Use of Historical Data for Confirmatory Trials

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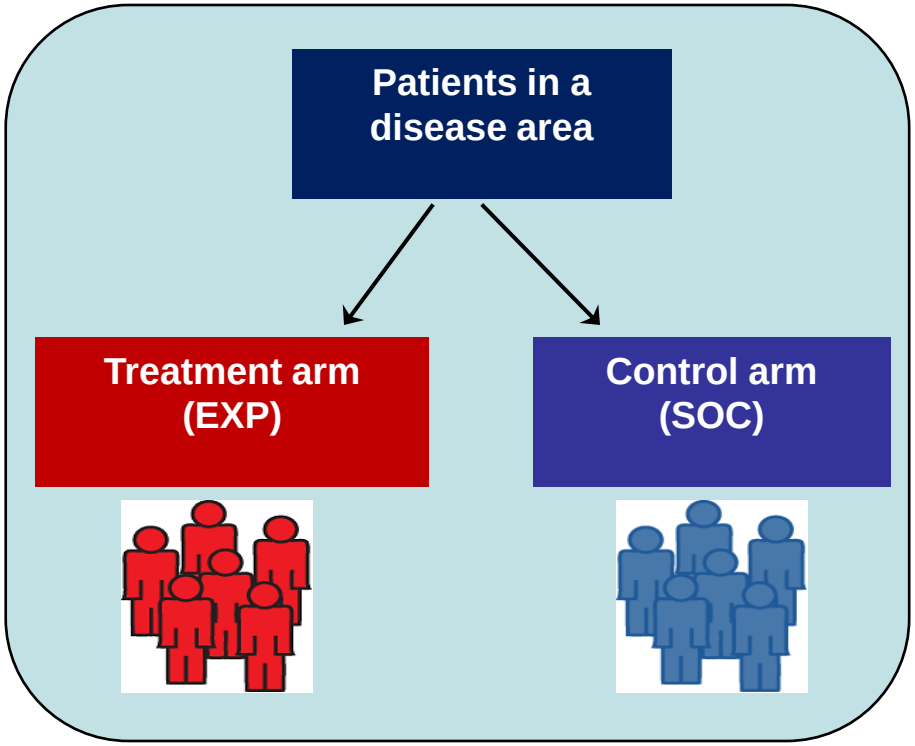
Decision Making in Clinical Trial

Evidence Based Approach

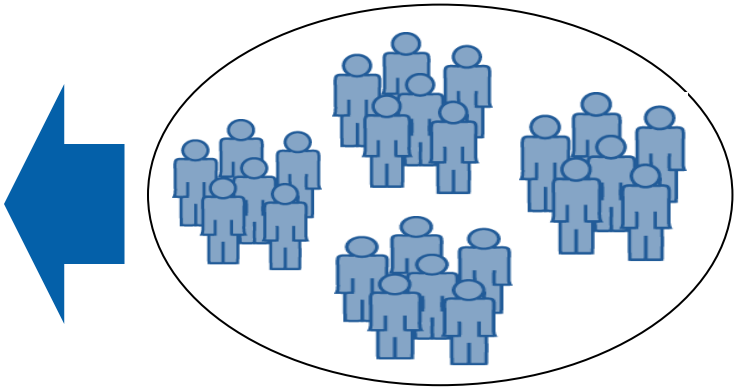
- Informed decisions should be based on all relevant information
- In particular, when
  - information is sparse (e.g. Pediatric population, rare disease)
  - new information is difficult to obtain
- Historical data may lead to
  - Increase efficiency: fewer patients
  - Ethical
  - Decreased costs and trial duration
- PUDUFA VI and MIDD encouraged the application of historical data in design and analysis
  - Pilot program launched August 30th

Efficient Clinical Trial Design

Use of Contextual Information



Trial external Information (Typically for SOC patients)



Can we bring this information in trial design and analysis?

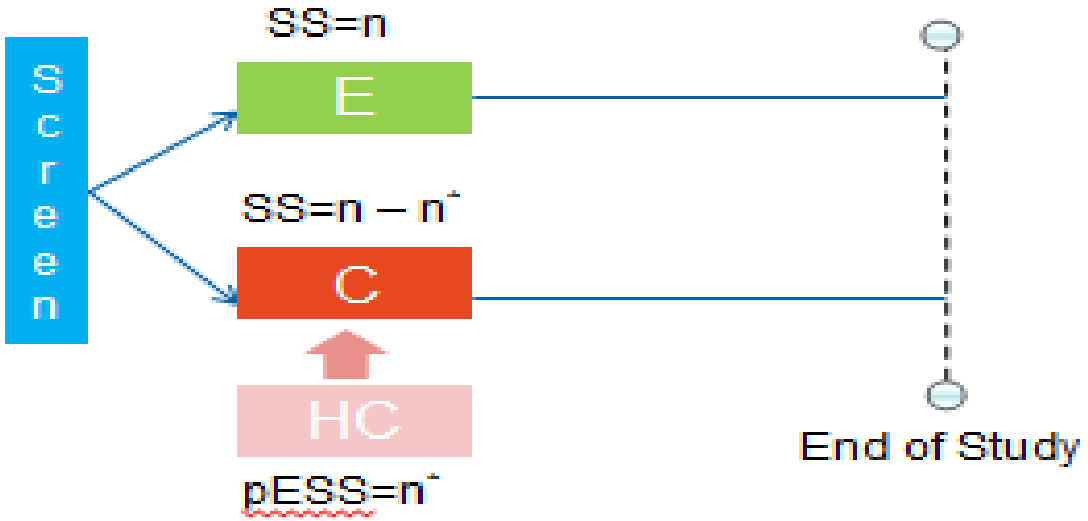
Trial Design with Historical Information

Leveraging Historical Information to Reduce Sample Size

- Assume a two arm trial: Experimental vs Control
- Size of Experimental arm= n
- For control arm:
  - discard historical study and allocate n patients (standard design)
  - use prior information for control worth n_* patients and allocate n additional patients
  - use prior information for control worth n_* patients and allocate n- n_* patients
    - known as *historical control* design
- The performance of historical design is better than standard design if prior is aligned with the true control mean

Historical Control Design

Design with "Relevant" Trial External Data



- Success at the end of trial: Traditional or Bayesian
- Design operating characteristics:
  - Type-I error/False positive, Power, Bias/ MSE
- OC needs to be assessed for both prior-data aligned and conflict scenarios

Choice of “Relevant” Historical Data

Gather Relevant Historical Data

- Proper choice of historical data: justification of “exchangeability” or “similarity”
  - Prior to start of trial
  - Choice must be “science” based not “result” based
  - Avoiding publication bias: often requires KOL and independent groups
  - Inter-disciplinary collaboration
  - Data gathering can be time-consuming
- Pocock’s (1976) criteria
  - Inclusion and exclusion criteria for patient population;
  - The type of study design;
  - The exact definition of the outcome;
  - The quality of study execution and management;
  - Potential biases due to time trends

Approaches for Historical Control Data

Overview of Statistical Methodology

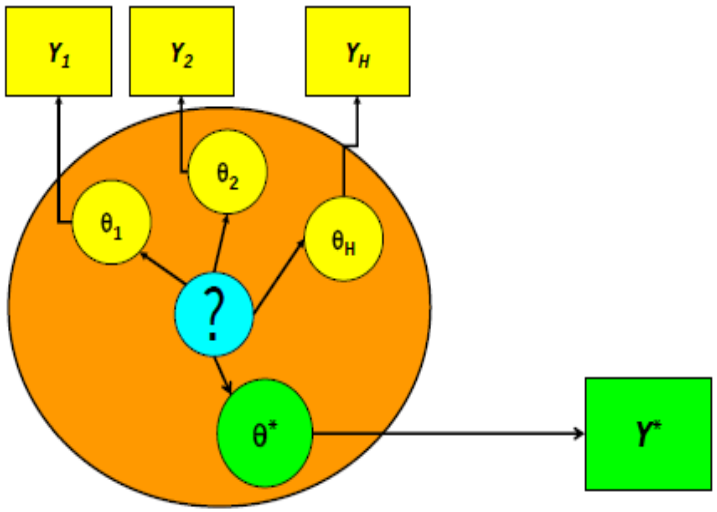
- Bayesian and Frequentist approaches
  - Both are powerful and requires “assumption” of similarity!
  - Bayesian methods have natural way through **“prior”**
- The main approaches include
  1. Test and pool (Viele et. al. 2014)
  2. Bias model (Pocock 1976)
  3. Commensurate prior (Hobbs and Carlin 2011)
  4. Power prior (Chen 2000, Duan 2006, Neuenschwander et al 2009)
  5. Meta-analytic-predictive (MAP) prior (Spiegelhalter 2004, Neuenschwander 2010, Hchmidli 2014)
- Approach 2-5 are similar: discounting of historical information due to between-trial heterogeneity

Prior-Data Conflict

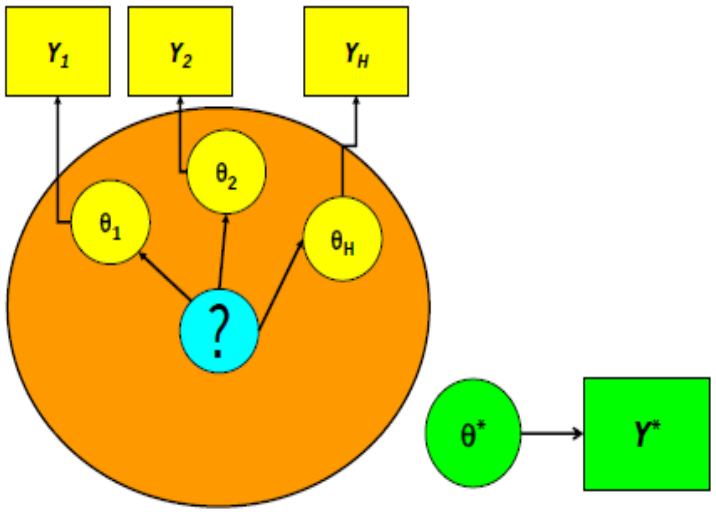
Accounting for Dissimilarity

- Prior-Data Conflict?
  - Most often referred as a primary «concen» for using historical data
  - Conflict means: actually observed Y* is in the tail of the prior predictive distribution: external data should not be used
  - Alternative: robust priors: mixture prior (Hchmdli 2014) and heavy-tailed t

Similarity Scenario



Dissimilarity Scenario



Application of Historical Control Design

Where are we now?

- Many applications with *historical data*
  - pediatric trials (adult data), non-inferiority trials (placebo, active control data), health-technology assessments, trials with disease subtypes
- Mainly used for early phase trials or trial adaptations
  - Phase 1 trials, POC trials, probability of success….
- What about using *historical data* for primary analysis in confirmatory trials?
  - Well established for CDRH
  - not commonly for drugs and biologics
  - recent example in epilepsy (historical controls) Katz (2006), French (2010), Wechsler (2014)

Let's Discuss……

Use of Historical Data in Confirmatory Trial

1. What are the primary concern for using historical data in confirmatory trial?

2. How the pilot program can help?

3. Choice of "relevant" historical data is always a primary concern. What are your experiences?

4. Any other key considerations?