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Strategies for Meta-Analyses of Randomized Clinical Trials Based on Individual Patient Data:

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Outline

- **Motivating Example**
- **Background**
- **Planning an IPD Meta-analysis, a.k.a. Pooled Analysis**
- **Methodology**
  - Endpoints
  - Assumptions regarding study homogeneity
  - Software
- **Meta-regression**
- **Current Practice**
- **Future Directions**

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Motivating Example - Avandia

- **NEJM Analysis by Nissen and Wolski demonstrating an increased risk of MI (OR=1.43, *P*=.03) and Cardiovascular Death (OR=1.64, P=.06)**
- **Re-analysis by Diamond, Bax and Kaul which showed lower OR and loss of statistical significance**
- **Additional ADCOM IPD analyses by FDA and GSK**
- **Relevant Issues**
  - Treatment effects fragile and dependent on choice of methodology
    - Dealing with sparse data (0s)
  - Homogeneity of treatment effects
    - Clinical versus statistical
  - One single best answer versus a variety of answers
  - IPD meta-analysis versus classic meta-analysis

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Classic meta-analysis

- **Developed in mid-1970s by psychologists and educational researchers**
- **Dramatic step forward from literature review in terms of objectivity and focus on quantitative results rather than statistical significance**
- **Now an academic 'industry' especially in clinical research**
  - Cochrane collaboration
  - 1500 meta-analyses between 1975 and 2000

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Basic Principles of Classic Meta-analysis

- Protocol (objectives, hypotheses, scope and methods)
- All-inclusive based on *a priori* specifications
- Assessment on methodological quality based on minimization of bias
- Identification of common set of outcome, explanatory and confounding variables
- Standardized and accurate abstraction of study data
- Meta-analysis using clearly stated and appropriate models - only when warranted. Otherwise, narrative summary.
- Assess robustness of study results
- Document, report and interpret results and limitations

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Development of Meta-analysis

- **Classic meta-analysis an unbiased tool for estimating a summary treatment effect across a series of studies**
  - Not as useful for estimating the effect of study-level or patient-level covariates
- **Meta-regression developed**
  - to estimate the effect of covariates
  - reduce heterogeneity
- **Individual Patient Data meta-analysis**
  - Estimate a summary treatment effect as well as the effect of patient and study-level covariates

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Advantages of IPD Meta-analysis Versus Classic Meta-analysis

- Data checking, assess randomization and follow-up
- Consistency, appropriateness of analyses
- Update follow-up
- Subgroup analyses
- Survival analyses
- Standardize inclusion/exclusion criteria
- Determine if treatment effect is constant over time
- Treatment by covariate interactions

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Disadvantages of IPD Meta-analysis Versus Classic Meta-analysis

- **Data access generally a challenge**
  - Straightforward for pharmaceutical company in the context of regulatory submission
- **More resource intensive**
- **Under conditions of homogeneity of treatment effect, classic meta-analysis produces identical results to IPD meta-analysis**

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Meta-regression

- **Tool for explaining and interpreting heterogeneous clinical trials results**
- **Assess variations in trial design, study cohorts, study quality (study-level factors)**
- **Consider as well individual patient characteristics (patient-level factors) based on aggregated results**
- **Assess treatment by subgroup interactions**

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Meta-regression Compared to IPD Analysis

- **Much lower power than IPD meta-analysis**
  - Standard deviations ≈ 3.4 times higher in all situations based on an extensive simulation study by Lambert et al.
- **Inadequate to identify a clinically moderate interaction**
- **In the absence of patient level data, meta-regression may be the only alternative**
- **Meta-regression more useful for identifying study-level factors compared to patient-level factors**

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Planning an individual patient data meta-analysis

- Write protocol (including objectives, inclusion/exclusion criteria, planned analyses)
- Identify all relevant trials
- Establish Secretariat, Advisory and Trialist groups
- Collect and validate data
- Assemble complete, integrated database
- Perform IPD meta-analyses
- Collaborators Conference
- Prepare report

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Pooling All Data Together as One Large Study

- Considering the data as arising from a common trial
- Generally not recommended as a final or most polished analysis
- Reasonable first or benchmark analysis
- Some publications are based on this approach
- Straightforward and easy to implement with existing software
- Not discussed further

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General Considerations for Models

- **Hierarchical models with patients as level-1 units and trials as level 2-units**
- **Some hierarchical models developed for multi-site clinical trials where sites are numerous and patients/site are small**
- **In IPD meta-analysis, trials are small/moderate in number and patients/trial are numerous**
- **Bayesian and non-Bayesian hierarchical random effect models**
  - Better if trials are moderate/large in number
  - Assumption of randomness reasonable?
- **Fixed effects models**

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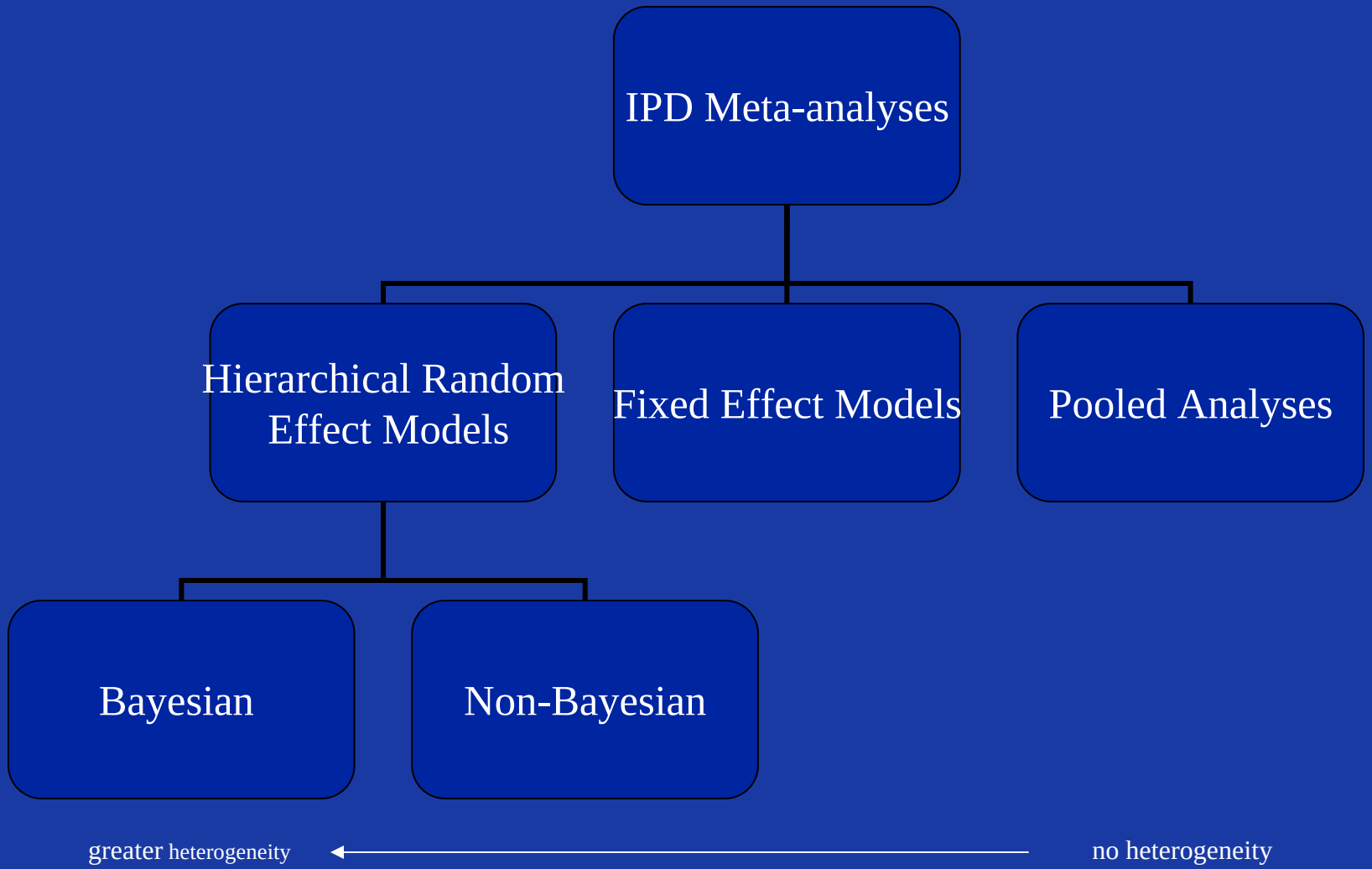
Structure of IPD Meta-analyses



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Time to Event Outcomes - Fixed Effect Models

- **Most work based on hierarchical Cox regression model**
- **Cox model with fixed trial effects and fixed treatment effects**
  - Treatment heterogeneity assessed via treatment by trial interactions
- **Cox model stratified by trial with fixed treatment effects**
  - Assume proportional hazards within trials, but not across trials
  - Treatment heterogeneity assessed via trial-specific effects

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Time to Event Outcomes - Random Effect Models

- **Cox model with fixed trial effects and random treatment effects**
  - Assumes proportional hazards across trials
- **Cox model stratified by trial with random treatment effects**
  - Assume proportional hazards within trials, but not across trials
- **Cox model with random trial effects and random treatment effects**

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Time to Event Outcomes - Bayesian Hierarchical Models Based on Cox Regression

- **Cox Regression model with random trial effects and random treatment effects**
  - Trial and treatment effects follow distributions (log-normal is convenient)
  - Prior distributions for parameters that characterize random effects
  - Vaguely informative prior works well in increasing stability of Markov Chain Monte Carlo estimates

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Software for Time-to-Event Outcomes

	SAS	Specialized	Other
Stratified	Yes		S+, StatA
Fixed	Yes		S+, Stata
Random	Yes, with SAS IML		S+
Bayesian	No	BUGS	Fortran

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Binary Outcomes

- **Generally based on logistic regression models**
- **Fixed effect models assume trial effect is fixed**
  - Fit using SAS
- **Random effect models which assume that treatment effect is random**
- **Random effect models assume both trial and treatment effect are random**
  - Fit using specialist (e.g. MLwiN) software
- **Bayesian hierarchical model for IPD meta-analysis an option**

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Ordinal Outcomes (Response Categories)

- **Based on proportional odds models**
- **Log odds follow a fixed effect model; trial effects are fixed**
  - SAS
- **Stratified fixed effect model in which study effects vary depending on the response category**
  - MLwiN, SAS, with IML
- **Random effect models**
  - MLwiN or specialist software
- **Bayesian model**
  - BUGS

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Continuous Outcomes

- **Straightforward to implement analyses compared to other outcomes**
- **Can allow treatment effect and trials effects to be fixed or random**
- **Can be formulated in terms of multilevel model or classical mixed model**
- **Fit using SAS PROC MIXED or MLwiN, other standard software packages**

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Treatment Coding

- **Experimental treatment group coded as 1 and control/placebo as 0**
- **Treatment effect is unchanged if treatment codes are switched**
- **Not necessarily the case for certain random effect models**
- **Group coded as 0 has no variability in treatment effect, all of the variability is forced into the other treatment effect**
  - May be reasonable if placebo control group
  - Alternative coding schemes to allocate variability into both treatment groups
- **Complication that needs to be managed**

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Testing of Homogeneity

- Focus in literature is binary outcomes, should generalize to time to event outcomes
- Breslow-Day and Cox MLE Score statistics best in terms of nominal levels of significance
- Homogeneity tests have modest power to detect random effects unless effects are large (based on simulation studies)
- Empirically, summary meta-analyses commonly find heterogeneity, more so for risk differences than odds ratios
- Failure to detect heterogeneity provides scant evidence of homogeneity
- Difficult to choose between fixed and random effect models based on tests of homogeneity
- Strategy: Examine clinical homogeneity first. Combine results quantitatively only if clinically homogenous. Test homogeneity at a conservative level (*P*=.01).
- Alternative Strategy: Always use a random effects model and assume for the possibility of heterogeneity

Current Practice

- **Based on publications 1999-2001**
  - Not representative of unpublished analyses
- **44 publications**
- **28 used two-stage models, 6 used one-stage, 8 used both**
- **24 based on time-to-event analyses**
- **29 assumed a fixed treatment effect only**
- **9 used some or all random effect models**
- **3 pooled all data as if it arose from a single trial**

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Key Issues for a Coherent IPD Meta-analysis

- **Clear objectives and analysis plan**
  - *A priori* strategy for dealing with study heterogeneity
- **Access to data**
- **Integrated database**
- **Number and diversity of models**
- **Software and required resource**

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Future Directions

- **Increasing usage and awareness**
- **Greater investment in integrated databases and more sophisticated analysis methodologies/software**
- **Assumptions of homogeneity – managing**
- **Agreement on how to manage/standardize treatment coding**
- **Software development**
  - Implementation in mainstream software packages
  - Standardization
- **Methodology**
  - Better understanding of treatment coding strategies
- **Drug labeling**
  - Based on primary and key secondary endpoints and strong control of family-wise Type 1 error
  - For secondary endpoints, utilize IPD meta-analyses
    - Utilization of information from all controlled trials providing more accurate and more precise estimate of treatment benefits
    - Important to develop a framework for control of multiplicity and *a priori* specification based on clinical importance
    - Dealing with heterogeneity

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