Bayesian Meta-Analysis in Drug Safety Evaluation

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Outline

- Personal Experience on Bayesian Applications in Drug Safety Evaluation
- Specific Examples on Bayesian Meta-analysis
  - Meta analysis for rare adverse event data
  - Meta-experimental design in evaluating CV risk for T2DM drug development
- Summary
  - Advantages of Bayesian Meta-analysis
  - Caveats and Recommendations

Current Use of Bayesian Methods in Industry

- Medical Device Industry
  - Regulatory support
    - Final FDA guidance released in Feb, 2010
  - It has been used regularly in support of clinical trial design and regulatory submission
- Biopharmaceutical Industry
  - Regulatory submission has been rare
  - Effectively used in
    - Early phase clinical trial design and monitoring for internal decision making
    - Analysis with complex modeling

Some Areas of Bayesian Impact/Applications

- Clinical trial design
  - Calculate posterior Pr (Success) to make E2L decision
  - Use of good prior information (historical data used via hierarchical modeling) appreciably reduced the size and the length of a trial
  - Use prediction to plan pilot and confirmatory studies as a whole
  - Bayesian adaptive design / dose finding
- Clinical trial sequential monitoring
  - Use posterior probability to continuously monitor an event of interest in a Phase 2 trial
  - Bayesian sequential monitoring plan to incorporate risk-benefit assessment for a clinical trial
- Analysis (hierarchical modeling)
  - Various applications in drug safety evaluation
  - Evidence synthesis/meta-analysis

Some Challenges in Drug Safety Evaluation

- How to detect unexpected adverse drug reactions while handling the multiplicity issue properly?
- How to synthesize data from different trials, or even different sources?
- How to deal with rare events?
- How to evaluate multi-dimensional, complex safety information as a whole?
- Can we monitor a potential safety issue in a continuous manner during a trial so patients can be better protected?

Specific Examples of Bayesian Applications in Safety Assessment

- Case 1: Clinical trial signal detection
-  Case 2: Meta analysis for rare adverse event data
-  Case 3: Meta-experimental design in evaluating CV risk for T2DM drug development
- Case 4: Joint modeling of longitudinal and time-to-event data
- Case 5: Continuously monitoring an adverse event of interest in a clinical trial

There are many more examples …

Case Studies

Meta analysis for rare adverse event data

- Example 1: Nissen Meta-analysis with Bayesian Fixed Effect Model
- Example 2: Bayesian Survival Meta-analysis Using Individual Patient Data

Statistical Issues with Meta-Analysis for Rare AE Data

- Standard inferences for meta-analysis rely on large sample approximations. They may not be accurate and reliable when
  - sample sizes from individual studies are small
  - total number of studies is small
  - total number of events is small
- Some serious AEs are often sparse, leading to zero events being observed in one arm or even both arms for some studies
- The problem with lack of power in evaluating heterogeneity is amplified when the number of studies is only modest or an event of interest is rare

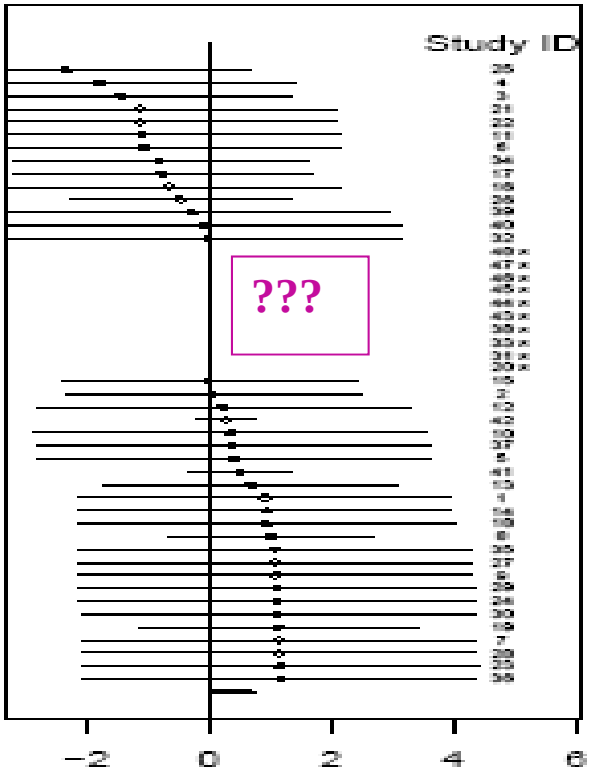
Example 1: Nissen Meta-Analyses

- Rosiglitazone (RSG) is a hypoglycemic drug licensed in 1999 for treating patients with type 2 diabetes mellitus
- Nissen meta-analyses* included 48 (Ph 2,3,and 4) RCTs with a similar duration between treatment groups, and at least 24 weeks of drug exposure
  - Primary outcomes: MI and CV death
  - 6 trials with zero events of MI and CV death were excluded so 42 trials were used in the analysis
  - Of 42 studies, 38 reported at least one MI and 23 reported at lease one CV death
  - Peto method was used (excluding double-zero studies)

*** Nissen and Wolski, NEJM, 2007**

Results from Nissen Meta-Analyses

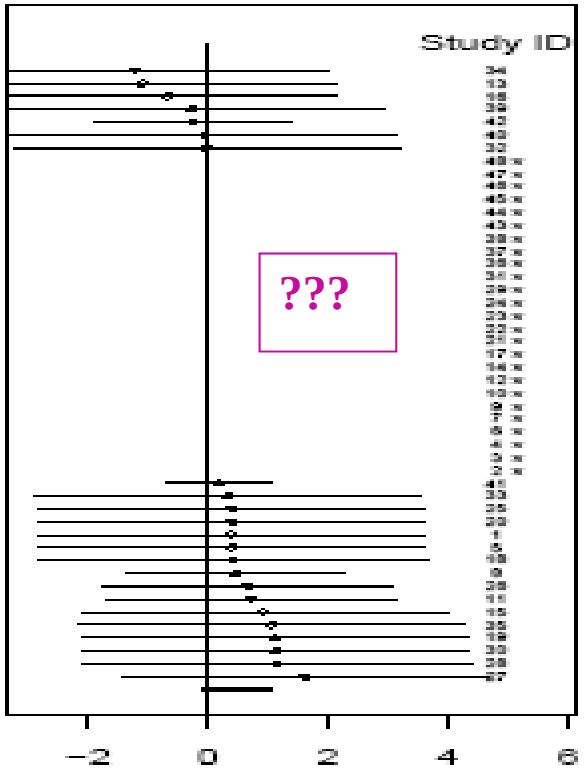
MI



Log Odds Ratio

N = 38; OR = 1.43;
95% CI: (1.03, 1.98); p-value = 0.03

CV Death



Log Odds Ratio

N = 23; OR = 1.64;
95% CI: (0.98, 2.74); p-value = 0.06

Courtesy Dr. Lu Tian

CVD Results Based on Bayesian Fixed Effect Model

	Fixed Effect (n=23)	Fixed Effect (n=48)
OR	1.73	1.68
95% Credible Set	[0.99, 2.86]	[0.95, 2.81]
Pr (OR > 1)	0.97	0.96
Pr (OR > 1.2)	0.89	0.86
Pr (OR > 1.5)	0.65	0.60
Pr (OR > 2.0)	0.25	0.22

	Fixed Effect (n=23)	Fixed Effect (n=48)
RD (%)	0.08	-0.05
95% Credible Set	[-0.02, 0.20]	[-0.15, 0.04]
Pr (RD > 0)	0.94	0.16
Pr (RD > 0.05%)	0.72	0.02
Pr (RD > 0.1%)	0.37	0
Pr (OR > 0.2%)	0.03	0

Example 2: Bayesian Survival Meta-Analysis with Individual Patient Data (IPD)

- Case study: a cross-company meta-analysis to investigate the short-term cancer risk in 3 TNF (tumor necrosis factor) inhibitors*
- 74 RCTs of TNF inhibitors across multiple indications (n = 22,904)
- Results:
  - All cancers excluding NMSC (non-melanoma skin cancer): RR = 0.99 (95% BCI 0.61-1.68)
  - NMSC: RR = 2.02 (95% BCI 1.11-3.95)

* Askling, Fahrbach, Nordstrom, et al *Pharmacoepi. and Drug Safety* 2011; 20: 119-130

Challenges in This Meta-analysis

- Re-analyzing RCTs for outcomes not originally planned, and comparing data across sponsors (as opposed to pre-planned meta-analyses of emerging data, using pre-defined safety endpoints)
  - Although centralized, blinded adjudication was used, the adjudication of many events was based on minimal information
- Dealing with rare events
- Using individual patient data (with covariates) with time-to-event endpoints with non-constant hazards over time

Meta-analysis of rare events based on RCTs is a powerful tool but poses a series of methodological challenges that require due attention and action

Bayesian hierarchical piecewise exponential survival models were used

- Dividing time into (0-3, > 3mos) with constant hazard in each interval, allowing for relaxing the proportional hazards assumption
- Assessing *class effects* and *drug-specific effects* among 3 anti-TNF agents
- Investigating differences in 'sponsor-specific control-group effect'
- Taking into account patient-level covariates, between study heterogeneity, and time-dependent covariates

Advantages of Bayesian Meta-Analyses for Rare AE Data

- Provide a powerful framework to model the uncertainty of all parameters
  - e.g. complex hierarchical piecewise exponential survival models
- 'Exact' methods allow meta-analyses without the need for continuity correction
- Inferences based on the exact full posterior distributions, relaxing the assumption of normality of the outcome (not sensible for rare event data)
- Straightforward and flexible to assess clinical important difference with different scales

Practical Considerations of Bayesian Meta-Analysis for Rare AE Data

- Non-informative priors may lead to convergence failure due to very sparse data
  - Weakly informative priors may be used to solve this issue, e.g.

Prior	Mean log(OR)	Std Dev	Translated Est. Mean HR (95% CI)
1	0.7	2	2 (0.04,110)
2	0	2	1 (0.02, 55)
3	0.7	0.7	2 (0.5, 8.2)

- Sensitivity analyses with regard to the choice of priors need to be performed

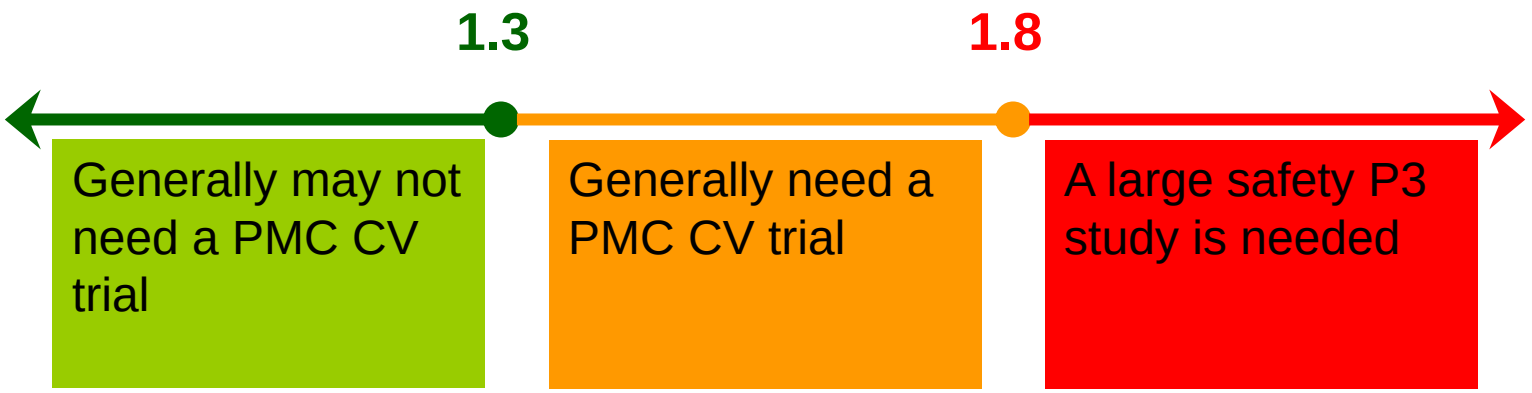
Case Study

Meta-experimental design in evaluating CV risk for T2DM drug development*

* Ibrahim, Chen, Xia and Liu, Biometrics, 2011.

Background – CV Evaluation of New Therapies to Treat Type 2 Diabetes (T2DM)

- FDA Guideline for Evaluating CV risk in a T2DM Product (12/2008) calls for a program-wide meta-analysis of CV outcomes
  - a meta-analysis of the randomized phase 2 and phase 3 studies, or
  - an additional single, large postmarketing safety trial.



An Overview of the New Bayesian Meta-experimental Design Approach

- Using survival models to assess whether the size of a clinical development program is adequate to evaluate a safety endpoint, after accounting for between study heterogeneity
- Extending the fitting and sampling priors of Wang and Gelfand (2002) to Bayesian meta-analysis design with a focus on controlling the type I error and power
- Proposing the partial borrowing power prior to incorporate the historical survival meta-data into the statistical design
- Applying the proposed methodology to the design of a phase 2/3 development program including a non-inferiority clinical trial for CV risk assessment in T2DM studies

A Hypothetical Design of Phase 2/3 Meta Studies with Two Categories

	Control Group	Experimental Drug	Total
Category 1: Randomized Efficacy Superiority Studies			
Individual Study			
Phase 2a – 4 weeks (5 doses, placebo)	25	125	150
Phase 2b – 24 weeks (3 doses, active control, placebo)	140	210	350
Phase 3 – 24 weeks (3 doses, placebo)	100	300	400
Phase 3 – 24 weeks (4 doses, placebo)	75	300	375
Phase 3 add on therapy – 24 weeks (3 doses, placebo)	185	555	740
Phase 3 add on therapy – 24 weeks (2 doses, placebo)	250	500	750
Phase 3 add on therapy – 24 weeks (2 doses, placebo)	188	376	564
Aggregated level			
Total sample size of the above 7 studies	963	2,366	3329
Assumed annualized event rate of death/MI/stroke	1.2%	1.2%	1.2%
Expected endpoints	5	12	17
Probability of upper 95% CI on HR $<$ 1.3		7.8%	
Category 2: Randomized CV outcome study (2 year equal enrollment, minimal of 2 years follow up)			
Sample size	5,000	5,000	10,000
Assumed annualized event rate of death/MI/stroke	1.5%	1.5%	1.5%
Expected endpoints	226	226	452
Probability of upper 95% CI on HR $<$ 1.3		79.6%	
Combined Categories 1 & 2			
Expected endpoints	231	238	469
Probability of upper 95% CI on HR $<$ 1.3		81.1%	

Historical Meta Data Used to Formulate Priors for the Control Arm

Study (publication year)	Group	*N*	Events	Total patient year	Annualized event rate
Saxagliptin (2009)	Total control	1251	17	1289	1.31%
Liraglutide (2009)	placebo	907	4	449	0.89%
	Active control	1474	13	1038	1.24%
ACCORD (2008)	Standard therapy	5123	371	16000	2.29%
ADVANCE (2008)	Standard therapy	5569	590	27845	2.10%

Power and Type I Error for Meta-Design

		$n_{18} = n_{28} = 4000$		$n_{18} = n_{28} = 4500$		$n_{18} = n_{28} = 5000$	
Model	a_0	Power	Type I Error	Power	Type I Error	Power	Type I Error
Random Effects	0	0.765	0.043	0.811	0.040	0.850	0.038
	0.00625	0.787	0.047	0.831	0.045	0.866	0.042
	0.0125	0.801	0.050	0.843	0.047	0.874	0.044
	0.015	0.805	0.051	0.846	0.048	0.876	0.045
	0.025	0.814	0.054	0.855	0.050	0.883	0.047
	0.0375	0.819	0.055	0.860	0.052	0.887	0.049
	0.05	0.821	0.057	0.862	0.053	0.889	0.051
	0.075	0.826	0.058	0.865	0.055	0.892	0.052
	0.1	0.829	0.059	0.867	0.056	0.893	0.053

Summary of Bayesian Meta-Design

- The proposed Bayesian method allows for
  - planning sample size for a phase 2/3 development program in the meta-analytical framework by accounting for between-study heterogeneity
  - incorporating prior information for the underlying risk in the control population through the partial borrowing power prior
- We assess the operating characteristics (type I error and power) of the Bayesian meta-design via simulations
  - recommended by the FDA Bayesian device trials guidance
- Further extension on Bayesian sequential meta-design has been published (Chen, et al, SIM, 2014)

Advantages of using Bayesian statistics for meta-analysis

- Provides a unified framework for synthesizing evidence from multiple data sources/studies/treatments in a formal, consistent and coherent manner, taking all the uncertainty at different levels into account
  - Ability of handling complex problems (e.g. IPD, non-constant hazards)
- Allows formal incorporation of other sources of evidence by utilizing prior distributions
- Provides direct probability statements about true treatment effects under different scales (e.g. OR, RR, or RD)
- Provides prediction of the treatment effect in a new trial
- Appealing for rare event meta-analysis
  - Models modulate the extremes in the zero event setting
  - Avoid the need for continuity correction
  - Bayesian inference is based on the full posterior distributions, relaxing the assumption of normality

Caveats and Recommendations

- Caveats
  - Careful specification of prior distributions and form of the model (e.g. form of hierarchy)
  - Computational intensity
- Recommendations
  - Bayesian expertise should be sought
  - Sensitivity analyses against a range of priors and model structures

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Thank you!