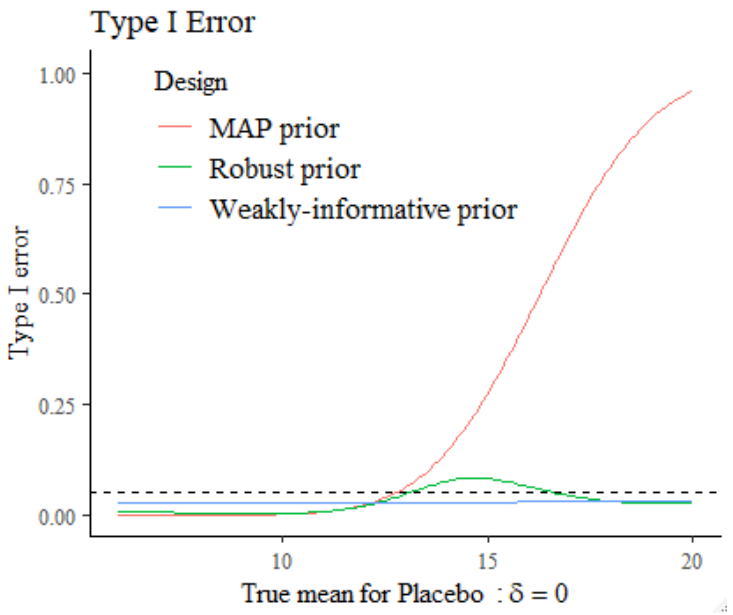
Weights

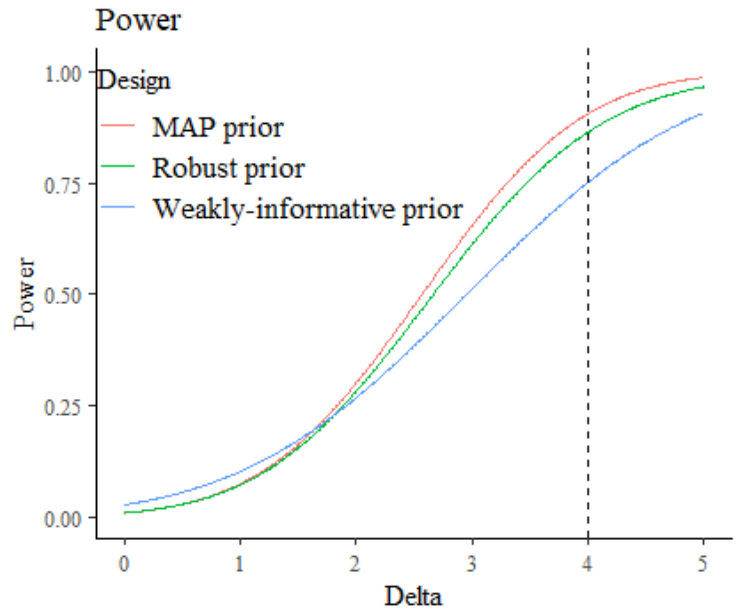
- **aprior** informative **75%** weak **25%**
- **postrior** informative **1%** weak **99%** ↑

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 δ= 4: considerable gain over traditional frequentist design
- Type-I error inflation is much higher with informative prior only under prior-data conflict

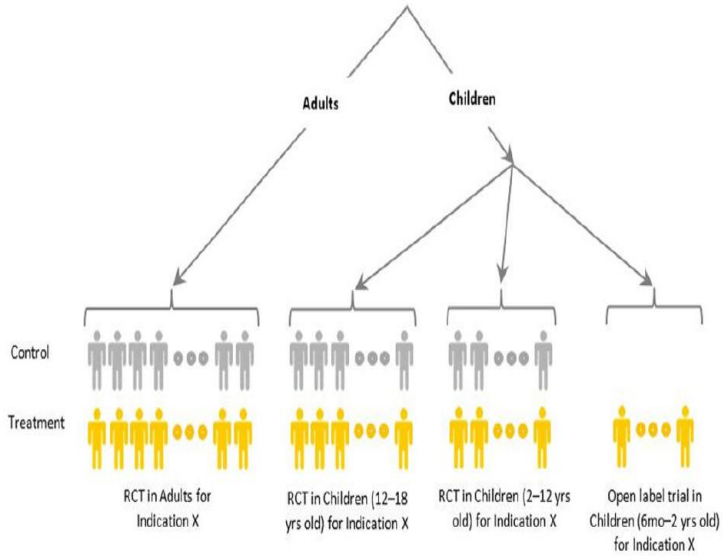




Meta-analytic framework can be extended for extrapolating information from adult to children

- **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)



Gamalo et. al. 2019

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)

Conclusion

- **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

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

- Winston Churchill

THANK YOU