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Epidemiology and Big Data (INFOMEBD)

Why systematic reviews (in general)?

true for all analysis

- Prevent waste in research
- Transparent overview of all relevant studies: revealing differences and shortcomings in design and conduct
- Meta-analysis (pooling) can increase the precision of the overall result
- Amount and sources of heterogeneity can be examined:
  - confirm or generate new hypotheses about relevant subgroups or impact design features
- Formulate recommendations about whether or which types of new studies to perform

what is the difference to independent participant data?

Next-generation systematic reviews: prospective meta-analysis, individual-level data, networks and umbrella reviews

John Ioannidis

IPD meta-analyses are the platinum standard of systematic reviews

Why IPD reviews and a specific course?

- Several potential advantages when IPD available
- Platinum standard of meta-analysis
- More time & effort to obtain IPD
- Specific threat: authors not providing data

- Increasingly popular
- Meta-analysis more complex
- Several recent methodological developments & remaining challenges

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IPD review: what is it?

Aggregate data (AD) reviews

- Traditional reviews are based on published summary (aggregate) data from individual (primary) studies

- Dataset: one row per included study with the effect measure, its precision and study characteristics (design features, summary patient characteristics like % male, mean age)

What is IPD?

- Individual Patient (Participant) Data meta-analysis uses the original (raw, crude) data from individual patients to estimate summary measures of effect across studies

- Dataset: each row is a individual patient with his/her outcomes, patient characteristics (like in the original study), and added study characteristics like design, intervention features
  blind of not and what features

- Data from different studies are stacked

Data structure IPD meta-analysis

not just patient ID but also the study ID as they are mixed in IPD meta-analysis

Example of individual participant data from 10 hypertension trials that assess effect of treatment versus placebo on systolic blood pressure

Study ID	Patient ID	Age (years)	Sex (1=male, 0=female)	Treatment group (1=treatment, 0=control)	Systolic blood pressure before treatment (mm Hg)	Systolic blood pressure after treatment (mm Hg)
1	1	46	1	1	137	111
1	2	35	1	0	143	133
...	...	...	...	...	...	...
1	1520	62	0	0	209	219
2	1	55	0	1	170	155
2	2	38	1	1	144	139
...	...	...	...	...	...	...
2	368	44	1	0	153	129
3	1	51	1	1	186	166
3	2	39	0	1	201	144
...	...	...	...	...	...	...
3	671	54	0	0	166	141
...	...	...	...	...	...	...
10	1	71	0	1	149	128
10	2	59	1	0	168	169
...	...	...	...	...	...	...
10	978	63	0	1	174	128

Dotted line indicates where non-displayed rows of data occur.

Hypothetical data based on Wang et al.[27]

patient ID not necessarily needed but for instance with multiple time points we need to be able to identify cases

Similarities IPD and AD review

both are

- Scientific enterprise
- Key review steps similar:
  - frame focussed review questions
  - systematic search to identify all relevant studies
  - appraise methodological quality included studies
  - sound statistical models to obtain pooled estimates, to assess heterogeneity and to perform meta-regression
  - complete, accurate and informative reporting

does it agree with conclusions and results

different:

- IPD requires an International collaborative effort

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IPD Reviews: Overview of Potential Benefits

Potential benefits IPD review [1]

Having a collaborative group of dedicated researchers may improve:

- Trial inclusion:
  - supplement published & unpublished studies
  - discuss and apply consistent eligibility criteria
- Data quality and integrity:
  - include unreported data like excluded patients, more outcomes (reduce outcome reporting bias), longer FU
  - standardize outcome definitions and patient characteristics across studies
  - check integrity of data and query investigators

collaborative group of researches to identify criteria - what needs to be included

is there additional data that wasn't published

original investigators are around to ask questions

Potential benefits IPD review [2]

Collaborative group of dedicated researchers may improve:

- Risk of bias assessment:
  - clarify trial design & conduct within IPD group
- Interpretation of results:
  - discuss the limitations & implications among the multidisciplinary group
- Designing new trials

and formulating the interpretation of the results

Potential benefits IPD review [3]

what benefits when it comes to data analysis

Having the IPD may improve and expand:

- Analysis:
  - derive measures of effect directly from IPD
  - use consistent unit and method of analysis
  - handling missing data in a uniform way
  - check validity of assumptions
  - more detailed analysis for time-to-event data
  - greater validity and power to examine interactions with patient-level covariates (effect modification, subgroup analysis)
  - conduct more complex analyses (modelling)
  - use IPD for secondary questions like building prognostic models from RCT data

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IPD Reviews:
Potential drawbacks & Challenges

Why not IPD: Drawbacks

- Obtaining the data (ethical and privacy issues), cleaning and recoding takes time and effort
  setup of the collaboration difficult and privacy issues are a big problem with sharing data from different institutions
- IPD meta-analysis requires more statistical expertise

- Researchers may decide not to share their data which could generate distorted results (availability bias next to publication bias):
  - combine IPD and summary data into one meta-analysis?

AD vs IPD: when results different?

can we expect a difference in the results?

- No or small differences when same underlying data and focus on single summary estimate

- Differences may arise through:
  - other underlying data (more or less studies / patients, longer follow-up, consistent in- and exclusion, quality check)
  - standardization of outcomes & variables
  - uniform approach to missing values
  - same analysis approach
  - more flexibility and higher validity when examining subgroup effects

when is it beneficial?

TABLE 2
Factors That May Influence the Systematic Review Approach

When Individual Patient Data May Be Beneficial	*When Individual Patient Data May Not Be Beneficial*
Poor reporting of trials: Information inadequate, selective, or ambiguous	Detailed and clear reporting of trials (CONSORT quality)
Long-term outcomes	Short-term outcomes
Time-to-event outcome measures	Binary outcome measures
Multivariate or other complex analyses	Univariate or simple analyses
Differently defined outcome measures	Outcome measures defined uniformly across trials
Subgroup analyses of patient-level characteristics important	Patient subgroups not important
Individual patient data available for high proportion of trials/individuals	Individual patient data available for only a limited number of trials

From: Stewart LA, et al. To IPD or not to IPD. Evaluation & the Health Professions 2002

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Summary

Indirect benefits IPD

collab. effort

- Improve trial identification & interpretation through collaborative approach
- IPD results better incorporated in guidelines
- Collaboration can lead to and improve the design of future studies
- Improve methods for IPD and other evidence synthesis approaches:
  - use IPD as resource for research into bias, analysis methods, e.g. how to impute missings (Koopman et al, Am J Epidemiol 2008)

To IPD or not to IPD

- Considerable investment of time & effort
- Potential benefits IPD meta-analysis:
  - use of additional data, in particular longer follow-up, other outcome data
  - check integrity of data
  - standardization across studies to repair inconsistencies in outcomes, effect measures, adjustment, subgroup definition, handling of missing values, etc
  - subgroup analysis: more flexibility & higher validity & more power

what would be a NO GO?
- amount of studies - the more the better
- incomplete data

not all issues can be fixed through statistics which is why a quality assessment is very important

- IPD no cure for poorly designed studies