Modelling individual patient data in network meta-analysis

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I have no actual or potential conflict of interest in relation to this presentation
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)  
  
  \[\text{Tierney and Stewart Int J Epidemiol 2005}\]

• 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.
  \[\text{Donegan et al Stat Med 2012}\]

• 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

\[\text{Riley et al BMJ 2009}\]
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

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![Number of publications chart](chart.png)

*Up to October 2014*
Scoping review of indirect comparisons with IPD

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**
- Cyan
- Cyan
- Purple
- Cyan
- Purple

**Intervention Group**
- Red

**Control Group**
- Blue
- Blue
- Purple

**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/](https://www.clinicalstudydatarequest.com/)
- The Yale University Open Data Access Project: [http://yoda.yale.edu/](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
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