

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



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



IPD Reviews: Overview of Potential Benefits

Potential benefits IPD review [1]

Having a collaborative group of dedicated researchers may improve:

- Trial inclusion: collaborative group of researches to identify criteria - what needs to be included
 - supplement published & unpublished studies
 - discuss and apply consistent **eligibility criteria**
- Data quality and integrity: is there additional data that wasn't published
 - 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

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

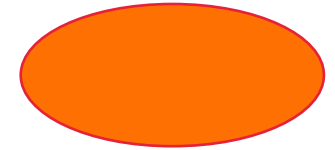
Having the IPD may improve and expand:

- 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



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

<i>When Individual Patient Data May Be Beneficial</i>	<i>When Individual Patient Data May Not Be Beneficial</i>
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



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

