Model Selection in Meta-Analysis of Clinical Safety Data
Fixed or Random Study Effect

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Personal Perspective

- Intersection of philosophy and statistics
- Fundamental difference between statistical models used in meta analysis
- Each model addresses a different research question
- Choice of model is dependent on whether variability within study alone or the variability both within and among studies is required to answer the research question
- For safety, regulatory purposes the question almost always requires only the within studies variability to answer the question
- Heterogeneity (of study results) and estimation (of treatment effect) do not imply one model or the other

Traditional Approach

Fixed Effect Model (Common Effect)

- All studies in the meta-analysis estimate the same treatment effect θ
- Differences in observed effects from study to study are due to sampling error measured by within-study variance V_i
- Estimation and inference concerning θ with the single source of variability V_i

Random Effect Model

- Treatment effect θ_i varies from study to study.
- Assumed to represent a random sample from a distribution function with mean effect size θ and variance σ^2
- Estimation and inference concerning θ with sources of variability V_i and σ^2

Traditional Approach (continued)

- Fixed and random effects models make different assumptions about the individual study estimates $\hat{\theta}_i$
- These assumptions lead to different definitions about θ and different methods of combining the $\hat{\theta}_i$ to estimate θ, i.e., assignment of weights to $\hat{\theta}_i$
- When θ is common to all studies weights are based on the amount of information that is contained in the study, $1/V_i$
- When θ is the mean of the distribution of $\hat{\theta}_i$ the weights are based on both the within and among study variability, $1/(V_i + \sigma^2)$
- As a consequence of the inverse variance weights, the random effect model will yield a more uniform weighting of the individual study estimates than will a fixed-effect model.

Alternative Approach

- Research question and statistical inference to be drawn from the data should determine the choice of model

- Question: Is the estimate of treatment effect in the **existing** studies consistent with chance or not - variability within study is required

- Question: Is the estimate of treatment effect from the (hypothetical) population of studies from which the existing studies constitute an (assumed) random sample, consistent with chance or not - variability within and among studies is required

- The assumption that the studies in the meta analysis estimate a common treatment effect is not required in a fixed-effect model. Similarly, the lack of a common treatment effect, or significant heterogeneity among the individual study estimates, does not imply the need for a random-effect model.

Alternative Approach

- There is no necessary connection between weights of the individual study estimates to obtain an overall estimate and random or fixed effects models. The choice of weights can be informed by other considerations.

- Equal weights of studies when only within-study variability is used

- More weight to larger studies when both within-study and among study variability are used. Poole C, Greenland S. *Am J Epidemiol.* Sep 1 1999;150(5):469-475

Benzodiazepine Example

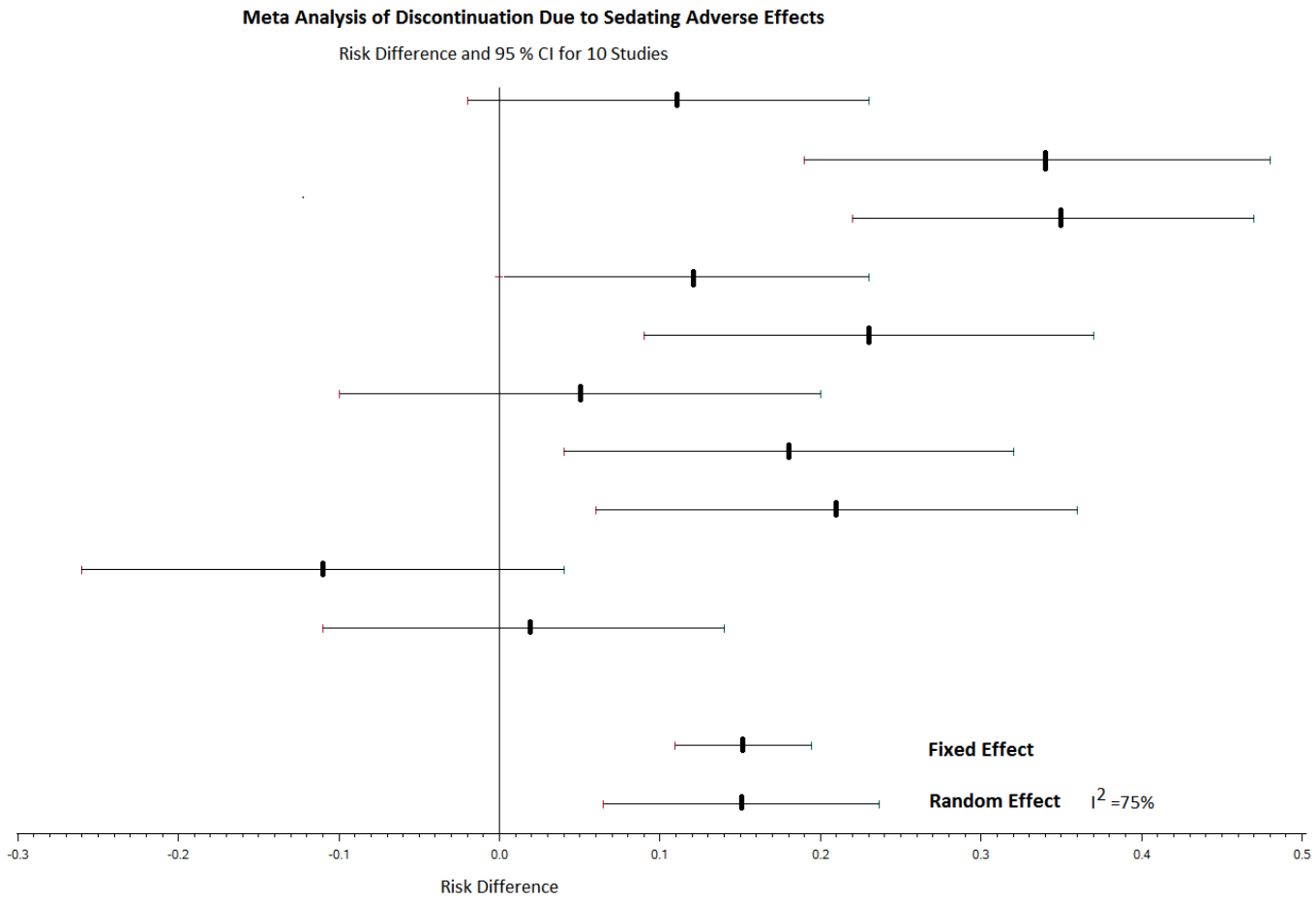
- Hypothetical Regulatory Question

Are benzodiazepines associated with sedation

- Hypothetical Drug Development Question

In a Proof-of-concept study what should be the criterion to indicate that a new benzodiazepine reduces sedation?

Meta Analysis of Discontinuation due to Sedation



Subtle Incorrect Thinking

- An assumption of a common treatment effect is required for a fixed-effect model
- A fixed-effect assumption is implausible. No reason to think that, under differing study conditions, the true effect size is the same
- The variance in the random effects model, $V_i + \sigma^2$, and the ensuing study weights reduce to the fixed-effect model if the among study differences are small. If not, the random effect model takes into account the two components of variability.
- Therefore, the random effects model should be the model of choice and let the data estimate the variance components
- "The model helps to define the goals of the analysis and the interpretation of the statistics" **I think it is the reverse**

Points on Heterogeneity

- Heterogeneity of treatment effect across studies is an important result in a meta analysis – explore, deconstruct the meta result.

- Choice of fixed or random effects model does not depend on heterogeneity and certainly should not be chosen after viewing the individual study results

- Test of overall heterogeneity may have low power (small studies) to detect clinically meaningful heterogeneity or may have high power (large studies) to detect clinically meaningless heterogeneity

Points on Estimation

- The choice of weights determines the way in which the individual study estimates of treatment effect are combined in order to obtain the overall estimate.
- Inverse-variance weights, and any set of weights, imply a relative importance to each study estimate.
- It may be that each of the k studies included in a meta analysis are considered to be of equal importance, in which case the weights would be 1/k.
- The weights (and more generally the analytical methods) should be consistent with the clinical question and specified beforehand in the SAP.
- The appropriate variability determines the fixed/random model choice .

Points on Estimation -among-study variability

- DerSimonian-Laird Method

  Straightforward, transparent calculation of among-study variability and hence random weights if inverse variance weighting is used

  Limitations, e.g. in the case of rare events, when inferences about heterogeneity across studies are important, confidence bounds that are too narrow when the number of studies is small

- Study as a random effect in a general linear or non-linear mixed-effects model

  Available in many statistical software packages - methods usually employ residual maximum likelihood methods to estimate the random effect

- Overall treatment effect is estimated jointly with the study variability and hence the weights of the individual study treatment effects are not transparent

Points on Estimation –among-study variability

Random-Effects Meta-analysis of Inconsistent Effects: A Time for Change

John E. Cornell, Cynthia D. Mulrow, Russell Localio, Catharine B. Stack, ; Anne R. Meibohm, Eliseo Guallar, and Steven N. Goodman. Annals of Internal Medicine (2014)

How does the DerSimonian and Laird procedure for random effects meta-analysis compare with its more efficient but harder to compute counterparts?

Dan Jackson, Jack Bowden, Rose Baker

Journal of Statistical Planning and Inference 140 (2010) 961–970

Example – GI Discontinuations NSAID v Placebo

Study	GIDC	N	log odds	Fixed W	Random W
1	8	93	-0.5180	0.0213	0.0327
2	28	413	-0.4742	0.0753	0.0729
3	36	172	0.2794	0.0824	0.0761
4	101	1057	-0.1826	0.2217	0.1070
5	13	218	-0.4306	0.0353	0.0471
6	19	121	0.3521	0.0465	0.0561
7	10	113	-1.2110	0.0264	0.0385
8	14	107	1.0859	0.0353	0.0471
9	40	457	0.7189	0.1052	0.0845
10	32	478	0.9091	0.0861	0.0776
11	12	243	1.0563	0.0330	0.0450
12	21	290	-0.3218	0.0562	0.0626
13	4	175	-0.1049	0.0113	0.0195
14	11	173	1.4657	0.0297	0.0419
15	6	165	-0.0125	0.0167	0.0271
16	4	115	0.0179	0.0112	0.0194
17	5	161	0.3975	0.0140	0.0234
18	4	105	0.0196	0.0112	0.0193
19	23	86	0.4785	0.0489	0.0578
20	12	182	1.1120	0.0324	0.0445

Results

	Log Odds (SE)	OR (95% CI)
Fixed	**0.222 (0.107)**	**1.25 (1.01, 1.54)**
DL	**0.259 (0.152)**	**1.30 (0.96, 1.74)**
GNL	**0.258 (0.155)**	**1.29 (0.96, 1.75)**
F-Uniform	**0.232 (0.147)**	**1.26 (0.95, 1.68)**
R-Uniform	**0.232 (0.172)**	**1.26 (0.90, 1.77)**