Get Real

Real-Life Data in Drug Development

Methods for IPD meta-analysis

A systematic review

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Project description

- Incorporating real-life clinical data into drug development
  - Pre-authorization versus post-authorization
  - (pragmatic) trials, observational studies, registries and electronic healthcare data
  - Translate clinical efficacy into “real world” clinical practice
- Public-private partnership between key stakeholders
  - Academic institutions
  - HTA agencies and reimbursement bodies
  - Industry
  - Patient organizations

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Work packages

- **WP1**: create shared platform for the inclusion of alternative study designs in development strategies
- **WP2**: understand the gap between efficacy and effectiveness
- **WP3**: address operational aspects of conducting pragmatic and adaptive clinical trial designs pre-launch
- **WP4**: promote best practice in evidence synthesis and predictive modelling
- **WP5**: management role of GetReal

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WP4: systematic reviews

Identify methodology and recommendations for

- Individual Participant Data (IPD) meta-analysis
- Network meta-analysis
- Predictive modeling of treatment effect

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Intervention research

- Randomized clinical trials (RCT)
  - Dose finding
  - Safety and efficacy testing
- Concerns
  - Small sample size
  - Narrow inclusion criteria
  - Differences in populations, doses and modes of treatments
  - Limited transportability to real life settings

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Meta-analysis

- Potential aims
  - Industry: investigate competitors, identify promising subgroups
  - HTA: investigate the added value of a novel drug
  - Policy makers: rank competing treatments by effectiveness or safety, inform decision making
- Traditional strategy
  - Systematically review published trials
  - Extract reported results
  - Pooling of extracted data

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Meta-analysis

- Typically based on aggregate data (AD)
  - Estimates of treatment effect (e.g. Odds Ratio)
  - Estimates of uncertainty (e.g. Standard error)
  - Study-level characteristics (e.g. Blinding level)

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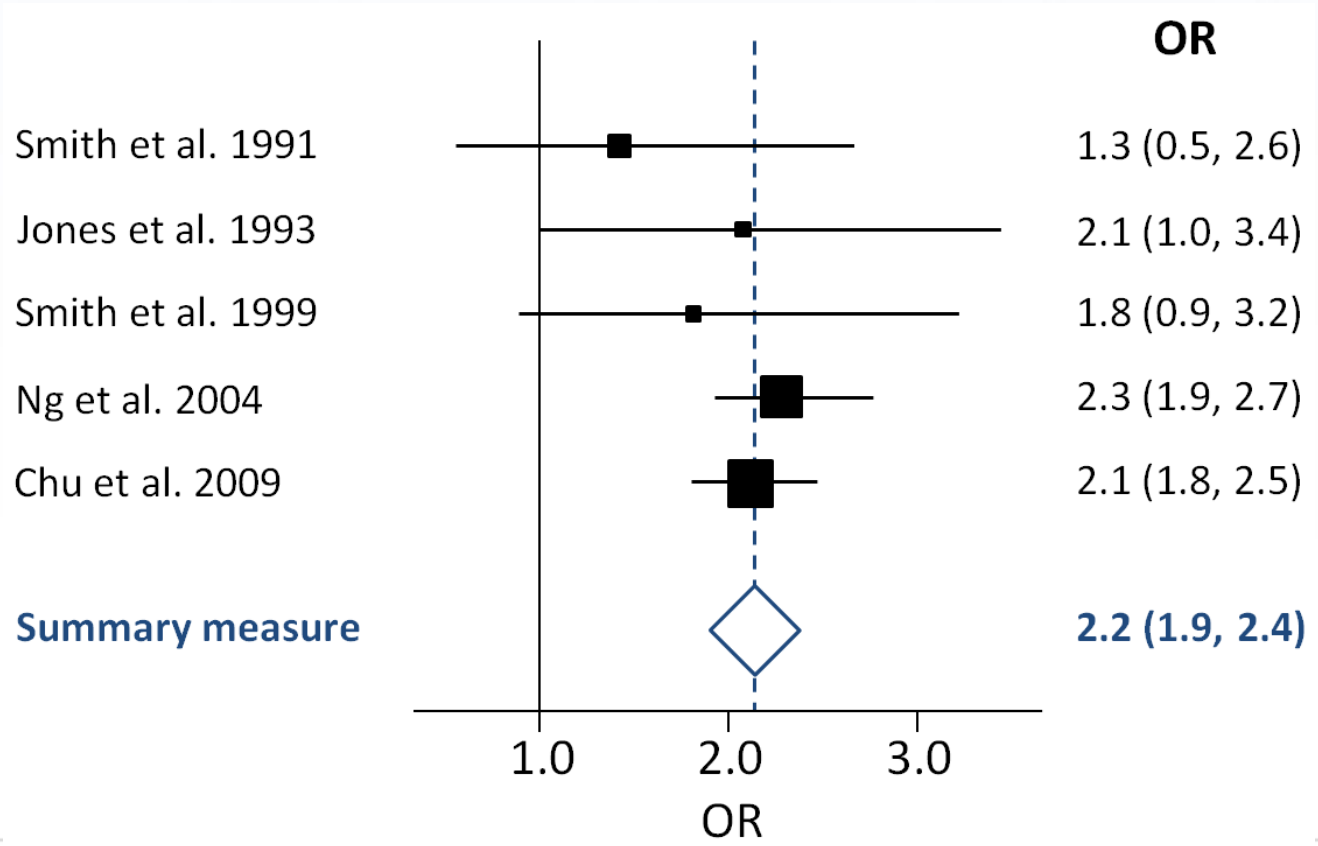
Meta-analysis



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Meta-analysis

- Problematic when trials are heterogeneous
  - Population
  - Outcome
  - Study design
  - Statistical model
- Limited capabilities of AD to
  - Harmonize variable definitions
  - Investigate treatment-covariate interactions
  - Adjust for study-specific biases
  - Include evidence from non-randomized intervention studies (NRIS)

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Meta-analysis of Individual Participant Data (IPD)

- Retrieve raw data from relevant studies
  - Information on treatment, outcome, subject-level characteristics, …
- Advantages
  - Explore heterogeneity in treatment effect
  - Examine effect modification
  - Adjust for confounding
  - Improve data quality & perform standardization
  - Account for differences in censoring and length of follow-up
  - Analyze multiple outcomes
  - Investigate long-term outcomes, rare exposures and interactions

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Methods for IPD meta-analysis - a systematic review

Identify (English) articles addressing issues relating to IPD meta-analysis in intervention research

- Statistical models
- Simulation studies
- Empirical comparisons
- Didactic
- Guidelines

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Systematic review: results

- 3360 unique records found eligible for screening
- 154 records eligible for full text assessment
- 138 full text records assessed
  - 1 record excluded due to inclusion criteria
  - 16 additional records included from cross-reference check
- 153 studies included in the review
  - Overview of included articles available at www.zotero.org/groups/wp4_-_ipd_meta-analysis

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Conceptual issues

Methods for meta-analysis

- Two-stage approach
  - Stage 1: Reduce IPD to AD
  - Stage 2: Pool AD using traditional approaches
- One-stage approach
  - Analyze the IPD from all studies simultaneously

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Two-stage approach

- Advantages
  - Relatively simple to perform
  - Does not borrow information ***across*** studies when estimating effect sizes ***within*** a particular study
- Disadvantages
  - Poor power: non-linear associations & interactions
  - Problematic in small samples, different follow-up times, recurrent events

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One-stage approach

- Advantages
  - Increased power due to borrowing of information **across** studies
  - Increased flexibility (e.g. interaction terms)
- Disadvantages
  - Requires substantial statistical expertise
  - Requires additional assumptions
  - Tends to yield similar results as two-stage approach when investigating overall treatment efficacy

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One-stage or two-stage?

- The one-stage approach is currently considered as a gold standard
  - The one-stage approach offers most flexibility
  - The one-stage approach offers increased efficiency
  - The two-stage approach can be viewed as a special case of the one-stage approach where no assumptions are made on the distribution of between-study heterogeneity

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One-stage approach: estimating a summary effect

- Generalized Linear Mixed Models
  - y_{ik}: observed outcome for subject *k* in study *i*
  - x_{ik}: treatment indicator for subject *k* in study *i*

$$g\left(E\left(y_{ik}\right)\right) = \alpha_i + \beta_i x_{ik}$$

  - α_i: study effect (e.g. Baseline risk) for study *i*
  - β_i: treatment effect for study *i*

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Investigate heterogeneity in treatment effect

- Heterogeneity between study results
  - Differences between studies
  - Differences between clinical subgroups
- Interaction
  - **Trial-level** interaction: Treatment interaction with factors that only vary between but not within studies
    - Typically investigated with subgroup analysis or meta-regression
    - Prone to ecological fallacy!
  - **Subject-level** interaction: Treatment interactions with factors that only vary within studies

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Investigate heterogeneity in treatment effect

$$g(E(y_{ik})) = \alpha_i + \beta_i x_{ik} + \gamma_i z_{ik} + \theta_i x_{ik} z_{ik}$$

- γ_i: effect of covariate *z* before treatment in study *i*
- θ_i: treatment-covariate interaction in study *i*
  caution: weighted average of trial-level and subject-level interaction
- Model subject-level interaction separately by replacing z_{ik} by:
  - $\overline{z_i}$: mean of z in study *i* → Interaction term θ_i^A
    quantifies presence of ecological bias
  - $(z_{ik}\text{-}\overline{z_i})$ → Interaction term θ_i^W
    quantifies subject-level interaction

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Investigate heterogeneity in treatment effect

- Extensions
  - Heterogeneity of interaction
  - Adjust for study-level covariates
  - Interaction between treatment and study-level covariates
  - Interaction between treatment, subject-level and study-level covariates
- Danger for data dredging and overparameterization!
  - Expert opinion
  - Study protocol

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Combining IPD and AD

- Advantages
  - Avoid data availability bias or reviewer selection bias
  - Increase statistical power
- Two-stage approaches
  - Reduce available IPD to AD and perform an AD-MA
  - Risk of ecological bias!
- One-stage approaches
  - Reconstruct IPD using 2 by 2 tables (information on covariates lost)
  - Hierarchical Related Regression (shared parameter models)

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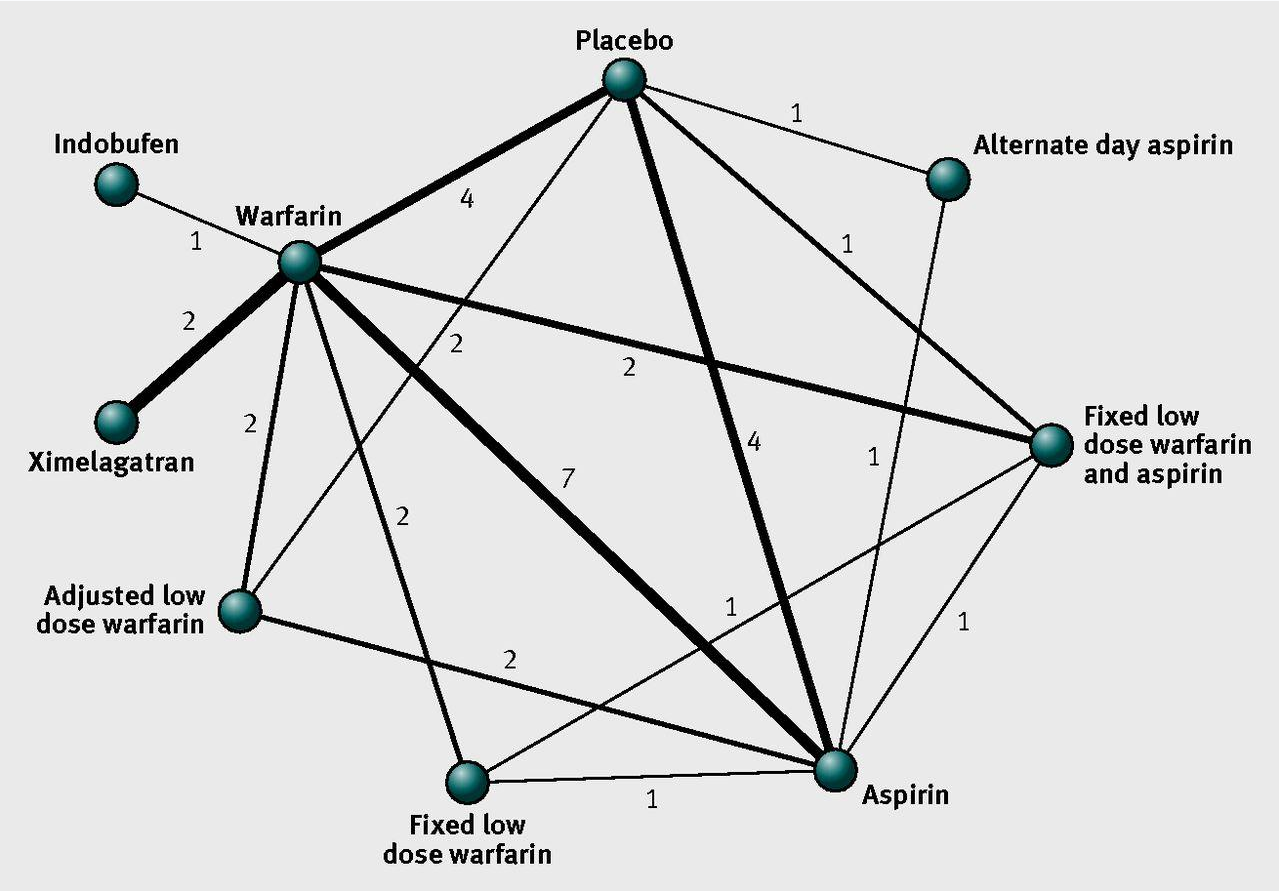
Network meta-analysis



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Network meta-analysis

- Summarize evidence from multiple treatment comparisons
  - Compare treatments for which no head-to-head trials exist
  - Rank treatments by efficacy or safety
- Concerns
  - Assumptions (some are difficult to test)
  - Direct versus indirect evidence
  - Model complexity
- Role of IPD even more crucial
- Systematic review of methods (GetReal)

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Cross-design synthesis

- Advantages
  - Increased sample size
  - Increased variability in inclusion criteria, follow-up information, undergone treatments, treatment patterns, the presence of co-morbidities and co-medication
    => improved reflection of "***the real world***"
- Disadvantages
  - Confounding
  - Inclusion of NRSI likely to increase heterogeneity
  - Limited options to correct for sources of bias

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Cross-design synthesis

- It is currently unclear when cross-design synthesis is justified
- The credibility of cross-design estimates may be challenged
- Key issues to consider
  - Evaluating risk of bias
  - Accounting for bias and confounding
  - Transparency

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Missing data

- Types of missing data
  - Missing completely at random (MCAR)
  - Missing at random (MAR)
  - Missing not at random (MNAR)
- Missing data in an IPD-MA
  - **Subject-level**: variabels that have not been measured or outcomes that are missing
  - **Study-level**: unavailable study-level covariates
  - **Meta-analysis level:** Missing studies (e.g. publication bias)

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Missing data

- (Traditional) Multiple Imputation
  - Replace missing values with a series of predictions
  - Impute each data set separately to account for heterogeneity
  - Problematic in the presence of systematically missing variables
- Multilevel Multiple Imputation
  - One-stage imputation model for the whole IPD-MA data set
  - Allows imputation of sporadically and systematically missing variables
  - Increased power

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Frequentist estimation techniques

- Maximum Likelihood estimation
  - Unbiased estimates of fixed effects
  - Under-estimation of variance components in small samples
- Estimation of a penalized likelihood function
  - Reduce bias in estimates of variance components
  - Examples: REML, PQL, EQL, PPL, SPL
- Software
  - R (lme4, nlme, survival, coxme, frailtypack, MASS, …)
  - SAS (PROC MIXED, PROC NLMIXED, …)
  - Stata (stmixed, XT, REGOPROB2, …)

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Bayesian estimation techniques

- Augment likelihood function with prior information
  - Different degrees of prior information possible
  - Variance components no longer assumed as fixed parameters
  - Use of exact likelihood functions less problematic
- Software
  - WinBUGS, JAGS, OpenBUGS

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Concluding remarks

- Access to IPD offers numerous advantages
- However …
  - IPD is still prone to several forms of bias
  - IPD is no panacea against poorly designed and conducted primary research
  - Combining IPD from multiple studies requires additional efforts and statistical expertise

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