Modelling individual patient data in network meta-analysis

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Aims of the presentation

• To increase knowledge about what an individual patient data (IPD) network meta-analysis (NMA) is
  • When an IPD-NMA may be preferred compared to an aggregated data (AD) NMA?

• To increase knowledge of the methods for conducting an IPD-NMA
  • Which methods are frequently performed for an IPD-NMA?

• To discuss methods to obtain IPD
  • Which are the most efficient methods to get IPD?
Aggregate data (AD) vs. Individual patient data (IPD) (network) meta-analysis

**AD meta-analyses**: use summary point estimates from all patients enrolled in each included trial
- Data are not available on individual patients

**IPD meta-analyses**: use data from each individual patient enrolled in each included trial
- Allows similar analysis across all trials
- Allows investigation of patient-level moderators

**Aggregate data meta-analysis**
- May suffer from relatively low statistical power
- It is challenging to:
  - Harmonize variable definitions
  - Harmonize inclusion and exclusion criteria
  - Combine studies with different follow-up times
  - Adjust for study-specific biases (e.g. aggregation bias)
  - Explore sources of between-study heterogeneity (e.g. due to treatment-covariate interactions)
AD vs. IPD (network) meta-analysis

- AD and IPD models can be equivalent if data & effect size are equivalent
  - Discrepancies arise because IPD data sets include different data than AD (e.g. may reinstate patients originally excluded, additional follow-up data)

- IPD meta-analysis in soft tissue sarcoma: 24% of patients were excluded in the treatment arm compared with 20% in the control arm – 99% of excluded patients were recovered
  - Meta-analysis with exclusions: HR=0.85 (p=0.06)
  - Meta-analysis reinstating all exclusions: HR=0.90 (p=0.16)  

- Empirical evidence suggests AD models might be misleading for the evaluation of consistency assumption, and might suggest different ranking due to differences in a patient-level covariate distribution within and across studies.

- IPD meta-analysis is the gold standard for synthesising evidence across clinical trials, as it can:
  - Increase precision
  - Explore the patient-level treatment effects
  - Tailor results to the patient characteristics
  - Use consistent inclusion/exclusion criteria across studies
AD vs. IPD (network) meta-analysis

**Individual patient data meta-analysis**

- Includes **checks** to ensure homogeneity, quality of randomization, and follow-up analysis
- Overcomes **outcome reporting bias**
- Allows participant-level covariates to be **directly modeled**, increasing statistical **power** and detects participant-treatment relationships if they are present.
  - Answers what interventions are most effective in (for example):
    - men versus women
    - older people versus younger people

- **Is time-consuming and costly**
- **May not be able to obtain all IPD = retrieval bias**
- “...the balance of gains and losses of the approach will vary according to the disease, treatment, and therapeutic questions explored”

*Stewart and Tierney Eval Health Prof 2002*
IPD in indirect comparisons

IPD indirect comparisons are published with increasing frequency in health care literature

The use of IPD in indirect comparisons and network meta-analysis (NMA) may:

- Increase confidence in the results
- Identify interactions that are otherwise undetectable
- Reduce both variation in treatment effects between studies within pairwise comparisons (heterogeneity) and variation in treatment effects between pairwise comparisons (inconsistency)
- Allow estimation of subgroup effects, which in turn allows tailoring of results to patient characteristics

*A up to October 2014
We identified 37 papers:
- 23 (62%) application articles
- 11 (30%) methodological articles
- 2 (5%) reviews, and
- 1 (3%) protocol.

Of the 33 empirical networks (including examples identified in methodological and review articles):
- 24 (73%) IPD-NMAs & 9 (27%) matching adjusted indirect comparison (MAIC) methods were performed
- **Included RCTs only**: 21 (64%) IPD-NMAs and 9 (27%) MAICs
- Only 9 (27%) IPD-NMAs reported the existence of a **study protocol**
- 15 (45%) IPD-NMAs applied a **random-effects** model (this model is not applicable for MAIC)
- 16 (52%) applied a **Bayesian hierarchical model**
- Only 3 (9%) IPD-NMAs provided their **statistical code**
Scoping review of indirect comparisons with IPD

- Of the 33 empirical networks
  - 21 (64%) networks with at least one closed loop:
    - 19 (90%) were IPD-NMAs, 13 (68%) of which evaluated the consistency assumption
    - Only 5 (38%) of the 13 IPD-NMAs used statistical approaches.
  - 10 (30%) were able to obtain IPD for all studies
  - 22 (67%) studies identified IPD from a collaborative group

- 17 (46%) studies of the total 37 articles, were industry sponsored
- For IPD alone or IPD+AD, models have been developed for dichotomous and continuous outcomes, whereas for IPD+AD, models also exist for time-to-event data.
- Typical IPD network: dichotomous, objective primary outcome, compared pharmacological and placebo/control interventions, and involved 5 interventions and 10 trials.

In summary...

- One in three approaches used to model IPD adjusted results from different trials to estimate effects as if they had come from the same, randomized, population.
- Key methodological and reporting elements were often missing, even for NMAs published in high impact journals.

Process for an IPD-NMA

- Eligible trials identified by search as in an AD review
- Identify contact information for authors published each eligible study

- Response to request may vary (e.g., no reply, no with reason provided, yes - will send the data, yes – here is the data)
- Data format and supporting material may vary per IPD received
How to obtain IPD

Aim
To examine the impact of providing incentives to the researchers responsible for the trials eligible for an NMA to submit their IPD.

RCT Authors
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Intervention Group

Control Group

Studies Within a Trial (SWAT) and Studies Within a Review (SWAR)
http://go.qub.ac.uk/SWAT-SWAR
How to obtain IPD

*Initiatives to encourage data sharing and clinical transparency*

- The Clinical Study Data Request System: https://www.clinicalstudydatarequest.com/
- The Yale University Open Data Access Project: http://yoda.yale.edu/

**Important consideration:**
protect the privacy and confidentiality of research participants
(anonymised data sharing)
Process when IPD are obtained...

- Understand the data (check the protocol and decipher the variable codes)
- Reproduce published results
- Check the data (e.g., missing participants, chronological randomization sequence)
- Raise queries and discuss them with original authors
- Clean and prepare data in a common format across all studies
  - Recode data to a consistent format
- Define outcomes of interest consistently across trials
- Perform analysis of the data
- Share results with data providers for discussion (if needed)
- Report findings according to the Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data (PRISMA-IPD) guidelines

Stewart et al JAMA 2015
**Network meta-analysis using IPD**

**Safety and effectiveness of long-acting versus intermediate-acting insulin for patients with type 1 diabetes mellitus (T1DM)**

Aim

To update our previous systematic review and perform an IPD-NMA to evaluate the comparative safety and effectiveness of long- vs. intermediate-acting insulin in different subgroups of patients with T1DM.
Network meta-analysis using IPD

Comparative safety and effectiveness of cognitive enhancers for Alzheimer’s dementia

Aim

To update our previous systematic review and perform an IPD-NMA to examine the comparative effectiveness and safety of cognitive enhancers for different patient characteristics.
In summary....

**Why applying an IPD-NMA?**

- Individual study results do not answer all potentially relevant clinical questions
  - Previous NMAs based on AD may have limitations
- Enables further research to benefit medical research and patient care
- Enables tailoring results to patient characteristics, and hence improving existing guideline recommendations
- Enables the validation of individual study results
- Helps in avoiding duplication of research, unnecessarily enrolling patients into clinical trials and exposing them to possible risks (e.g., serious adverse events)
- Increases transparency

**But...**

- Further studies are needed to evaluate the assumptions and the properties of an IPD-NMA in complex networks of interventions
References...


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