Historical Data in Clinical Trials

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The difference is in the data.™

Overview

- What is historical data (from a clinical trial perspective).
- Sources and Applications.
- Methods of direct data inclusion (Historical Control Arms).
- Resources for further reading.

What is Historical Data?

- Data already collected (e.g. completed clinical trials…past 4 years and not ancient trials).
- Usually from similar/closely-related studies with accessible data.
- Other sources other than completed clinical trials.

Column	Row	Cubit	Treasure Numbers		Treasure	Extra Numbers	Greek Letter
C7	30	24	Talents	400		4	
	31	6	Silver Bars	6			
	32	7	Talents	22			
	33	3	Talents	60	2 Gold Talents		
C8	34				a Silver Bar		
	35	17	Talents S&G	17			
	36	3	Talents	7			
	37	24	Talents	66			
	38	11	Silver Talents	70			
C9	39	13	Talents	7	4 coins	7	2 pits
	40	8 1/2	Talents	23 1/2		2nd	
	41	16	Talents	22			
	42				a Mina		
	43	7	Talents	9			
	44			No Numbers			
C9-10	45		Talents	9		2nd	
C10	46		Talents	12			
	47	10	Silver Talents	62			
	48	2	Gold Talents	300	20 Vessels	A black stone = 1	
	49	12	Talents	90			
	50		Talents	17		4 Angles	
C11	51			No Numbers	Inventory		
	52			No Numbers			
	53			No Numbers	Inventory		
	54						
	55		Talents	40			
	56			No Numbers			
	57	3		No Numbers		2 Reservoirs	
	58		Silver Talents	900			
C12	59		Talents	60	5 Gold Talents	The black stone	
	60		Talents	42			
	61		Silver Talents	60	One or a ghost		
	62		Talents	600	Gold and Silver		
	63		Talents	71	20 Mina		
	64			Duplicate Inventory			

Sources of Historical Data

- Past clinical trials
  - Same indication, same program.
  - Same indication, different program.
  - Similar indication(s), different program, same study disease.

- Natural history data
  - Academic natural history studies.
  - Data recorded by institutions or manufacturers (RWE)
  - Patient records (With proper consents!)
  - FDA supported rare disease NH studies.

- Research materials
  - Publication through reputable media (e.g. Wiley Interscience)
  - University research reports.
  - Mostly used in meta-analyses

Application in Clinical Trials

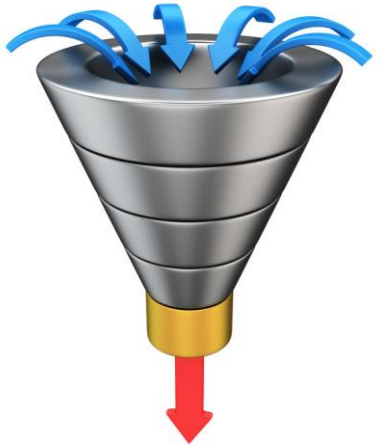
Two Applications:

- Indirect use as indicative input to current trial.
  - Used as supplemental information for decision making in new trial aspects.
  - Usually takes the form of meta-analysis or comparative investigation.

- Direct use within current trial.
  - Actual control subject data to various extents.
  - Placebo control or active control subject data.

Indirect Use: Examples

- Sample Size Calculations.
- Margin decision making (for example non-inferiority).
- Informative to single arm trial benchmark setting (Oncology).
- Decision on new study trial design.



Levels of Usability

The different possible levels of relevancy historical data may have towards a current trial:

- Full Equality: Historical data is completely relevant to current trial.
- Equal but discounted: Same underlying parameters but accuracy of historical trial parameters are discounted.
- Biased: Historical data gives a biased version of the parameter from the current trial.
- Similar: parameters from historical and current trial drawn from the same distribution (random effects model).
- Irrelevant: Historical data unusable for current trial since not related.

Assessment of Historical Data Usability

- Chi-square tests of homogeneity.
- Q-statistic.
- Breslow-Day Test.
- F-test for equality of variances.

Existing Methods of Direct Historical Data Inclusion

- Pooling
- Test-then-Pool.
- Power Priors
- Paired Availability.
- Hierarchical Modeling.
- Meta-Analytic Predictive Priors (MAPP).

Pooling: Overview

- Control arm is one part from Historical trial and other part recruited in new trial.
- Control arm less sensitive to current control data.
- Natural history study an applicable example.
- Eteplirsen phase III example (2016)

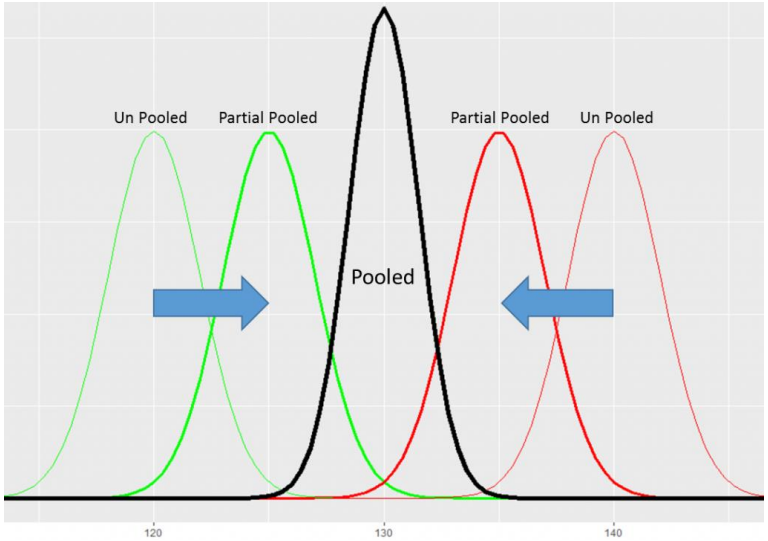
Pooling: Pros & Cons

- Benefits:
  - Lower Type I error & Higher statistical power.
  - Double your control data.

- Drawbacks:
  - Possible control data drift.

Test-then-Pool: Overview

- Extreme method: either all or none of historical data used.
- Historical data tested for homogeneity with current/new trial.
- If deemed close enough, historical and current trial data pooled for analysis.
- Otherwise historical data discarded.



Test-then-Pool: Pro's &Con's

- Benefits:
  - Potential extra data at no additional trial recruitment cost.
  - Helps meet trial N for difficult to enroll populations.
  - Type I error capped.
  - Mean Square Error (MSE) tends to be lower and power higher when pooling with closely related data (*Viele et al*).

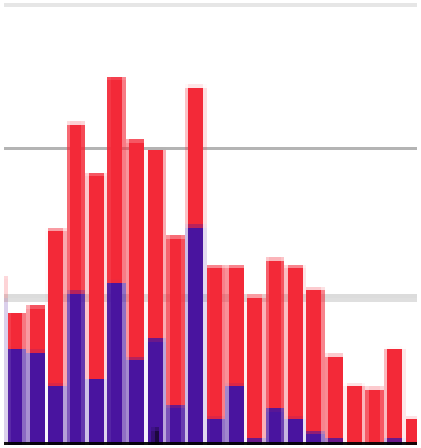
- Drawbacks:
  - Doing all the tests – then discarding the historical data.
  - Additional work for effective testing of homogeneity.

Power Priors: Overview

- Dynamic in the amount of historical data used.
- Down weighs historical data based on homogeneity with current trial data.
- Usually for binomial response data.
- Entail calculating a power prior (calculated weight).
  - Done through the use of a ‘power parameter’ (a_0).

Power Prior: Subtypes

- Conditional Power Prior (PP).
- Full or joint PP.
- Commensurate PP.
- Partial discounting PP.
- Partial borrowing PP.
- Normalized PP [$f(\Theta|a_0)$].



	Dance	Sports	TV
Men	2	10	8
Women	16	6	8
Total	18	16	16

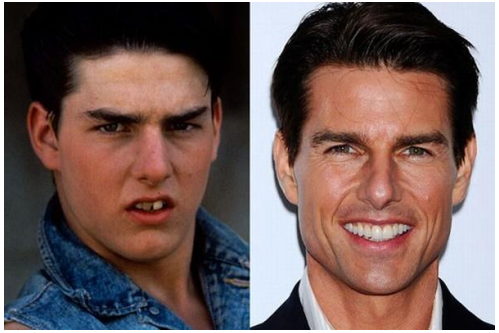
Power Prior: Pro's & Con's

- Benefits:
  - Avoid arbitrarily selecting observations to limit impact of historical data. Instead, all historical data included and collective impact down weighted.
  - Objective: informativeness data focused, instead of experts input.
  - Since it is a likelihood function (weighted by a_0), all the likelihood theory applies/holds.
- Drawbacks:
  - Can get computationally complex depending on the type of power prior used, distribution of the data being worked with (Normal, Binomial etc.)

Paired Availability: Overview

- Comparing set of subjects at a later period in time with the same set (or set type) at an earlier period in time using availability of treatment as approximation to the effect of treatment administration.

- The time periods are usually defined with a interval border (<2019 Vs >= 2019) related to some key change (e.g. increased availability of spinal anesthetic options).



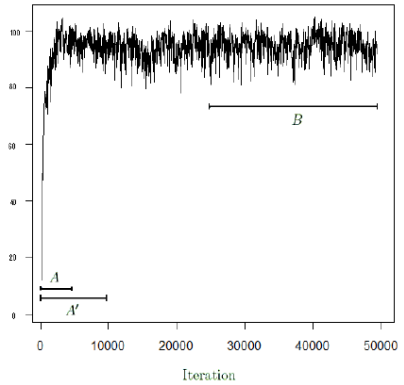
Paired Availability: Pro's and Con's

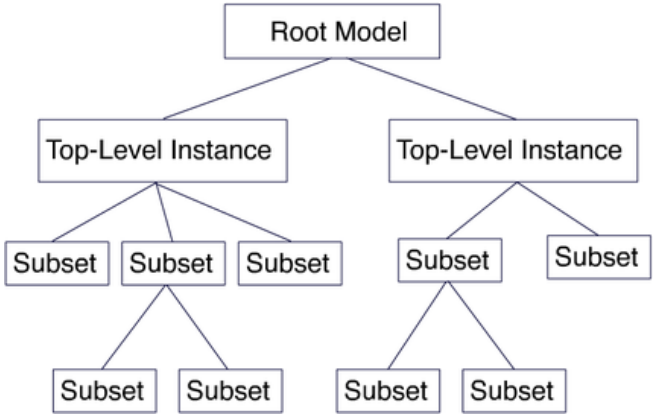
- Benefits:
  - Less intensive but similar in results to a full meta-analysis (Baker & Lindeman).

- Drawbacks:
  - Investigator Bias: Since investigators often cannot be blinded to the approximating factor.
  - Causal uncertainty: Not so easy to show that approximating event influence is not coincidental.
  - Difficult obtaining a pair on subject level.

Hierarchical Modelling: Overview

- Assume current and historical data share a common underlying distribution with variation measure τ.
- Prior distribution assigned to τ.
- Current data used to update τ distribution.
- Mostly uses MCMC for this.





Hierarchical Modeling: Simple Example

Revertant Salmonella colonies (SALM)

- $SALM_i \sim Poisson(\lambda_i)$

$\log(\lambda_i) = \boldsymbol{X_i\beta}+\gamma_{i,j}$

$\pi(\beta_1), \pi(\beta_2), \pi(\beta_3) \sim N(0,1000)$

$\gamma_{i,j} \sim N(0,\sigma^2)$

$\sigma^2 \sim iGamma(shape=0.1, scale=0.1)$

Table 1 Salmonella Data Set

Doses of Quinoline (μg per plate)					
0	10	33	100	333	1000
15	16	16	27	33	20
21	18	26	41	38	27
29	21	33	60	41	42

Hierarchical Modeling: Simple Example Cont.

In SAS:

```
proc mcmc data=assay outpost=postout thin=5 seed=248601 nbi=10000 nmc=100000
   monitor=(beta1-beta3 Pearson) dic;
   parms beta1 2 beta2 0.01 beta3 0.5;
   parms s2 1;

   prior beta: ~ normal(0,var=1000);
    prior s2 ~ igamma(0.01, s=0.01);
    w = beta1 + beta2*dose + beta3*l_dose10;
    random gamma~ normal(0,var=s2) subject=plate;
    lambda = exp(w+gamma);
    model salm ~ poisson(lambda);

   mu = exp(w + s2/2);
   sigma2 = mu + (exp(s2) - 1)*(mu**2);
   if plate eq 1 then Pearson = 0;
   Pearson =  Pearson + ((salm - mu)**2/(sigma2));
run;
```

$\pi(\beta_1), \pi(\beta_2), \pi(\beta_3) \sim N(0,1000)$

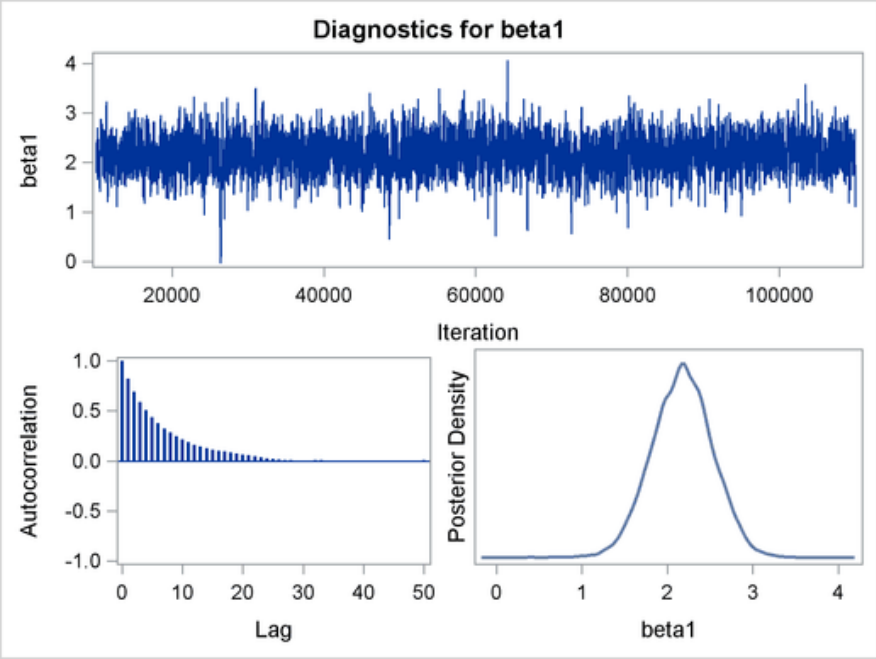
$\sigma^2 \sim$ iGamma(shape=0.1, scale=0.1)

$\gamma_{i,j} \sim N(0,\sigma^2)$

$\log(\lambda_i) = \boldsymbol{X_i\beta}+\gamma_{i,j}$

$SALM_i \sim$ Poisson(λ_i)

Hierarchical Modeling: Simple Example Cont.



Posterior Summaries						
Parameter	N	Mean	Standard Deviation	Percentiles		
				25%	50%	75%
beta1	20000	2.1710	0.3635	1.9361	2.1770	2.4082
beta2	20000	-0.00097	0.000442	-0.00125	-0.00097	-0.00069
beta3	20000	0.3117	0.0994	0.2462	0.3105	0.3754
Pearson	20000	19.4658	7.1714	14.2401	18.6810	23.8964

Posterior Intervals					
Parameter	Alpha	Equal-Tail Interval		HPD Interval	
beta1	0.050	1.4646	2.8591	1.4874	2.8794
beta2	0.050	-0.00185	-0.00012	-0.00182	-0.00010
beta3	0.050	0.1235	0.5078	0.1155	0.4976
Pearson	0.050	7.8557	35.4789	6.7314	33.5488

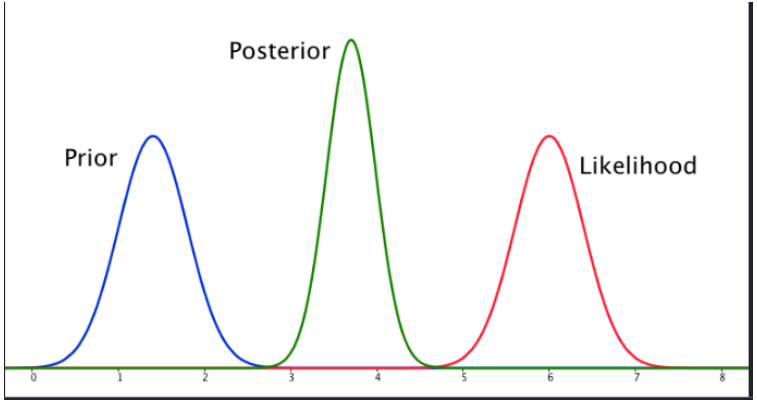
Hierarchical Modeling: Pro's & Con's

- Benefits:
  - Measures of variability arise naturally from the framework (Lehman et al 2013).
  - Allows for multiple sources of uncertainty.
  - Very flexible and powerful.

- Drawbacks:
  - Lot of 'up-front' work needed.
  - Some playing around needed.
  - Computationally intensive.

Meta Analytic Predictive Prior (MAPP): Overview

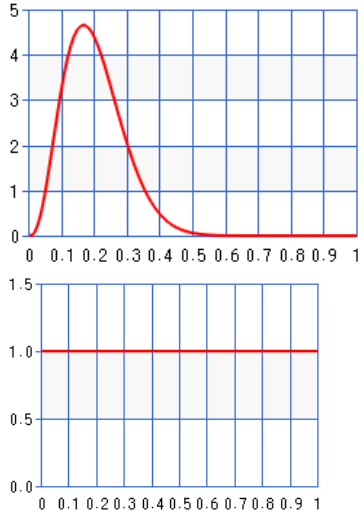
- Prospective approach – meta analysis of historical data at current trial design stage.
- Gives prior distribution for interest parameter (Θ).
- Combined in Bayesian manner for posterior distribution on Θ.
- Historical data influence weighted.
- Sensitivity analysis advised.



Meta Analytic Predictive Prior (MAPP): Pro's & Con's

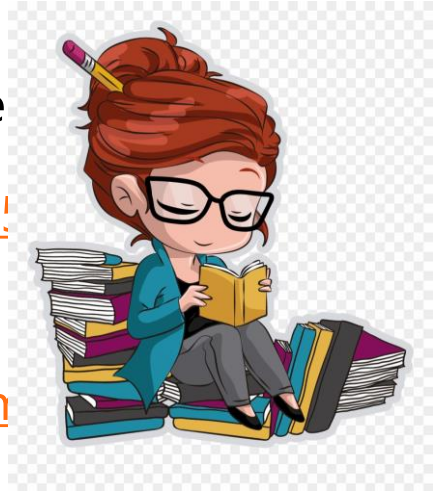
- Benefits:
  - Meta-analytical priors are naturally robust.
  - Even more robust with weakly informative component added.
    E.g. prior = 0.5xBeta(4,16) + 0.5xBeta(1,1)
  - MAP prior gives power gain.
  - Historical inference can help with trial design

- Drawbacks:
  - Much 'up-front' work needed.
  - MAP prior quality dependent on studies included.
  - Publication bias may threaten accuracy.



Sources for Further Reading

- General information:
  - Use of historical control data fro assessing treatme in clinical trials (viel et al). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC39
- Power Priors:
  - The Power Prior: theory and Applications (Ibrahim https://onlinelibrary.wiley.com/doi/abs/10.1002/sin
- Paired Availability:
  - Rethinking Historical Controls (Baker & Lindeman) https://www.ncbi.nlm.nih.gov/pubmed/12933631



Sources for Further Reading (Cont.)

- Bayesian Hierarchical Modeling:
  - Bayesian Hierarchical modeling of Rainfall extremes (Lehmann et al) https://pdfs.semanticscholar.org/be8f/1bf35ec688b39ed4909a2dd69fba0b6028ad.pdf
- MAPP:
  - Robust meta-analytic-predictive priors in clinical trials with historical control information (Schmidli et al) https://onlinelibrary.wiley.com/doi/abs/10.1111/biom.12242 http://www.bayes-pharma.org/wp-content/uploads/2014/10/Schmidli-2015-BayesPharma.pdf

Questions