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# Application of Hierarchical Bayesian Linear Model in Meta-Analysis

**Geetha R Menon**
*Indian Council of Medical Research*
*V. Ramalingaswami Bhavan, Ansari Nagar, New Delhi-110029*
*Email: drgmenon@yahoo.co.in*

**K. R. Sundaram, R. M. Pandey & K. Prasad**
*All India Institute of Medical Sciences Ansari Nagar, New Delhi-110029*

**B. R. Handa**
*Indian Institute of Technology, New Delhi*

**Padam Singh**
*Indian Council of Medical Research, Ansari Nagar, New Delhi-29*

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## Abstract

Meta-analysis is an evidence based tool for combining results from independent studies to obtain a concise estimate. Broadly the two parametric statistical models used in this method are the fixed effect model and the random effect model. The appropriateness of these models in incorporating variability between studies and resolving the problem of unpublished studies in meta-analysis has long been debated among statisticians. The Bayesian inference has been adopted extensively in clinical decision making. This communication provides a detailed account of the theory of Hierarchical Bayesian Linear Model (HBLM) in determining the summary estimates in meta-analysis of clinical trials. It has been shown that HBLM is a generalized model from which the results of the classical fixed effect and random effect model can be derived by treating the value of variation between studies, $\tau$ as either 0 or the non-iterative estimate by the methods of moments. It also provides a method for estimating the study specific estimate that helps in computing predictive probabilities. The Bayesian model has been found to be more useful in incorporating other sources of variation as it is based on Generalized Linear model.

**Keywords and Phrases:** Hierarchical Bayesian Linear model, posterior probabilities, Gauss-Hermite polynomial.

**AMS Classification:** 62P10, 62J12, 65D32, 65R20

# 1 Introduction

Meta-analysis is the science of integrating results from independent studies to obtain a concise estimate. It has been identified as an analytical and methodological tool to aid the researchers to combine information from similar studies to arrive at a conclusion. In contrast to the traditional literature review which is narrative in nature, meta-analysis uses quantitative methods to combine published results from primary studies to arrive at a combined estimate. Over the past two decades, researchers have developed several statistical models to describe the combining methods. While most of them fall under the frequentist models, some Bayesian models have also been developed. Hierarchical Bayesian Linear model is one such technique that has been found to have great potentials as a meta-analytic technique. Many researchers especially Dr William Dumouchel (1983, 1996) have used this model in their studies. The same model has been used by us in the PhD work. This communication describes the theoretical development of the summary measures of a hierarchical model as a tool for meta-analysis. The method has been applied on meta-analysis of stroke clinical trials.

# 2 Review of literature

Lewis et al (1993) has highlighted the advantages of Bayesian analysis in yielding the probability that one treatment is more efficacious than the other. He contrasts the Bayesian and the Classical methods of inference and points out that Bayesian analysis scores over the classical method in the ability to incorporate prior information regarding treatment efficacies, the ability to make multiple unscheduled inspections of accumulating data without increasing the error rate of the study and the ability to calculate the probability that one treatment is more effective than the other.

Some of the properties of the Bayesian inference have motivated Berger et al (1984), Spiegethalter et al (1988) and Spiegelhalter et al (1994) to develop techniques for using Bayesian approaches for interpretation and analysis of data from clinical trials. All the authors have highlighted the incorporation of available evidence in the Bayesian analysis.

Donner (1982) has developed a Bayesian approach to interpret subgroup results in clinical trials. He observed that in treatment comparisons if a clinician is able to determine a priori the association between two groups by experience it is possible to incorporate this knowledge to interpret the results of the clinical trial.

Greenhouse et al (1994) has tried to describe robust Bayesian approach to address the major criticism of the Bayesian approach on the need to specify a prior distribution of the parameters of interest. He defines a class of prior distributions and investigates how the inferences might change when the prior changes.

Raudenbush and Bryk (1985) were one of the earliest advocates of empirical Bayesian methods in meta-analysis. They have used a mixed effect model with both fixed and random effects by assuming a two stage hierarchical linear model in meta-analysis. In the first stage, within-study variance is estimated and in the second stage between studies variation is estimated.

Carlin (1992) has developed a fully Bayesian approach to meta-analysis of studies when the results are in the form of 2X2 tables. He has used a hierarchical normal model with the assumption that the parameters of interest are the effects from individual studies that are represented by an exchangeable prior distribution.

Smith et al (1995) have described a fully Bayesian analysis which can deal with some of the unresolved issues such as a choice between the random and fixed effect models, the treatment of small studies and extreme results and incorporation of study specific covariates.

Prof. Donald Berry did pioneering work in Bayesian interpretation of clinical trials. In their publication, Berry et al (1985, 1990,1992) have described that for strict interpretation of results, the Bayesian approach is more appropriate in analyzing clinical trials and meta-analysis than the frequentist approach. According to him, the frequentist inference is a strict interpretation of Neyman-Pearson inference. In this approach the design of the experiment induces a sample space that can be used in calculating probabilities of statistics under various hypotheses. When the design is not known a frequentist analysis is not possible. In a meta-analysis with a frequentist approach since no overall design for gathering data is specified in advance, each study should be analyzed separately in a meta-analysis. As a result, although frequentist measures are used for representing data summaries in Meta analysis no inferential meaning could be justified by frequentist measures.

DuMouchel(1983) developed a Bayesian model using the generalized least square method for application in meta-analysis. The concept of 'borrowing strength' from individual studies is highlighted in his paper. The technique has been applied on papers developed by DuMouchel and Harris (1994) and the NASA report (1996) on Hierarchical Bayesian Linear Modeling and meta-analysis.

The NASA report is a pioneering work of DuMouchel which explains the role of Hierarchical model in meta-analysis. The same model has been applied by the author in another paper (Canner, 1983) on Canner's review of six trials of myocardial infarction.

Spiegelhalter et al(1994) have discussed the use of Bayesian framework for analyzing clinical trials. The paper gives the various sources of evidence that could be used

as prior information for incorporating in the analysis. These include clinical opinion, evidence from non-randomized studies and evidence from other randomized trials apart from the reference prior as defined by Jeffreys (1961).

Freedman (1983) has discussed the use of subjective opinion in stopping rules for clinical trials in his paper. The clinical opinion was elicited by interviews with clinicians who were asked to specify two values d1 and d2 where d1 is the lower limit of the range of equivalence below which the clinician would certainly not use the treatment and d2 is the level above which the clinician will certainly use the treatment.

Chaloner et al (1993) describes a graphical method of elicitation of prior distribution for a clinical trial.

Parmar et al (1994) have designed a postal questionnaire to elicit the prior judgment of clinicians who were to take part in the CHART lung trial and head an neck trial. The prior opinion of the participating clinicians regarding the advantage of CHART over conventional radiotherapy was elicited by marking their opinion (range of equivalence) on a scale of treatment differences.

Tweedie et al (1996) had applied Bayesian meta-analysis on lung cancer studies and they have demonstrated that compared to the random effects model Bayesian methods allow more detailed modeling of study heterogeneity to be incorporated, are robust against a wide choice of specifications of heterogeneity and allow more detailed statements to be made not only about the overall effect by also about the individual study effects. The paper has employed the Markov Chain Monte Carlo techniques for implementing Bayesian hierarchical models but the details of the technique have not been given.

The main drawback of Bayesian method is the difficulty in computing complicated likelihood and posterior functions. Naylor (1982) has outlined a numerical integration method using Gaussian quadrature that leads to efficient calculation of posterior densities for a wide range of problems. The method has shown that in comparison to standard maximum likelihood methods, this method can handle complex likelihoods or prior densities with ease and maximum likelihood methods are sensible if the log-likelihood contours are ellipsoidal which is a more restrictive assumption.

Reilly (1976) has described a method in which the prior probabilities are described as arrays using the parameters of a linear or non-linear model. These are then used in the Bayes theorem to get joint posterior distributions of the parameters.

# 3 Methodology

A formal Hierarchical Linear Model assumes that the sample estimate $y_i$ is approximately normally distributed with known variances, conditional on the true parameter value $\theta_i$ i.e.

$$y_i/\theta_i \sim N(\theta_i, s_i^2) \tag{1}$$

Further, $\theta_i$ follows normal distribution with mean and variance given by the hyperparameters $\mu$ and $\tau^2$ respectively i.e.

$$\theta_i/\mu, \tau^2 \sim N(\mu, \tau^2) \tag{2}$$

Meta-analysis could be considered as a hierarchical process with the effect $y_i$ from the $i^{th}$ trial that estimates the parameter $\theta_i$ for the selected set of trials. These trials could then be thought of as a subset from a larger population of trials with an unknown effect $\mu$. Thus, the problem simplifies to the estimation of the population parameters $\mu$ and $\tau^2$ given the data $Y$. From (1) and (2) the sample effect measure $y_i/\mu, \tau^2$ follows normal distribution with mean $\mu$ and variance $\tau^2 + s_i^2$. The probability density function for $y_i$ is then given as

$$f\left(y_i/\mu, \tau^2\right) = \frac{1}{\sqrt{2\pi(\tau^2 + s_i^2)}} e^{\frac{-1(y_i-\mu)^2}{2(\tau^2+s_i^2)}}$$

In the Bayesian paradigm $\mu$ and $\tau$ are estimated from the posterior density function $f(\mu/Y)$ and the marginal posterior density function of $f(\tau/Y, \mu)$ respectively. Using the Bayes formula for two parameters, the marginal posterior distribution of $\mu$ is

$$\pi(\mu/Y, \tau^2) = \frac{\pi(Y/\mu, \tau^2)\pi(\mu/\tau^2)}{\int\limits_{\mu} \pi(Y/\mu, \tau^2)\pi(\mu/\tau^2)d\mu} \tag{3}$$

where $\pi(\mu/\tau^2)$ is the conditional distribution of $\mu$ if $\tau^2$ is known. Similarly the posterior distribution of $\tau$ is given as

$$\pi(\tau/\mu, Y) = \frac{\pi(Y/\mu, \tau^2)(\mu/\tau^2)\pi(\tau)}{\int\limits_{\tau} \pi(Y/\mu, \tau^2)\pi(\mu/\tau^2)\pi(\tau)d\tau} \tag{4}$$

where $\pi(\tau)$ is the prior distribution of $\tau$. Thus, the Bayesian estimates for $\mu$ and $\tau$ were found to depend on the prior distribution of $\mu$ and $\tau$.

In meta analysis of clinical trials with binary outcome the effect is the absolute difference in event rates in the treatment group and the control group (pt-pc). This measure follows a normal distribution. The corresponding population measure should also follow normal distribution. Assuming a non-informative normal prior for $\mu$ given $\tau$

with arbitrary mean m and variance $d^2 \to \infty$ i.e $\mu \sim N(m, d^2)$ and a non-informative prior distribution $\pi(\tau)$ for $\tau$ it is possible to obtain estimates for $\mu$ and $\tau$ using a Bayesian approach. In particular, we are interested to obtain the following summary estimates

*a*. Mean and variance of $\mu$ , the parameter for the larger population

*b*. Mean and variance of $\theta$, the parameter for the subset of population

The two summaries are obtained in Bayesian terms using conditional and unconditional probabilities.

The conditional summaries are:

• Conditional posterior mean $\mu^*(\tau) = E(\mu/Y, \tau)$ and variance $\mu^{**}(\tau) = V(\mu/Y, \tau)$ where $\mu$ is a function of $\tau$.

• Conditional posterior mean $\theta_i^*(\tau) = E(\theta_i/Y, \tau)$ and variance $\theta_i^{**}(\tau) = V(\theta_i/Y, \tau)$ where $\theta_i$ is a function of $\tau$.

The unconditional summaries are:

• Unconditional posterior mean and variance of $\mu, \mu^*, \mu^{**}$.

• Unconditional posterior mean and variance of $\theta_i, \theta_i^*, \theta_i^{**}$.

The posterior probabilities.

*a*. **Conditional combined mean and variance,** $\mu^*(\tau)$ **and** $\mu^{**}(\tau)$

$$\mu^*(\tau) = E(\mu/Y, \tau) = \int_{\mu} \mu.f(\mu/y, \tau)d\mu \qquad -\infty < \mu < \infty$$

$$f(\mu/y, \tau) = \frac{f(\mu, y, \tau)}{f(y, \tau)} = \frac{f(\mu, y, \tau)}{\int_{\mu=-\infty}^{\mu=\infty} f(\mu, y, \tau)d\mu} = \frac{f(y/\mu, \tau).f(\mu/\tau)}{\int_{\mu=-\infty}^{\mu=\infty} f(y/\mu, \tau).f(\mu/\tau)d\mu}$$

$$E(\mu/y, \tau) = \frac{\int_{\mu=-\infty}^{\mu=\infty} \mu f(y/\mu, \tau).f(\mu/\tau)d\mu}{\int_{\mu=-\infty}^{\mu=\infty} f(y/\mu, \tau).f(\mu/\tau)d\mu} \tag{5}$$

$$f(y/\mu,\tau).f\left(\mu/\tau\right)=\frac{1}{\left(\sqrt{2\pi}\right)^{k}\prod_{i=1}^{k}\sqrt{\left(s_i^2+\tau^2\right)}}e^{-\frac{1}{2}\sum_{i=1}^{k}\frac{\left(y_i-\mu\right)^2}{\left(s_i^2+\tau^2\right)}}\times\frac{1}{d\sqrt{2\pi}}e^{-\frac{1}{2}\left(\frac{\mu-m}{d}\right)^2}$$

$$=\frac{1}{\left(\sqrt{2\pi}\right)^{\mathrm{k+1}}\prod_{\mathrm{i=1}}^{\mathrm{k}}\sqrt{\left(\mathrm{s_i^2}+\tau^2\right)}\mathrm{d}}\mathrm{e}^{\frac{-1}{2}\left[\left(\frac{\mu^2+\mathrm{m}^2-2\mathrm{m}\mu}{\mathrm{d}^2}\right)+\sum_{\mathrm{i=1}}^{\mathrm{k}}\left\{\frac{\mathrm{y_i^2}+\mu^2-2\mu\mathrm{y_i}}{\left(\mathrm{s_i^2}+\tau^2\right)}\right\}\right]}$$

$$=\frac{1}{\left(\sqrt{2\pi}\right)^{\mathrm{k+1}}\prod_{\mathrm{i=1}}^{\mathrm{k}}\sqrt{\left(\mathrm{s_i^2}+\tau^2\right)}\mathrm{d}}\mathrm{e}^{\frac{-1}{2}\left[\mu^2\left(\frac{1}{\mathrm{d}^2}+\sum_{\mathrm{i=1}}^{\mathrm{k}}\frac{1}{\left(\mathrm{s_i^2}+\tau^2\right)}\right)-2\mu\left(\frac{\mathrm{m}}{\mathrm{d}^2}+\sum_{\mathrm{i=1}}^{\mathrm{k}}\frac{\mathrm{y_i}}{\left(\mathrm{s_i^2}+\tau^2\right)}\right)+\left(\frac{\mathrm{m}^2}{\mathrm{d}^2}+\sum_{\mathrm{i=1}}^{\mathrm{k}}\frac{\mathrm{y_i^2}}{\left(\mathrm{s_i^2}+\tau^2\right)}\right)\right]}\tag{6}$$

To simplify (6) let us define the following three expressions

$$\mathrm{A}=\sum_{\mathrm{i=1}}^{\mathrm{k}}\frac{1}{\left(\mathrm{s_i^2}+\tau^2\right)}+\frac{1}{\mathrm{d}^2}$$

$$\mathrm{B}=\sum_{\mathrm{i=1}}^{\mathrm{k}}\frac{\mathrm{y_i}}{\left(\mathrm{s_i^2}+\tau^2\right)}+\frac{\mathrm{m}}{\mathrm{d}^2}$$

$$\mathrm{C}=\sum_{\mathrm{i=1}}^{\mathrm{k}}\frac{\mathrm{y_i^2}}{\left(\mathrm{s_i^2}+\tau^2\right)}+\frac{\mathrm{m}^2}{\mathrm{d}^2}\tag{7}$$

Expressing the exponent in (6) in terms of $A$, $B$ and $C$

$$=\frac{-1}{2}\mathrm{A}\left[\mu^2-2\mathrm{B/A}+\mathrm{C/A}\right]$$

$$=\frac{-1}{2}\mathrm{A}\left[\left(\mu-\frac{\mathrm{B}}{\mathrm{A}}\right)^2-\frac{\mathrm{B}^2}{\mathrm{A}^2}+\frac{\mathrm{C}}{\mathrm{A}}\right]$$

$$=\frac{-1}{2}\left[\left(\frac{\mu-\mathrm{B/A}}{1\Big/\sqrt{\mathrm{A}}}\right)^2+\left(\mathrm{C}-\frac{\mathrm{B}^2}{\mathrm{A}}\right)\right]\tag{8}$$

Thus, the RHS of (6) is simplified

$$\Rightarrow \frac{1}{\sqrt{2\pi}} e^{\frac{-1}{2}\left(\frac{\mu - B/A}{1/\sqrt{A}}\right)^2} \times \frac{1}{d\left(\sqrt{2\pi}\right)^k \prod_{i=1}^{k} \sqrt{(s_i{}^2 + \tau^2)}} e^{\frac{-1}{2}(C - B^2/A)} \tag{9}$$

The integral of the denominator of (5) is given by

$$= \int_{\mu} \left(\frac{1}{\sqrt{2\pi}}\right)^{k+1} \times \frac{1}{d \prod_{i=1}^{k} \sqrt{\left(s_i^2 + \tau^2\right)}} e^{\frac{-1}{2}\left[\left(\frac{\mu - B/A}{1/\sqrt{A}}\right)^2 - \left(C - B^2/A\right)\right]} d\mu$$

Multiplying and dividing by $1/\sqrt{A}$ the above expression could be written as

$$= \left[\frac{1/\sqrt{A}}{\left(\sqrt{2\pi}\right)^k} \times \frac{e^{-\frac{1}{2}(C - B^2/A)}}{d \prod_{i=1}^{k} \sqrt{s_i^2 + \tau^2}}\right] \times \left[\frac{1}{\sqrt{2\pi}\left(1/\sqrt{A}\right)} \int_{\mu} e^{\frac{-1}{2}\left(\frac{\mu - B/A}{1/\sqrt{A}}\right)^2} d\mu\right]$$

$$= \frac{1/\sqrt{A}}{\left(\sqrt{2\pi}\right)^k} \times \frac{e^{-\frac{1}{2}(C - B^2/A)}}{d \prod_{i=1}^{k} \sqrt{\left(s_i^2 + \tau^2\right)}} \tag{10}$$

(since the second expression being normal cdf is equal to 1).

The integral in the numerator of (5) is given by

$$\int_{\mu} \mu \left(\frac{1}{\sqrt{2\pi}}\right)^{k+1} \times \frac{1}{d \prod_{i=1}^{k} \sqrt{\left(s_i^2 + \tau^2\right)}} e^{\left(\frac{-1}{2}\left(\frac{\mu - B/A}{1/\sqrt{A}}\right)^2 - \frac{1}{2}\left(C - B^2/A\right)\right)} d\mu$$

$$\Rightarrow \left(\frac{1}{\sqrt{2\pi}}\right)^k 1/\sqrt{A} \times \frac{1}{d \prod_{i=1}^{k} \sqrt{\left(s_i^2 + \tau^2\right)}} e^{-\frac{1}{2}(C - B^2/A)} \frac{1}{1/\sqrt{A}\sqrt{2\pi}} \int_{\mu} \mu e^{\frac{-1}{2}\left(\frac{\mu - B/A}{1/\sqrt{A}}\right)^2} d\mu$$

$$\Rightarrow \left(\frac{1}{\sqrt{2\pi}}\right)^k \times \frac{1}{d \prod_{i=1}^{K} \sqrt{\left(s_i^2 + \tau^2\right)}} e^{-\frac{1}{2}(C - B^2/A)} \times \frac{B}{A} \tag{11}$$

Dividing (11) by (10) we get

$$\mathrm{E}(\mu/\mathrm{y},\tau) = \mu^*(\tau) = \frac{\mathrm{B}}{\mathrm{A}} = \frac{\sum_{\mathrm{i}=1}^{\mathrm{k}} \frac{\mathrm{y_i}}{\left(\mathrm{s_i^2}+\tau^2\right)} + \frac{\mathrm{m}}{\mathrm{d^2}}}{\sum_{\mathrm{i}=1}^{\mathrm{k}} \frac{1}{\left(\mathrm{s_i^2}+\tau^2\right)} + \frac{1}{\mathrm{d^2}}} \tag{12}$$

$$\mathrm{V}(\mu\mathrm{y}/\tau) = \mu^{**}(\tau) = \frac{1}{\mathrm{A}} = \frac{1}{\sum_{\mathrm{i}=1}^{\mathrm{k}} \frac{1}{\left(\mathrm{s_i^2}+\tau^2\right)} + \frac{1}{\mathrm{d^2}}} \tag{13}$$

*b*. **Conditional study specific mean and variance $\theta_i^*(\tau)$ and $\theta_i^{**}(\tau)$**

$$\mathrm{LetB_i}(\tau^2, \mathrm{s_i^2}) = \frac{\mathrm{V(y_i)}}{\tau^2 + \mathrm{V(y_i)}} = \frac{\mathrm{s_i^2}}{\mathrm{s_i^2} + \tau^2}$$

The mean of $\theta_i(\tau)$ the study specific estimate is given by

$$\begin{aligned}
&\mathrm{E}(\theta_\mathrm{i}/\mathrm{y_i},\tau) = \mathrm{B_i}(\tau^2, \mathrm{s_i^2}) \times \mu^*(\tau) + \left[1 - \mathrm{B_i}(\tau^2, \mathrm{s_i^2})\right] \times \mathrm{y_i} \\
&= \mu^*(\tau) \times \tfrac{\mathrm{s_i^2}}{\mathrm{s_i^2}+\tau^2} + \left(1 - \tfrac{\mathrm{s_i^2}}{\mathrm{s_i^2}+\tau^2}\right) \times \mathrm{y_i} \\
&= \mu^*(\tau) \left(\tfrac{\mathrm{s_i^2}+\tau^2-\tau^2}{\mathrm{s_i^2}+\tau^2}\right) + \left(\tfrac{\tau^2}{\mathrm{s_i^2}+\tau^2}\right) \times \mathrm{y_i} \\
&= \mu^*(\tau) + (\mathrm{y_i} - \mu^*(\tau)) \left(\frac{\tau^2}{\mathrm{s_i^2} + \tau^2}\right)
\end{aligned} \tag{14}$$

$$V\left(\theta_i/y_i, \tau\right) = \theta_i^{**}\left(\tau\right) = \left(\frac{s_i^2}{s_i^2 + \tau^2}\right)^2 \mu^{**}\left(\tau\right) + \frac{\tau^2 s_i^2}{s_i^2 + \tau^2} \tag{15}$$

*c*. **Unconditional combined mean and variance, $\mu^*$ and $\mu^{**}$**

The marginal posterior summaries $\mu^*$ and $\mu^{**}$ i.e. the overall mean and variance of the effect estimates are obtained by integrating the conditional summaries $\mu^*(\tau)$ and $\mu^{**}(\tau)$ w.r.t the posterior distribution of $\tau$.

Posterior distribution of $\tau$ is given by $\pi(\tau/y)$

$$\pi(\tau/\mathrm{y}) = \frac{\mathrm{f(y,\tau)}}{\mathrm{f(y)}} = \frac{\int_\mu f(y,\mu,\tau)d\mu}{\int_\tau \int_\mu f(y,\mu,\tau)d\mu d\tau} = \frac{\int_\mu f(y/\mu,\tau).f(\mu/\tau).\pi(\tau)d\mu}{\int_\tau \int_\mu f(y/\mu,\tau).f(\mu/\tau).\pi(\tau)d\mu d\tau} \tag{16}$$

The numerator of (16) is nothing but $\pi(\tau).(10)$

$$= \pi(\tau) \frac{1}{\sqrt{A}\left(\sqrt{2\pi}\right)^k} \cdot \frac{1}{d} \frac{1}{\prod_{i=1}^{k} \sqrt{\left(s_i^2 + \tau^2\right)}} e^{\frac{-1}{2}\left(C - B^2/A\right)}$$

Thus

$$\pi(\tau/\mathrm{Y}) = \frac{1}{\rho}\pi(\tau)\frac{1}{\sqrt{\mathrm{A}}}.\frac{1}{\prod\limits_{\mathrm{i}=1}^{\mathrm{k}}\sqrt{\left(\mathrm{s}_\mathrm{i}^2+\tau^2\right)}}\mathrm{e}^{\frac{-1}{2}\left(\mathrm{C}-\mathrm{B}^2/\mathrm{A}\right)} \tag{17}$$

where $\rho$ is the normalizing constant to make $\pi(\tau/Y)$ a probability density function and is given as

$$\rho = \int_0^\infty \pi(\tau)\frac{1}{\sqrt{A}}.\frac{1}{\prod\limits_{i=1}^{k}\sqrt{\left(s_i^2+\tau^2\right)}}e^{-\frac{1}{2}\left(C-B^2/A\right)}$$

Simplifying (17) and substituting the values of $A$, $B$ and $C$

$$\pi(\tau/\mathrm{y}) \propto \pi(\tau)\frac{1}{\prod\limits_{\mathrm{i}=1}^{\mathrm{k}}\sqrt{\left(\mathrm{s}_\mathrm{i}^2+\tau^2\right)}}.\frac{1}{\sqrt{\sum\limits_{\mathrm{i}=1}^{\mathrm{k}}\frac{1}{\left(\mathrm{s}_\mathrm{i}^2+\tau^2\right)}+\frac{1}{\mathrm{d}^2}}} \times \mathrm{e}^{\frac{-1}{2}\left(\frac{\mathrm{m}^2}{\mathrm{d}^2}+\sum\limits_{\mathrm{i}=1}^{\mathrm{k}}\frac{\mathrm{y}_\mathrm{i}^2}{\left(\mathrm{s}_\mathrm{i}^2+\tau^2\right)}-\frac{\left(\sum\limits_{\mathrm{i}=1}^{\mathrm{k}}\frac{\mathrm{y}_\mathrm{i}}{\mathrm{s}_\mathrm{i}^2+\tau^2}+\frac{\mathrm{m}}{\mathrm{d}^2}\right)^2}{\sum\limits_{\mathrm{i}=1}^{\mathrm{k}}\frac{1}{\left(\mathrm{s}_\mathrm{i}^2+\tau^2\right)}}\right)} \tag{18}$$

Recognizing the fact that $\mu^*(\tau) = \frac{\mathrm{B}}{\mathrm{A}} = \frac{\sum\limits_{\mathrm{i}=1}^{\mathrm{k}}\frac{\mathrm{y}_\mathrm{i}}{\left(\mathrm{s}_\mathrm{i}^2+\tau^2\right)}+\frac{\mathrm{m}}{\mathrm{d}^2}}{\sum\limits_{\mathrm{i}=1}^{\mathrm{k}}\frac{1}{\left(\mathrm{s}_\mathrm{i}^2+\tau^2\right)}+\frac{1}{\mathrm{d}^2}}$ we can write the expression in the exponent of (18) as

$$\begin{aligned}
&\frac{m^2}{d^2}+\sum_{i=1}^{k}\frac{y_i^2}{\left(s_i^2+\tau^2\right)}-\left(\sum_{i=1}^{k}\frac{y_i}{\left(s_i^2+\tau^2\right)}+\frac{m}{d^2}\right)\mu^*(\tau)\\
&=\sum_{i=1}^{k}\left(\frac{y_i^2}{\left(s_i^2+\tau^2\right)}-\frac{y_i}{\left(s_i^2+\tau^2\right)}\mu^*(\tau)\right)+\frac{m}{d^2}\left(m-\mu^*(\tau)\right)\left(m-\mu^*(\tau)\right)\\
&=\sum_{i=1}^{k}\frac{1}{\left(s_i^2+\tau^2\right)}\left[\left(y_i-\mu^*(\tau)\right)^2+y_i\mu^*(\tau)-\left(\mu^*(\tau)\right)^2\right]+\frac{m}{d^2}\\
&=\sum_{i=1}^{k}\frac{1}{\left(s_i^2+\tau^2\right)}\left(y_i-\mu^*(\tau)\right)^2+\mu^*(\tau)\left[\sum_{i=1}^{k}\frac{y_i}{\left(s_i^2+\tau^2\right)}-\mu^*(\tau)\sum_{i=1}^{k}\frac{1}{\left(s_i^2+\tau^2\right)}\right]+\frac{m}{d^2}\left(m-\mu^*(\tau)\right)\\
&=\sum_{i=1}^{k}\frac{1}{\left(s_i^2+\tau^2\right)}\left(y_i-\mu^*(\tau\tau)\right)^2+\mu^*(\tau)\\
&\qquad\times\left[\mu^*(\tau)\left(\sum_{i=1}^{k}\frac{1}{\left(s_i^2+\tau^2\right)}+\frac{1}{d^2}\right)-\frac{m}{d^2}-\mu^*(\tau)\sum_{i=1}^{k}\frac{1}{\left(s_i^2+\tau^2\right)}\right]+\frac{m}{d^2}\left(m-\mu^*(\tau)\right)\\
&=\sum_{i=1}^{k}\frac{1}{\left(s_i^2+\tau^2\right)}\left(y_i-\mu^*(\tau)\right)^2-\frac{\mu^*(\tau)}{d^2}\left(m-\mu^*(\tau)\right)+\frac{m}{d^2}\left(m-\mu^*(\tau)\right)\\
&=\sum_{i=1}^{k}\frac{1}{\left(s_i^2+\tau^2\right)}\left(y_i-\mu^*(\tau)\right)^2+\frac{1}{d^2}\left(m-\mu^*(\tau)\right)^2
\end{aligned}$$

The complicated integrand $f(Y)$ in the denominator of (17) in not integrable by analytical methods. To obtain the value of this integral numerical integration approach has to be applied. One such method of integration is the Gauss-Hermite integration formula(DuMouchel, W. (1989).

*Integrals of the type* $\int_{-\infty}^{\infty} e^{-t^2}f(t)dt$ *may be approximated with a Gaussian − type formula* $\sum_{i=1}^{n} w_{i,n}f(t_{i,n})$ *where the weights* $w_{i,n}$ *are defined as* $\frac{2^{n-1}n!\sqrt{p}}{n^2[H_{n-1}(t_i)]^2}$ *where* $t_{i,n}$ *is the set of roots of by* $H_n(t_i)=0$ *and* $H_n(t_i)=(-1)^n e^{t_i^2}\frac{d^n\left(e^{-t_i^2}\right)^n}{dt_i^2}$ *is a Hermite polynomial of nth order.*

The integral in (17) is over the range $(-\infty,\infty)$ . To write the integral in the Gaussian form we transform the variable $\tau$ into $\gamma=ln(\tau)$ so that the range of $\gamma$ is from 0 to $\infty$. Then the posterior density in terms of $\gamma$ becomes $\mathrm{f}\left(\gamma/\mathrm{Y}\right)=\pi\left(\tau/Y\right)|J|$ where $J$ is the jacobian of transformation $|J|=\delta\tau/\delta\gamma=e^{\gamma}$

$$f\left(\gamma/Y\right)=\pi\left(e^{\gamma}/Y\right)e^{\gamma}$$

To determine the points of integration the procedure is to first maximize the log likelihood of $\gamma$ i.e. $L\left(\gamma\right)=\log\left(f\left(\gamma/Y\right)\right)=\gamma+\log\left(\pi\left(e^{\gamma}/Y\right)\right)$ . Let $\gamma_0$ be the value of $\gamma$ that maximizes $L(\gamma)$. Then we choose a small value say $\varepsilon=0.01$ and compute

$$H = \frac{-L(\nu_0 + \varepsilon) + L(\nu_0 - \varepsilon) - 2L(\nu_0)}{\varepsilon^2}$$

$H$ is the Bayesian version of Fisher Information that takes into account the prior distribution and the actual data rather than the expected data . The points used in the numerical integration are $\gamma_{\mathrm{i}} = \gamma_0 + \mathrm{x_i} \times \sqrt{\frac{2}{\mathrm{H}}}$ where $x_i$ are the $x$-values given in the table 25.10 in the book "Handbook of mathematical functions " (Abramowitz, M. and Stegun, I. (1972)). Depending on the order of the Hermite polynomial the table gives the values of the abscissa. Thus if we choose nine points of the integration we obtain the values of x corresponding to $n = 9$ in the table. From the values of $\gamma_I$ we compute the values of $\tau_I$ from the relation $\tau_I = e^{\gamma}$ The posterior probabilities $\pi(\tau/Y)$ are thus computed from the following equation $\pi\left(\tau/\mathrm{Y}\right) = \frac{\pi(\tau_{\mathrm{i}}).\tau_i\lambda_i}{\sum\limits_{i=1}^{k} \pi(\tau_{\mathrm{i}}).\tau_i\lambda_i}$ where $\lambda_i$ is the weight assigned to each value of $\tau_i$ .

The marginal posterior expectation and variance of $\mu$ viz. $\mu^*$ and $\mu^{**}$ are obtained by weighing the conditional posterior expectation and variance $\mu^*(\tau)$ and $\mu^{**}(\tau)$ by $\pi(t/Y)$ and summing it over the values of $\tau_i$ obtained by Gauss Hermite integration. The overall mean and variance of an effect measure is then expressed by the values of $\mu^*$ and $\mu^{**}$. The posterior probability of $\mu$ for a particular value could also be obtained from these expressions. The derivation of these quantities is given as under:

$$\begin{aligned}
\mu^* &= E(\mu/Y) = \sum_{j=1}^{n} \mu^*(\tau_j)\pi(\tau_j/Y) \\
\mu^{**} &= V(\mu/Y) = E(V(\mu/Y)) + V(E(\mu/Y)) \\
&= \sum_{j=1}^{n} \left\{\mu^{**}(\tau_j) + (\mu^*(\tau_j) - \mu^*)^2\right\} \pi(\tau_j/Y)
\end{aligned}$$

*d.* **Unconditional study specific mean and variance, $\theta_i^*$ and $\theta_i^{**}$**

The marginal posterior expectation and variance q*i and q**i for each study is also obtained likewise by weighing the conditional posterior expectation and variance by $\pi(\tau/Y)$. Thus, we obtain

$$\begin{aligned}
\theta_i^* = E(\theta_i|\, Y) = \int_{\tau} \theta_i^* \pi\left(Y\right) d\tau &= \int \left\{\mu^*\left(\tau\right) + \left[y_i - \mu^*\left(\tau\right)\right] \frac{\tau^2}{\left(\tau^2 + s_i^2\right)}\right\} \pi\left(\tau/Y\right) d\tau \\
&\cong \sum_{j=1}^{n} \left\{\mu^*\left(\tau\right) + \left[y_i - \mu^*\left(\tau\right)\right] \frac{\tau^2}{\left(\tau^2 + s_i^2\right)}\right\} \pi\left(\tau/Y\right) \\
\theta_i^{**} = V(\theta_i|\, Y) = \int \left\{V\left[\theta_i|\, Y, \tau\right] + \left[{\theta_i}^*\left(\tau\right) - \theta_i^*\right]^2\right\} &\pi\left(\tau/Y\right) d\tau \\
&\cong \sum_{j=1}^{n} \left\{V\left[\theta_i|\, Y, \tau\right] + \left[{\theta_i}^*\left(\tau\right) - \theta_i^*\right]^2\right\} \pi\left(\tau_i/Y\right)
\end{aligned}$$

*e.* **Posterior probabilities** $P(\mu > Q/y)$

The posterior probability of $\mu$ given $\tau$ is defined as

$$\mathrm{P}(\ \mu > \mathrm{Q}|\, y) = E\left[\mathrm{P}(\ \mu > \mathrm{Q}|\, y, \tau)\right] = E\left(\int_{Q}^{\infty} \frac{f(y/\mu,\tau)f(\mu/\tau)}{\left(\int_{\mu} f(y/\mu,\tau)f(\mu/\tau)\right)} d\mu\right)$$

$$= \sum_{\mathrm{j}=1}^{\mathrm{n}} \left( \int_{Q}^{\infty} \frac{f(y/\mu,\tau)f(\mu/\tau)}{\left(\int_{\mu} f(y/\mu,\tau)f(\mu/\tau)\right)} d\mu \right) \pi(\tau_j/y)$$

$\frac{f(y/\mu,\tau)f(\mu/\tau)}{\left(\int_{\mu} f(y/\mu,\tau)f(\mu/\tau)d\mu\right)}$ is the conditional posteior distribution of $y$ given $\mu, \tau$ which is normally distributed with mean $B/A$ and variance $1/A$. The integral in the summation is thus

$$= \int_{Q}^{\infty} \frac{1}{\sqrt{2\pi}.\frac{1}{\sqrt{A}}} e^{\frac{-1}{2}\left\{\left(\frac{\mu - B/A}{1/\sqrt{A}}\right)^2\right\}} d\mu$$

Let $\left(\frac{\mu - B/A}{1/\sqrt{A}}\right) = z$ $\qquad d\mu = \frac{1}{\sqrt{A}} dz$

$\mu = Q = z = \left(\frac{Q - B/A}{1/\sqrt{A}}\right)$

$\mu = \infty = z = \infty$

$= \frac{1}{\sqrt{2\pi}.\frac{1}{\sqrt{A}}} \int_{\left(\frac{Q-B/A}{1/\sqrt{A}}\right)}^{\infty} e^{-\frac{z^2}{2}} \frac{1}{\sqrt{A}} dz$

$= \Phi\left(\frac{Q - B/A}{1/\sqrt{A}}\right) = \Phi\left(\frac{Q - \mu^*(\tau)}{\sqrt{\mu^{**}(\tau)}}\right).$

where $\Phi(x)$ is the standard normal variate defined as

$\Phi(x) = \int_{-\infty}^{x} \frac{1}{\sqrt{2\pi}} e^{\frac{-x^2}{2}} dx$

$\Phi(-x) = 1 - \Phi(x)$ Hence $\mathrm{P}(\ \mu > \mathrm{Q}|\, y) = \sum_{j=1}^{n} \Phi\left(\frac{Q - \mu^*(\tau_j)}{\sqrt{\mu^{**}(\tau_j)}}\right) \pi(\tau_j/y)$

**An illustration:**

This example is extracted from the corresponding authors Ph.D thesis (Geetha Menon, unpublished ) Acute ischaemic stroke is a major cause of death and disability worldwide yet, despite advances in stroke prevention, there is no effective routine treatment for the stroke once it has occurred. Thrombolysis is an effective treatment for acute myocardial infarction (MI), a vascular disease with some similarities to acute

ischaemic stroke, but it has taken many years and the randomization of many thousands of MI patients in multicentre trials to prove that thrombolysis works. Indeed, the benefit of thrombolysis was almost missed; it was not until a systematic review in 1985 that led to very large trials that confirmed the benefit in acute MI. Yet, a cumulative meta-analysis of the published MI trials showed - in retrospect - that there was clear evidence of benefit as long ago as 1973. An overview of the literature on thrombolysis in acute ischaemic stroke identified six randomized controlled trials (RCTs) on a total of 700 patients (plus various non-randomized studies and case reports).

The present Cochrane Review combines those earlier studies with the more substantial information that has recently become available from larger trials. Thus the total number of patients now randomized (and published) in trials of thrombolysis in acute ischemic stroke is 3286, relatively few compared with the acute MI trials, but still probably enough to begin to draw some useful conclusions about thrombolytic treatment, and certainly enough to guide trialists interested in the further testing of thrombolytic treatment for acute ischemic stroke. 12 trials have been included in this review covering a total of 3438 patients (1777 in the treatment group and 1661 in the control group). Table1 below gives the description of these trials.

**Table 1: Characteristics of trials included in the systematic review on thrombolysis in acute ischaemic stroke. Wardlaw, J.M. et al (1999)**

| S.No | Trial | Year | Exp | Cont | Intervention | Type of Participants | |
|---|---|---|---|---|---|---|---|
| | | | | | | Inclusion | Exclusion |
| 1. | ABE | 1981 | 54 | 53 | Urokinase vs Placebo | All grades of presumed thrombotic stroke <2 wks, pre- entry CT, age >18 years | Presumed embolic stroke, severe neurological deficit. |
| 2. | ATARASHI | 1985 | 192 | 94 | Urokinase vs placebo | Presumed cerebral arterial thrombosis, < 5 days, age> 18 years , entry CT | Presumed embolic stroke, severe neurological deficit. |
| 3. | OHTOMO | 1985 | 169 | 181 | Urokinase vs placebo | Presumed "non-embolic" ischaemic stroke < 5 days, no age limit, pre-entry CT. | |
| 4. | ASK | 1986 | 174 | 166 | Streptokinase vs placebo | Any acute ischaemic stroke within 4 hours of onset; age =18-85 years; CT scan mandatory | Recent trauma or surgery, stroke <3 months, pregnancy, anticoagulants in the previous 48 hours (except aspirin), uncontrolled hypertension (SBP >200, DBP>120 |
| 5. | MAST-E | 1996 | 156 | 154 | Streptokinase vs placebo | With acute ischaemic stroke within 6 hours of onset; age > 18yrs, pre-entry CT | Patients with mild neurological deficit or rapidly improving when assessed; previous stroke; pregnancy; SBP>220, DBP>110; oral anticoagulants (not aspirin); recent trauma, surgery, peptic ulcer disease, etc. |
| 6. | MORRIS | 1995 | 10 | 10 | Streptokinase vs placebo | Acute ischaemic stroke within 6 hours of onset, pre entry CT age= 40-80 years, | No previous stroke. |
| 7. | ECASS | 1995 | 313 | 307 | tPA vs placebo | Acute ischaemic stroke within 6 hours ofonset. Pre entry CT to exclude cerebral haemorrhage and patients whose infarct was already visible); age =18-80 years. | With mild or rapidly improving strokes, in coma, DBP >110 and SBP>200; recent trauma or surgery, pregnancy, weight > 100 kg |
| 8. | HALEY | 1993 | 14 | 13 | tPA vs placebo | Ischaemic stroke <90 or <180 minutes from onset, 18-80 years, pre entry CT. | TIA, very mild and very severe neurological deficits. |
| 9. | JTSG | 1993 | 51 | 47 | tPA vs placebo | Thromboembolic stroke < 6 hrs, aged 18-80 years, pre entry CT and angiography. | haemorrhagic stroke or patent cerebral arteries at angiography |
| 10. | MORI | 1992 | 19 | 12 | tPA vs placebo | Ischaemic stroke< 6 hrs from onset, age= <80 yrs, pre entry CT and angiography. | Patients in deep coma. |
| 11. | NINDS | 1995 | 312 | 312 | tPA vs placebo | Ischaemic stroke , pre entry CT ,within 180 minutes of onset; age=18-80 years; cortical and lacunar strokes | Previous stroke, head trauma within 3 months, pregnancy/lactation, abdominal surgery, heparin within 48 hours or deranged clotting factors/platelets, SBP>180 or DBP>110 |
| 12. | MAST-I | 1995 | 313 | 312 | SK , asp and combination of both | All acute ischaemic stroke within 6 hours from onset; pre-entry CT mandatory to exclude cerebral haemorrhage. | Rapidly improving symptoms likely to be a TIA; recent trauma or surgery; oral anticoagulant treatment (not aspirin); aspirin or SK not either definitely indicated or contraindicated; SK in the past year, |

tPA- Tissue Plasminogen Activator

The results of these trials have been systematically reviewed for evidence of the treatment effect on a few important clinical outcomes like Death or dependency at the end of follow-up, Death within the first two weeks of onset of stroke, Fatal Intracranial haemorrhage during treatment period, Death or dependency in patients randomized within 3 hours of onset of stroke. This illustration examines the application of HBLM on the results of those trials that reported the number of patients who died or became dependent at the end of follow-up.

Seven trials have reported this outcome as shown in table 2. Two regimens tPA and Streptokinase were compared to conventional treatments. A fixed effect analysis has shown that a comparison of the effect of tPA with a conventional treatment has yielded a statistically significant result. The fixed effect estimate for risk difference (pt-pc) was $-12.58$, ($95\%$ $CI = -17.70, -7.45$) meaning there were more events in the conventional group as compared to the treated group. This difference was statistically significant. Similar fixed effect analysis on comparison of the effect of Streptokinase in reducing this event has however shown a statistically non-significant effect. ($ in Table 2)

**Table 2: Meta-analysis of thrombolytic trials that reported death or dependency at the end of followup**

| S.no | Study | Experimental n/N | Control n/N | RD (SD) [95%CI] |
|---|---|---|---|---|
| **STREPTOKINASE VS CONTROL** | | | | |
| **1** | **ASK** | 84/174 | 74/166 | 3.70 (5.41) [-6.90, 14.29] |
| **2** | **MAST-E** | 124/156 | 126/154 | -2.33 (4.48) [-11.12, 6.46] |
| **3** | **MAST-I** | 97/157 | 106/156 | -6.17 (5.39) [-16.72, 4.39] |
| **4** | **MORRIS** | 6/10 | 5/10 | 10.0 (22.14) [-33.39,53.39] |
| $\chi^2_H$ **=1.98** | **Fixed effect estimate** | | | **-1.51 (2.88) [-7.16, 4.14]** $ |
| **TPA VS CONTROL** | | | | |
| **5** | **ECASS** | 198/313 | 220/307 | -8.4 (3.75) [-15.75, -1.06] |
| **6** | **MORI** | 11/19 | 10/12 | -25.44 (15.62) [-56.06, 5.18] |
| **7** | **NINDS** | 179/312 | 229/312 | -16.03(3.75) [-23.38,-8.67] |
| $\chi^2_H$ **= 2.76 (p<0.05)** | **Fixed effect estimate** | | | **-12.58(2.61) [-17.70,-7.45]** |
| **Between studies variance** | | | | **9.90** |
| **Random effect estimate** | | | | **-12.81 (3.38) [-19.44, -6.18]** |
| **8** | **MAST-I** | 99/156 | 106/156 | -4.49(5.37) [-15.01, 6.04] |
| **Combined Fixed effect estimate** | | | | **-7.22 (1.82) [-10.79,-3.65]** |
| **Between studies variance** | | | | **24.73** |
| **Combined Random effect estimate** | | | | **-6.55(2.72) [-11.88,-1.22]** |

n-number of events; N-No. examined; RD-Risk Difference; SD-Standard deviation; $\chi^2_H$= Chi-square test for homogenity

The data in table 2 was subjected to Bayesian analysis (Table 3). In the absence of an informative prior a non-informative prior with an arbitrary mean and large variance was incorporated in the analysis. The individual effect estimates were obtained along with the posterior probability of beneficial effect. The combined Bayes estimate with all the studies yielded an absolute reduction of 6.72% with posterior probability of a beneficial effect being 98.4%. Stratified analysis under streptokinase group however yielded a reduction of 1.29% with the treatment group and a posterior probability of 64.8%. The trials that used tPA as the treatment yielded a large beneficial effect of 13.28% and a high posterior probability of 98.4%. This large difference is reflected in the combined estimate

**Table 3 Bayesian meta-analysis of thrombolytic trials that reported death or dependency at the end of follow-up**

| **STUDY** | **RD** | **P** |
|---|---|---|
| ***Streptokinase Vs Control*** | | |
| **ASK** | 0.10 (4.11) [-7.96, 8.16] | 0.519 |
| **MAST-E** | -1.74(3.50) [-8.58, 5.11] | 0.693 |
| **MAST-I** | -2.82 (4.02) [-10.70, 5.06] | 0.761 |
| **MORRIS** | -0.72 (6.47) [-13.39,11.95] | 0.598 |
| **Combined Bayes** | **-1.29(4.53) [-10.17,7.59]** | **0.648** |
| ***tPA vs control*** | | |
| **ECASS** | -10.66(3.47) [-17.4, -3.85] | 0.998 |
| **MORI** | -14.81(7.47) [-29.44, -0.18] | 0.986 |
| **NINDS** | -14.38(3.43) [-21.1, -7.66] | 1.0 |
| **Combined Bayes** | **-13.28(6.74) [-26.49 -0.07]** | **0.984** |
| ***All studies*** | | |
| **ASK** | -2.90 (4.54) [-11.80,5.90] | 0.753 |
| **MAST-E** | -4.86 3.52) [-11.76,2.63] | 0.907 |
| **MAST-I** | -6.57(3.62) [-13.71,0.56] | 0.96 |
| **MORRIS** | -5.83(5.87) [-17.39,5.67] | 0.873 |
| **ECASS** | -7.63(2.94) [-13.39, -1.28] | 0.995 |
| **MORI** | -8.53(5.68) [-19.66,2.59] | 0.96 |
| **NINDS** | -11.45( 3.76) [-18.82,-4.08] | 1.0 |
| **MAST-I** | -5.94(3.69) [-13.18,1.29] | 0.939 |
| **Combined Bayes** | **-6.72(2.87) [-12.34,1.10]** | **0.984** |

Figure 1 shows the trace plot of the posterior distribution of tau and the conditional means of the combined and individual estimates. It is observed that the most plausible range of tau is 0.46 to 8.44. The studies specific expectations shrink towards a common value of $-6.89$ for low values of tau and for very large values of tau these assume the observed values of $y_i$ .The most deviant study with a large $s_i$ (MORI) is the one that undergoes maximum shrinkage. For $\tau < 8.44$ MORI is actually estimated to have a larger $\theta$ than NINDS.

The summary plot in figure 2 explains the shrinkage property of the Bayesian approach. According to this property the individual studies borrow strength from other studies in meta-analysis thus reducing their uncertainty and improving their precision. The property of 'regression to the mean' is also clearly shown by the individual bayes estimates.

# 4 Discussion

Hierarchical Bayes linear model integrates the fixed effect and the random effect models into one framework and provides unified approach to meta-analysis. These models were popularized by Lindley and Smith.(1972) The descriptive form of the model consists of the Observational model in stage $I(y_i/\theta_i) \sim f(y_i/\theta_i)$ for the data and the Structural model in stage $II(\theta_i/\mu, \tau^2) \sim g(\theta_i/\mu, \tau^2)$ for the parameters and Hyperparameter model $\mu, \tau^2 \sim h(\mu, \tau^2)$. This form is more natural for model building and describes well in meta-analysis. It also overcomes the limitation of the random effect method in assigning a prior distribution for $\tau$ which has a location and an uncertainty parameter. If the prior for $\tau$ is concentrated near $\tau = 0$, the HBLM is equivalent to the fixed effect model and if it is concentrated near the estimate of $\tau$ then it is equivalent to the random effect model. Bayesian specification is completed by assigning prior distributions to $\mu$ and $\tau^2$.

In the event of no specific information for $\mu$ it could be assumed to follow a diffuse prior. Informed priors could be the clinical prior obtained from prior beliefs of clinicians. Spiegelhalter, has suggested that in application of Bayesian methods in clinical trials one can use skeptical priors where the belief is that large differences are unlikely or even enthusiastic priors where very large differences could also be believed to occur with smaller uncertainty. He has shown the application of clinician prior on MRC Neutron therapy trial and has compared this with the prior obtained from meta-analysis of previous randomize trials.cusssion: DuMouchel[27] has proposed a prior distribution of the form $\lambda/\chi^2_q$ for $\tau^2$ which follows from the sampling theory of the distribution of $\sigma^2$ in a normal distribution with parameters $\mu$ and $\sigma^2$. Here $ns^2/\sigma^2$ follows $\chi^2$ with $q-1$ d.f. The prior distribution of $\mu$ is assumed to follow multivariate Student $t$ - distrubutions. The posterior distribution then follows multivariate Student $t$-distributions. The author has shown that this model is flexible and the computations are readily programmed for $\tau^2$ . In another paper, the author proposes the same model with a flat prior for $\mu$ and a log-logistic prior The advantage of this type of a prior is that it is a compromise between opposing philosophies about meta-analysis: those who believe that $t$ is near 0 (the philosophy of a fixed effect meta-analysis) and those who believe that $t$ is large (the you can't combine apples and oranges philosophy). The plot of this function is a curve with a maximum value at $\tau = 0$ progressively decaying as $\tau$ increases and is asymptotically parallel to $x$-axis for very large value of $\tau$. DuMouchel has observed that the Bayes method provides the researcher more flexibility in arriving at a conclusion by means of providing the posterior probability at any point.

Carlin assumes a locally uniform prior for $\mu$ and $\tau^2$. He adopts a Monte Carlo method for first maximizing the product of the prior and the likelihood function. Next, suitable lower and upper limits for $\tau^2$ was obtained such that the posterior density at each extreme is very small compared to the maximum density value. The

range is then divided into 100 equal parts and the posterior distribution is discretised at equal number of intervals. This communication attempts to provide the readers a simplistic approach to determine the summary estimates in a hierarchical model. It could also be used to develop numerical algorithm for the purpose of computing the estimates on a computer in any high level language.

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## References

[1] Abramowitz, M. and Stegun, I. (1972). *Handbook of Mathematical Functions with Formulas, Graphs and Mathematical Tables* (Applied Mathematics series, 55), Washington, DC: National Bureau of Standards.

[2] Berger, J.O. and Wolpert, R.L. (1984). *The Likelihood principle.* Institute of Mathematical Statistics, Hayward, California.

[3] Berry, D.A. (1985). *Interim analysis in clinical trials; Classical vs Bayesian approaches. Statistics in Medicine.* 4, 521-526.

[4] Berry, D.A. (1990). *A Bayesian approach to meta-analysis and multicenter Trials. Proceedings of the Pharmaceutical Section of the American Statistical Association.* 1-10.

[5] Berry, D.A. Berry, S.M. and Gillingham, K. (1992). *Bayesian meta-analysis for treatment comparisons, dichotomous responses. Proceedings of the Pharmaceutical Section of the American Statistical Association.*

[6] Canner, P.L. (1983). *Aspirin in coronary heart disease: Comparison of six clinical trials. Israel Journal of Medical sciences.* 19, 413-423.

[7] Carlin, J.B. (1992). *Meta-analysis for 2X2 tables: A Bayesian approach. Statistics in Medicine.* 11,141-158.

[8] Chaloner, K., Church, T., Louis, T. and Matts, J. (1993). *Graphical elicitation of a prior distribution for a clinical trial. The Statistician.* 42, 341-353.

[9] Donner, A. (1982). *A Bayesian approach to the interpretation of subgroup results in clinical trials. Journal of Chronic Diseases.* 35, 429-435.

[10] DuMouchel, W. and Harris, J.E. (1983). *Bayes methods for combining the results of cancer studies in humans and other species (with discussion). J. Amer. Statist. Assoc.* 78, 382, 293-315.

[11] DuMouchel, W. (1989). *Bayesian Meta-analysis.* Statistical Methodology in the Pharmaceutical Sciences, Marcel Dekker, New York, 509-529.

[12] DuMouchel, W. September (1994). *Hierarchical Bayes Linear Models for Meta-Analysis.* Technical Report # 27, National Institute of Statistical Sciences.

[13] DuMouchel, W. (1996). *Predictive Cross-validation of Bayesian Meta-analyses. Bayesian Statistics.* 5, 107-127.

[14] Freedman, L.S. and Spiegelhalter, D.J. (1983). *The Assessment of subjective opinion and its use in relation to stopping rules for clinical trials. The Statistician.* 32, 153-60.

[15] Geetha R. Menon, July 2002. *Bayesian approach to meta-analysis -A comparative study.* Unpublished Ph.D Thesis.

[16] Greenhouse, J.B. and Wasserman, L. (1994). *Robust bayesian methods for monitoring clinical trials. Statistics in Medicine* 14, 1379-1391.

[17] Jeffreys, H. (1961). *Theory of probability.* 3rd ed. London: Oxford University Press. 1-56, 432-41,245-331.

[18] Lewis, R.J. and Wears, R.J. (1993). *An introduction to the Bayesian analysis of clinical trials. Ann Emerg Med.* 22, 1328-36.

[19] Lindley, D. V. and Smith, A. F. M. (1972). *Bayes Estimates for the Linear Model. Journal of the Royal Statistical Society*, B, 34, 1-41.

[20] Naylor, J.C. and Smith, A.F.M. (1982). *Applications of a method for the Efficient Computation of posterior distributions. Applied Statistics*, 31, 214-225.

[21] Parmar, M.K.B, Spiegelhalter, D.J. and Freedman, LS. (1994). *The CHART trials: Bayesian design and monitoring in practice. Statistics in Medicine* 13, 1297-1312.

[22] Raudenbush, S.W. and Bryk, A.S. (1985). *Empirical Bayes Meta-analysis. J Ed Statistics* 10, 2, 75-98.

[23] Reilly, P.M. (1976). *The numerical computation of posterior distributions in Bayesian statistical inference. Applied Statistician.* 25, 3, 201-208.

[24] Smith, T.C. Spiegelhalter, D.J. and Thomas, A. (1995). *Bayesian approaches to random-effects meta-analysis: A comparative study. Statistics in Medicine.* 14, 2685-2699.

[25] Spiegelhalter, D.J. and Freedman, L.S. (1988). *Bayesian approaches to clinical trials.* Bayesian statistics Vol. 3., J.M. Bernado, M.H. DeGroot, D.V. Lindley, A.F.M. Smith, Oxford University Press, Cambridge, 453-477.

[26] Spiegelhalter, D.J. Freedman, L.S. and Parmar, M.K.B. (1994). *Bayesian approaches to Randomized trials. J. R. Stat. Soc* A 357, Part 3, 357-416.

[27] Tweedie, R.L. Scott, D.J. Biggerstaff, B.J. and Mengersen, K.L. (1996). *Bayesian meta-analysis, with application to studies of ETS and lung cancer. Lung cancer.* 14, Suppl 1, S171-S194.

[28] Wardlaw J.M., Yamaguchi T., del Zoppo, G. and Hacke W. (1999). Thrombolyis for acute ischemic review. In Cochrane Library, Issue No.4. Oxford updated software.