

Guidance on the implementation and reporting of a drug safety Bayesian network meta-analysis

PSI Pharmaceutical Statistics Journal Club Meeting

David Ohlssen, Novartis

25th November 2014

Overview of DIA Bayesian Scientific Working Group (BSWG)

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On behalf of the DIA BSWG

Who are we?

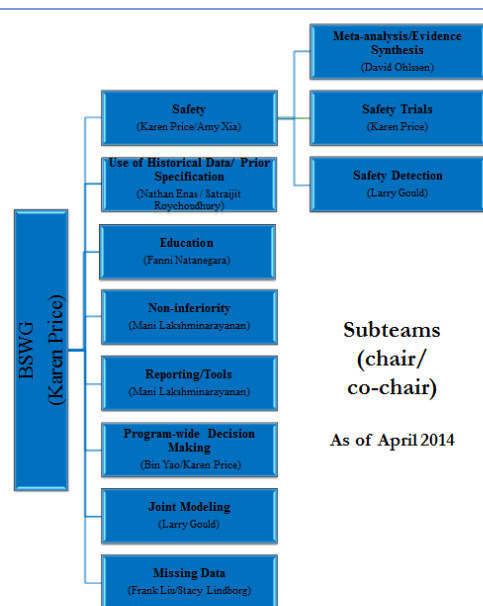
Group of representatives from Regulatory, Academia, and Industry, engaging in scientific discussion/collaboration

- facilitate appropriate use of the Bayesian approach
- contribute to progress of Bayesian methodology throughout medical product development



Structure

- Formally housed under Drug Information Association (DIA)
- Charter exists for full working group and subteams
- BSWG currently chaired by Karen Price
- Full working group teleconferences every quarter
- Face-to-face meeting annually
- To make progress, we prioritized several topics and subteams generally meet monthly



Vision

Ensure that Bayesian methods are **well-understood, accepted, and broadly utilized** for design, analysis, and interpretation to **improve patient outcomes** throughout the medical product development process and to improve decision making.

Mission

To facilitate the appropriate use of Bayesian methods and contribute to progress by:

- **Creating** a scientific forum for the discussion and development of innovative methods and tools
- **Providing** education on, and promoting the dissemination of, methods and best practices for Bayesian methods
- **Engaging** in dialogue with industry leaders, the scientific community, and regulators
- **Fostering** diversity in membership and leadership

Opportunity Statement

- Bayesian methods provide framework to leverage prior information and data from diverse sources
- Bringing together academic, industrial, and regulatory representatives is essential to overcome hurdles
- Provides opportunity to influence proactively by engaging in scientific discussion
- Improved patient outcomes

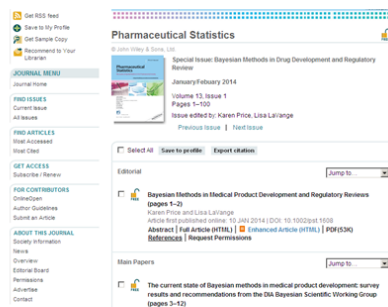


Pharmaceutical Statistics

Special Issue

Bayesian Methods in Medical Product Development and Regulatory Review

- The current state of Bayesian methods in medical product development: Survey results and recommendations from the DIA Bayesian Scientific Working Group: Fanni Natanegara, Beat Neuenschwander, John W. Seaman, Nelson Kinnerley, Cory R. Hellmann, David Ohlssen, George Rochester
- Bayesian Methods for Design and Analysis of Safety Trials: Karen Price, H Amy Xia, Mani Lakshminarayanan, David Madigan, David Manner, John Scott, James Stamey, Laura Thompson
- Guidance on the implementation and reporting of a drug safety Bayesian network meta-analysis: David Ohlssen, Karen Price, H Amy Xia, Hwanhee Hong, Jouni Kerman, Haoda Fu, George Quartey, Cory Hellmann, Haijun Ma, Bradley Carlin
- Use of Historical Control Data for Assessing Treatment Effects in Clinical Trials: Kert Velle, Scott Berry, Beat Neuenschwander, Billy Amzal, Fang Chen, Nathan Enas, Brian Hobbs, Joseph Gibrat, Nelson Kinnerley, Stacy Lindborg, Sandrine Micallef, Satrajit Roychoudhury, Laura Thompson



Invited Session at JSM 2013

Forward Looking

- Broader appropriate use of Bayesian approach
- Presentations/publications/short courses
- Collaborations with Adaptive Design SWG where synergies exist
 - Simulations
 - Program-wide decision making
- Collaborations with DIA communities where synergies exist (e.g., Pediatric community)
- Continued open conversation with Regulators
- Influence Regulatory position

Conclusions

- Thank you to DIA for support of SWG's
- DIA Bayesian Scientific Working Group's mission is to facilitate the use and progress of Bayesian methods by **creating** a scientific forum, **providing** education on best practices, and **engaging** in dialogue.
- Bringing together representatives from the academic, industry, and regulatory is essential for overcoming hurdles

Activities for 2014 / 2015

- Subteams continue to make progress
- Several publications planned
 - Bayesian signal detection (Therapeutic Innovation & Regulatory Science accepted)
 - Joint modeling (Stat in Med, early view available)
 - Missing data
 - Noninferiority trials
- Several presentations planned
 - DIA/FDA Statistics Forum
 - DIA Annual Meeting
 - JSM
- Short courses in 2014
 - DIA/FDA Statistics Forum: Bayesian Methods for Drug Safety Evaluation and Detection (David Ohlssen, Amy Xia, and Haijun Ma)
 - DIA Annual Meeting/Deming Conference: Bayesian Network Meta-analysis (Brad Carlin and Karen Price)
- Bayesian SWG and Adaptive Design SWG planning joint conference in February 2015

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Outline

- Overview of meta-analysis and Bayesian meta-analysis using summary data
- Critical aspects of a Bayesian safety meta-analysis
- Bayesian **network** or **mixed treatment comparison** (MTC) meta-analysis
- Case-study involving cardio-vascular safety and NSAIDS
- Extensions and future directions
- Concluding remarks

Review of Bayesian Meta-Analysis

Some definitions

‘Meta-Analysis’ (*Glass, 1976*)

“The statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating the findings.”

Or (Huque, 1988)

“A statistical analysis which combines the results of several independent studies considered by the analyst to be combinable”

Why Meta-analysis might be performed

- **Aggregate** results / evidence / data to obtain more precise estimates of treatment effects
- Assess the extent to which individual studies differ (**heterogeneity**)
- Identify sources of heterogeneity in response to treatment
- Analyze endpoints for which information is too **sparse** (e.g. Events are too rare) in the individual studies.
- Analyze **subpopulations** that are too small in individual trials.

Why use Bayesian statistics for meta-analysis?

- **Unified modelling** and the ability to explore a wide range of modelling structure
 - Synthesis of evidence from multiple sources / multiple treatments
- Formal **incorporation of other sources of evidence** by utilizing **informative prior distributions**
 - Ability to incorporate prior information regarding background event rates
 - Ability to model between-study variability properly in random effects models
- **Probability statements** about true effects of treatment easier to understand than confidence intervals and p-values

Meta-analysis notation

Data

- Let T represent the experimental treatment group and C the control group
- Suppose y_i is the (summary) data from N studies, $i=1,\dots,N$
- y_i could individual patient outcome data associated with the study
- Could represent summary data (sufficient statistics) from each treatment group (e.g binary outcome data (y_{iT}, n_{iT}) (y_{iC}, n_{iC}))
- Could represent a treatment effect estimate and corresponding standard error (y_i, s_i)

Notation for individual Study

- Let μ_{iC} be the control group parameter (e.g background rate or population mean) and μ_{iT} be the corresponding treatment group parameter μ_{iT}
- Let δ_i Parameter of interest
- compares T with C
 - absolute metric: e.g. mean difference $\mu_{iT} - \mu_{iC}$
 - relative metric:
 - Ratio: μ_{iT} / μ_{iC} (risk ratio, odds-ratio, hazard ratio)
 - log-ratio: $\log(\mu_{iT} / \mu_{iC})$

Meta analysis modeling assumptions

*Standard meta-analyses

		Treatment Effects δ (T vs.C)		
		(C) common	(U) unrelated	(R) related/similar/ random effects
Control Parameters μ	(C) common	*complete pooling crude estimates (often done, not recommended)		
	(U) unrelated	* common/fixed effect analysis ("fixed effects" analysis)	full stratification (useful for data description)	* random effects analysis
	(r) related/similar/ random	common effect, similar control parameters (useful for rare events)		bivariate random-effects analysis

Bayesian random effects meta-analysis of summary data

Let y_i denote the observed treatment effect in trial i and s_i^2 be the corresponding estimated standard error

$$y_i \mid \delta_i \sim N(\delta_i, s_i^2)$$

$$\delta_i \sim N(d, \tau^2)$$

- Add prior distributions for unknowns:

$$d \sim N(?, ?)$$

– Heterogeneity

$$\tau \sim \text{halfN}(0, ?)$$

$$\tau \sim \text{Unif}(0, ?)$$

Example responder summary data

Binomial sampling model u-C and u-R models

$$y_{iT} \sim \text{Bin}(n_{iT}, p_{iT}); y_{iC} \sim \text{Bin}(n_{iC}, p_{iC})$$

$$\text{Logit}(p_{iT}) = \mu_{iC} + \delta_i \quad \text{Logit}(p_{iC}) = \mu_{iC}$$

$$\delta_i \sim N(d, \tau^2) \text{ (uR) or } \delta_1 = \dots = \delta_N = d \text{ (uC)}$$

Add prior distributions for unknowns:

$$p(\mu_{iC}) p(d) p(\tau)$$

$$\text{e.g. } \mu_{iC} \sim N(0, 100^2); d \sim N(0, 100^2); \tau \sim \text{Unif}(0, 2)$$

Example event count and exposure data

Poisson sampling model u-C and u-R models

$$y_{iT} \sim \text{Pois}(E_{iC} \lambda_{iC}); \quad y_{iC} \sim \text{Pois}(E_{iT} \lambda_{iT})$$

$$\text{Log}(\lambda_{iT}) = \mu_{iC} + \delta_i \quad \text{Log}(\lambda_{iC}) = \mu_{iC}$$

$$\delta_i \sim N(d, \tau^2) \text{ (uR) or } \delta_1 = \dots = \delta_N = d \text{ (uC)}$$

Add prior distributions for unknowns:

$$p(\mu_{iC}) p(d) p(\tau)$$

$$\text{e.g. } \mu_{iC} \sim N(0, 100^2); \quad d \sim N(0, 100^2); \quad \tau \sim \text{Unif}(0, 2)$$

Bayesian method - extending the basic model

- Characterizing heterogeneity and prediction (See Higgins et al; 2009)
 - **Heterogeneity**: quantification – but not homogeneity test
 - **Prediction**: effect in new study most relevant and complete summary (predictive distribution)
- Flexibility
 - **Alternative scales** and link function - see Warn et al (2002)
 - **Flexible random effects** distributions – see Lee et al (2007) and Muthukumarana (2012)
 - **Combining individual patient data with aggregate data** - see Sutton et al (2008)
 - **Subgroup analysis** – see Jones et al (2011)
 - **Prior information** - see Turner et al (2009 & 2012)

Critical aspects of a Bayesian safety meta-analysis

Combining data to examine rare events in drug safety

- When **examining rare safety events**, it is usually necessary to identify a number of **relevant studies** and then **use meta-analytic techniques** to combine results.
- However, this leads to a number of **tricky issues** regarding the **selection of relevant information**
 - Studies with **varying levels of exposure**
 - How events were recorded (**adjudicated v non adjudicated**)
 - Purpose of the study (safety study v efficacy study)

Critical aspects of the statistical analysis

- Meta-analysis v naive pooling
 - Meta-analysis is generally recommended
- Choice of analyses method
 - Fixed effect v Random effects; Choice of estimation method: (conditional v unconditional) (classical v Bayesian) (approximate v exact)
- How to handle studies with no events
 - Remove them; use continuity corrections; random effects; choice of metric (e.g. risk difference)
- In the drug development setting, multiplicity is challenging

Acknowledgements

Based on the work of the Bayesian DIA safety meta-analysis team

MAIN PAPER

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Guidance on the implementation and reporting of a drug safety Bayesian network meta-analysis

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The Drug Information Association Bayesian Scientific Working Group (BSWG) was formed in 2011 with a vision to ensure that Bayesian methods are well understood and broadly utilized for design and analysis and throughout the medical product development process, and to improve industrial, regulatory, and economic decision making. The group, composed of individuals from academia, industry, and regulatory, has as its mission to facilitate the appropriate use and contribute to the progress of Bayesian methodology. In this paper, the safety sub-team of the BSWG explores the use of Bayesian methods when applied to drug safety meta-analysis and network meta-analysis. Guidance is presented on the conduct and reporting of such analyses. We also discuss different structural model assumptions and provide discussion on prior specification. The work is illustrated through a case study involving a network meta-analysis related to the cardiovascular safety of non-steroidal anti-inflammatory drugs. Copyright © 2013 John Wiley & Sons, Ltd.

Keywords: drug safety meta-analysis; rare events; mixed treatment comparisons; network meta-analysis; multiple outcomes; reporting Bayesian analysis; prior sensitivity

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Checklist for Bayesian Safety Meta-analysis

- **Methods**

- Study design
- Outcome measure
- Statistical model
- Prior distribution
- Computation / software
- Planned analyses for model checking, prior to posterior sensitivity, and convergence diagnostics

Checklist for Bayesian Safety Meta-analysis (cont.)

- Results

- Describe **posterior distribution of** parameters and other quantities of interest
- Results for **modeling checking and convergence diagnostics**

- Interpretation

- **Bayesian interpretation**
- Impact of **prior** to posterior **sensitivity**

Priors for τ and μ_{ic}

sensitivity analysis

- Prior sensitivity analysis is important in meta-analysis of rare adverse events
- For μ_{ic} Switch the treatment labels (Parameterization change)
Increase the variance in the prior distributions associated with fixed effects (e.g. $\text{Normal}(0, 1000^2)$ instead of $\text{Normal}(0, 100^2)$)
- **On a log(ratio) scale**, in the (UR) model Consider both the half normal and uniform[0,2] prior for τ
- In each case, **if the posterior distributions for the key parameters substantially** change, conclude that the analysis is sensitive to choice of prior. This **lack of robustness** must be **clearly reported** when describing the results.

Informative priors for τ

- With small numbers of studies there is little information to identify variance components (e.g. τ)
 - Just focus on a fixed effect (uC) model
 - Fit a random effects model with a range of fixed values of for τ
 - Weakly informative (e.g half normal[0,1] for log ratio scales)
 - Use an informative prior based on empirical evidence
- Using an informative prior seems promising
- See Turner et al (2012)

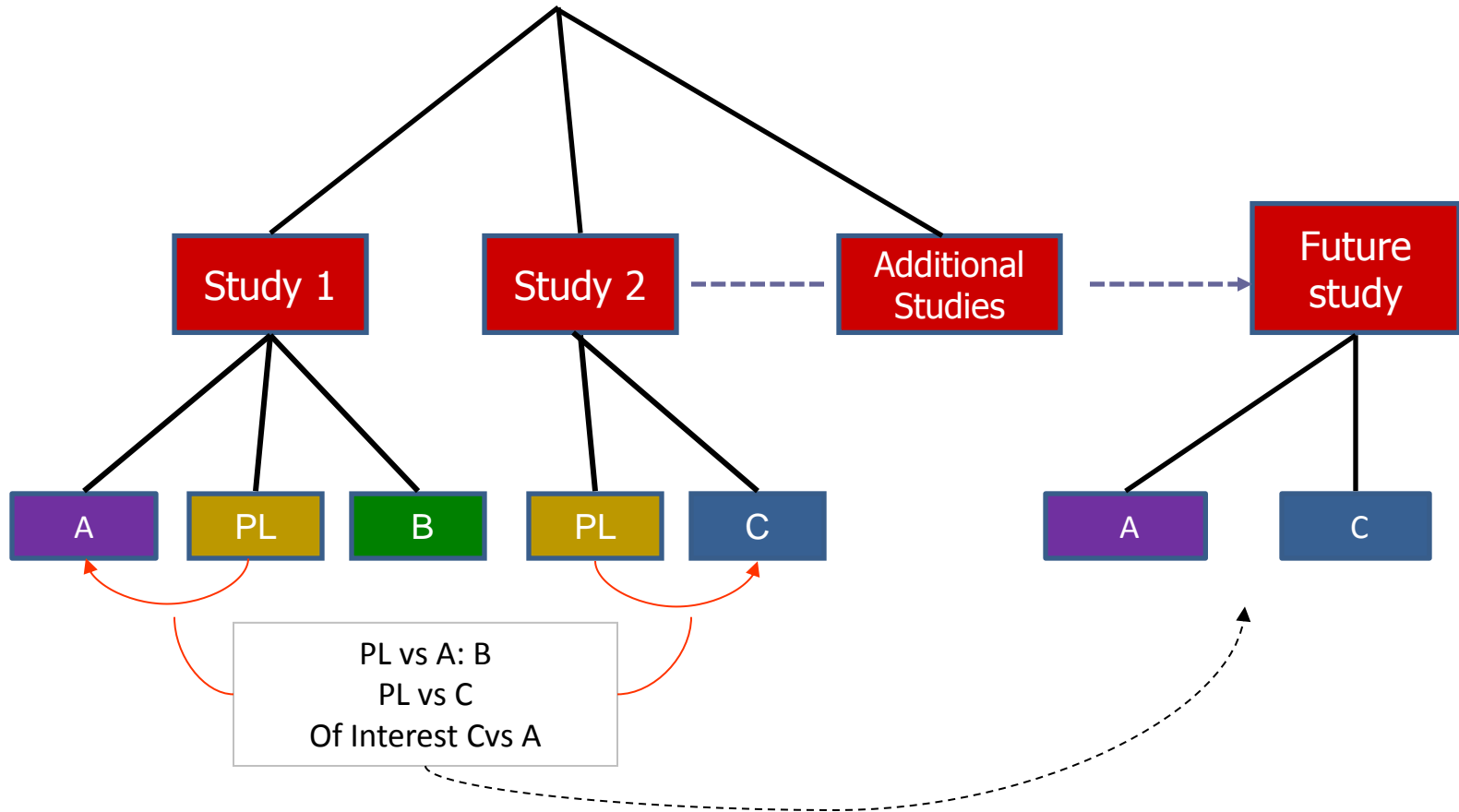
Bayesian network meta-analysis And NSAIDs case-study

Bayesian Network Meta-Analysis

- Bayesian network meta-analysis (mixed treatment comparisons) have been presented as an extension of traditional MA by including multiple different pairwise comparisons across a range of different interventions
- Several Guidances/Technical Documents recently published



Basic Framework



Network meta-analysis models

Based on the work of Lu and Ades (LA) (2006 & 2009)

Linear predictor

$$\eta_{ik} = \begin{cases} \mu_i & k = b \\ \mu_i + \delta_{ibk} & k > b \end{cases}$$

b is the control treatment associated with trial i

$$\delta_{ibk} \stackrel{ind}{\sim} N(d_{1k} - d_{1b}, \sigma^2)$$

- μ_j is the effect of the baseline treatment b in trial i and δ_{ibk} is the trial-specific treatment effect of treatment k relative to treatment b (the baseline treatment associated with trial i)
- Note baseline treatments can vary from trial to trial
- Different choices for μ 's and δ 's. They can be: *common* (over studies), *fixed* (unconstrained), or *“random”*
- Consistency assumptions required among the treatment effects
- Prior distributions required to complete the model specification

Alternative way to describe the model

Two way layout via MAR assumption

- All studies can in principle contain every arm, but In practice most arms will be missing.
- As the network meta-analysis model implicitly assumes MAR (Lu and Ades; 2009) a common (though possibly missing) baseline treatment can be assumed for every study (Hong and Carlin; 2012)

$$\eta_{ik} = s_i + t_k + \nu_{ik}$$

$$(\nu_{i2}, \dots, \nu_{iK})' \sim \text{MVN}(\mathbf{0}, \Sigma)$$

$$\Sigma = \sigma^2 \begin{bmatrix} 1 & \rho & \cdots & \rho \\ \rho & 1 & \cdots & \rho \\ \vdots & \vdots & \ddots & \vdots \\ \rho & \rho & \cdots & 1 \end{bmatrix}$$

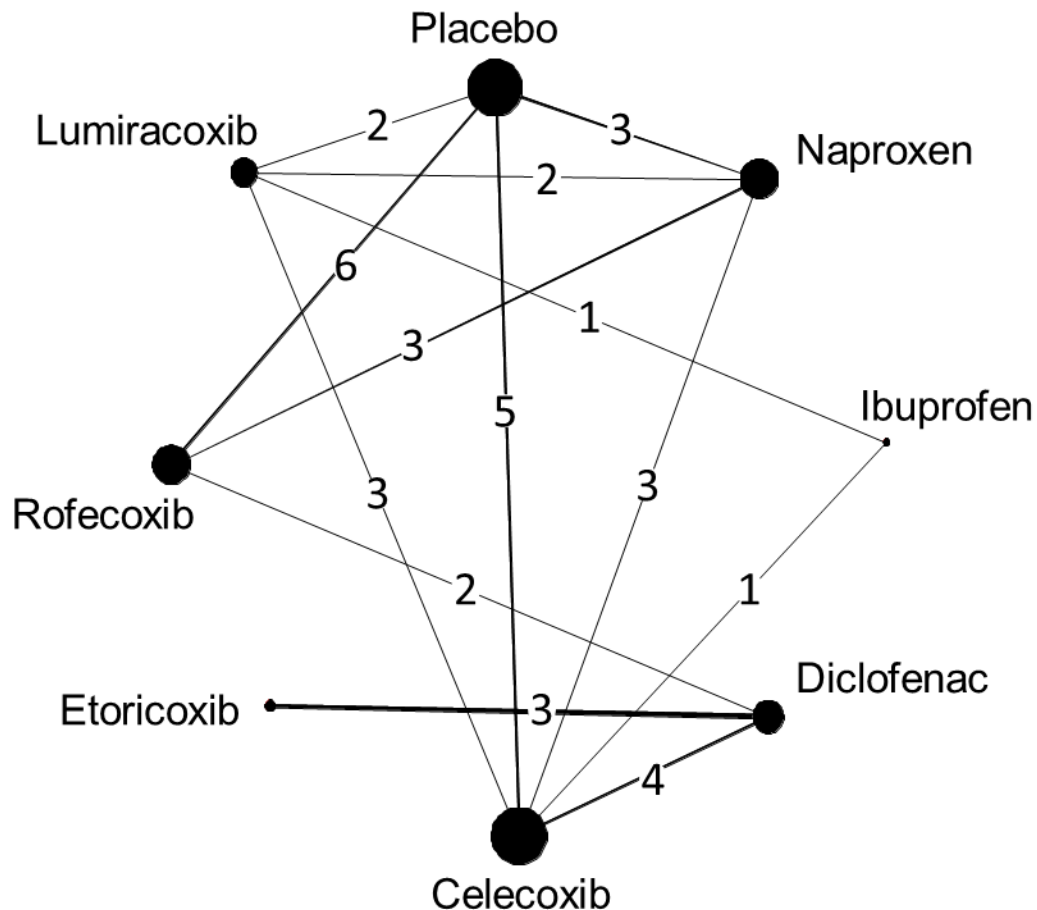
s_i study effect associated with study i

t_k is treatment effect associated with treatment k

ν_{ik} is the random treatment by study interaction term

Network meta-analysis Example

Trelle et al (2011) - Cardiovascular safety of non-steroidal anti-inflammatory drugs:



- Primary Endpoint was myocardial infarction
- Data synthesis 31 trials in 116 429 patients with more than 115 000 patient years of follow-up were included.
- A Network random effects meta-analysis were used in the analysis
- Critical aspect – the assumptions regarding the consistency of evidence across the network
- How reasonable is it to rank and compare treatments with this technique?

Results from Trelle *et al*

Myocardial infarction analysis

Relative risk with 95% confidence interval compared to placebo

Treatment	RR estimate	lower limit	upper limit
Celecoxib	1.35	0.71	2.72
Diclofenac	0.82	0.29	2.20
Etoricoxib	0.75	0.23	2.39
Ibuprofen	1.61	0.50	5.77
Lumiracoxib	2.00	0.71	6.21
Naproxen	0.82	0.37	1.67
Rofecoxib	2.12	1.26	3.56

Authors' conclusion:

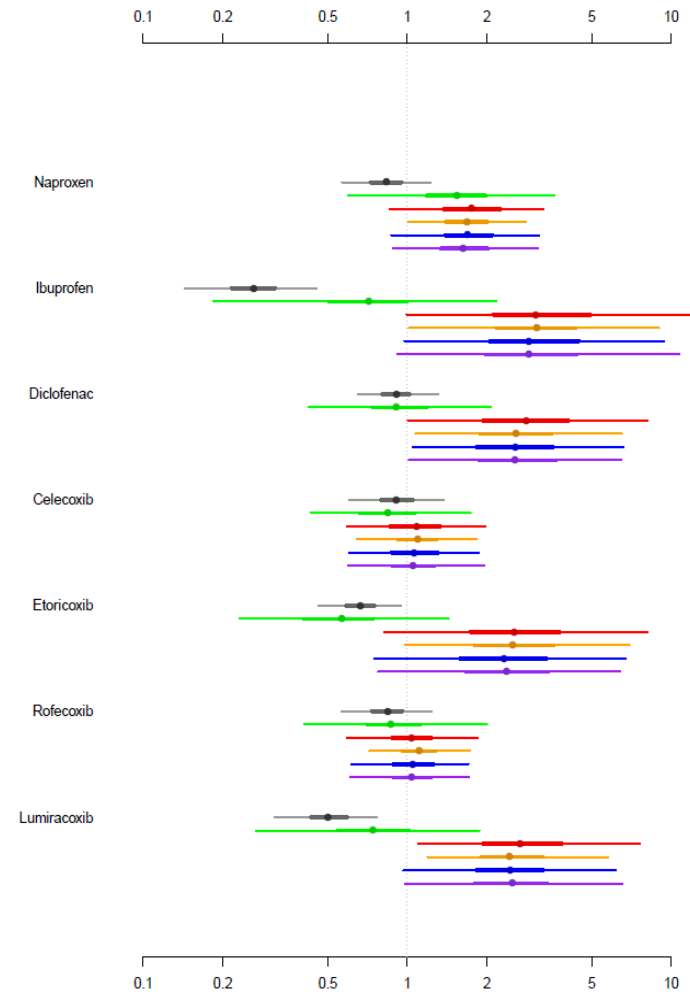
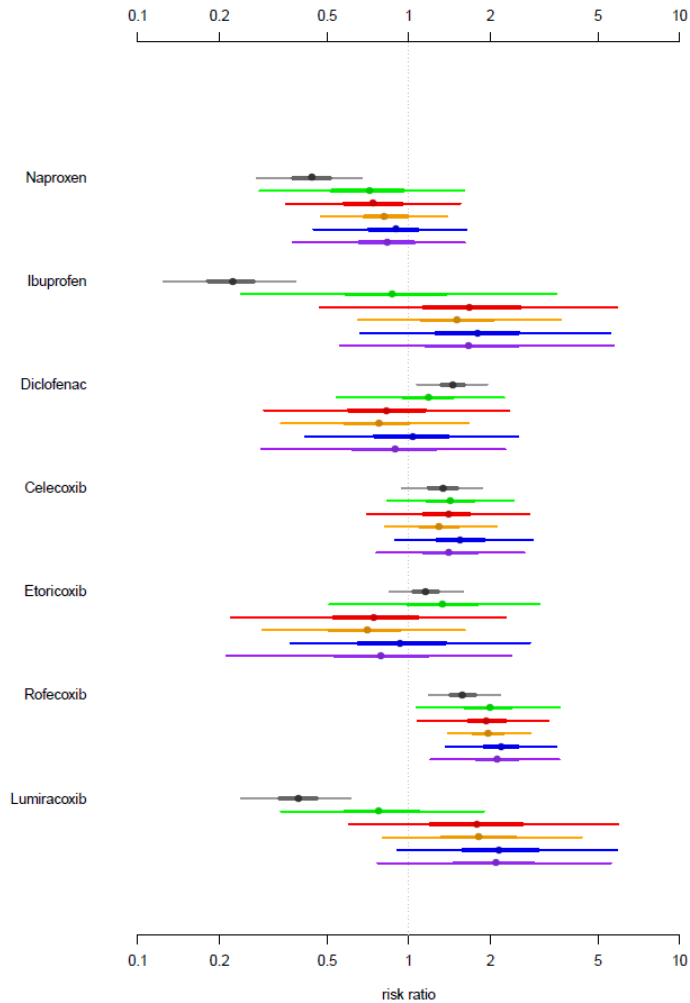
Although uncertainty remains, little evidence exists to suggest that any of the investigated drugs are safe in cardiovascular terms. Naproxen seemed least harmful.

Comments on Trelle *et al*

- Drug doses could not be considered (data not available).
- Average duration of exposure was different for different trials.
- Therefore, ranking of treatments relies on the strong assumption that the risk ratio is constant across time for all treatments
- The authors conducted extensive sensitivity analysis and the results appeared to be robust

MI and stroke results from Trelle et al

Comparing LA FE RE model with the TW RE model and MV RE



Grey- c-C green r-R red LA u-R yellow LA u-C blue TW (1) u-R purple TW (2) u-R

Future directions

- Network meta-analysis with multiple outcomes
 - Sampling model (multinomial?)
 - Borrow strength across treatment effects
 - Surrogate outcome meta-analysis combined with a network meta-analysis
- Network meta-analysis with subgroup analysis
- Combining network meta-analysis; meta-analysis of subgroups and multivariate meta-analysis
- More work on informative priors for variance components and baseline parameters

Final remarks

- In standard random effect meta-analysis the Bayesian approach has the advantage of:
 - Flexibility in modeling assumptions
 - Allowing the incorporation of full uncertainty in all parameters
 - Informative prior information particularly for the variance component
- Additional information provided by network meta-analysis could be very valuable when looking at rare safety events
- Good systematic review principles should be adopted and models should be carefully examined

References

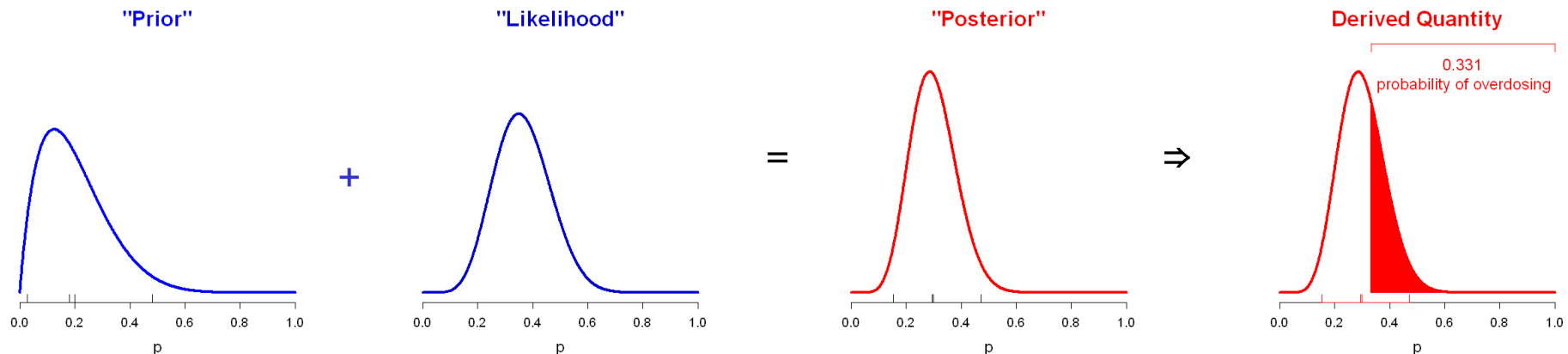
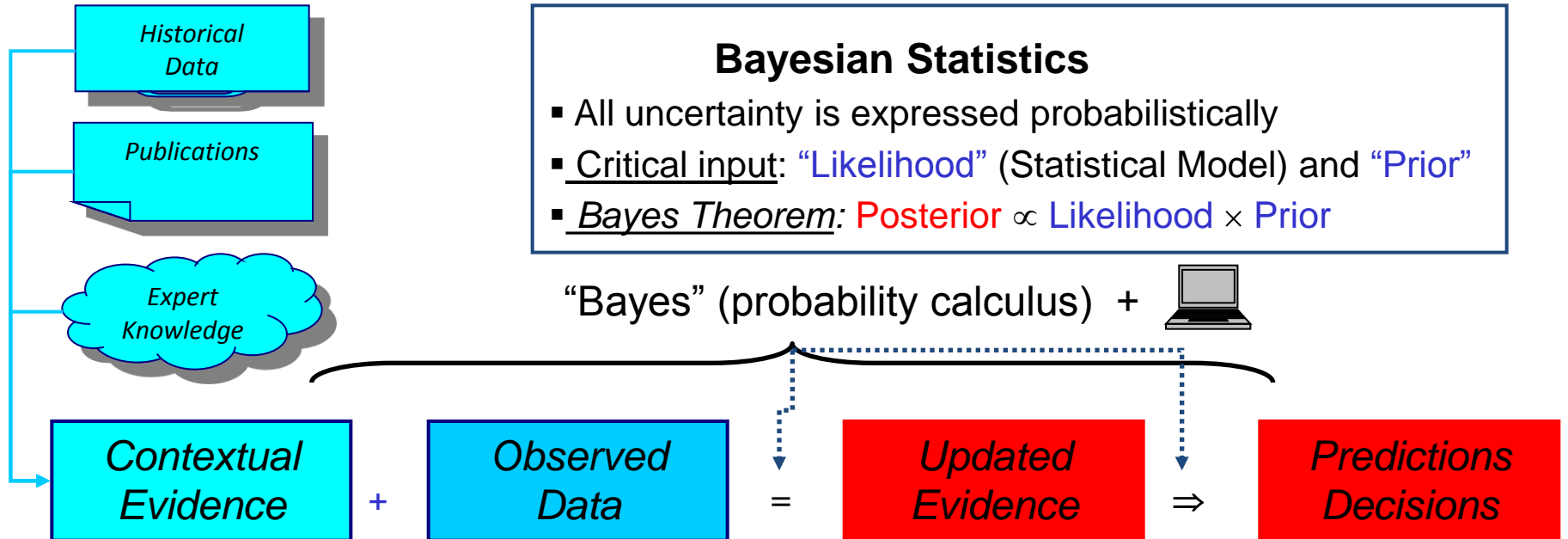
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Back-up Slides

Brief review of Bayesian methods

Introduction Bayesian methods

Summary



Some comments on Bayesian methods

A personal perspective

- For a given problem, Bayesian statistics provides:
 - A framework to combine relevant sources of information,
 - using a realistically complex probability model
- In addition, if this model is useful:
 - it should be reasonably well calibrated
 - and lead to predictions that can form the basis for rational decision making
- However, the big challenge for a Bayesian, is convincing others that their model(s) are useful
- In other words, the posterior distributions and predictive distributions are approximately correct

Simple to code in WinBUGS or SAS

```
model{  
  for (i in 1:k) {  
    y[i] ~ dnorm(theta[i], w[i])  
    w[i] <- 1/(SE[i]*SE[i])  
    theta[i] ~ dnorm(mu, prec)  
  }  
  prec <- 1/(tau*tau)  
  # prior distributions  
  mu ~ dnorm(0,0.001)  
  tau ~ dunif(0,100)  
  # predictive distribution  
  theta.new ~ dnorm(mu, prec)  
}
```

`dnorm(mu,prec)` is normal distribution with mean μ and variance $1/\text{prec}$.

```
proc mcmc data=dat ... ;  
  
  array theta[&nstudy];          *  
    vector of study effects;  
  
  parms mu 0 tau 1 theta: 0;    *  
    initial values;  
  
  prior mu: ~  
    normal(m=0,var=1000);      *  
    priors;  
  
  prior tau: ~ uniform(0,100);  
  
  prior theta: ~  
    normal(m=mu,sd=tau);  
  
  theta0 =  
    rand('normal',mu,tau);      * new  
    study;  
  
  thetas = theta[STUDY];  
  
  model y ~  
    normal(m=thetas,sd=SE);    * ES  
    and SE;
```

Other topics discussed in the paper

- The construction of a prior for background rate
 - Development of a Baseline history model using predictive distributions from a Bayesian hierarchical model
 - Utilizing observational data that is discounted based on rigor and relevance
 - Directly forming an informative prior using the Sheffield elicitation framework (SHELF)
- Priors for variance components
 - Utilizing empirical evidence
- Guidance on developing and reporting Bayesian safety meta-analysis
 - Following good systematic review principles
 - Bayesian models and priors (Was this pre-defined)
 - MCMC checks, reporting metrics...