Disclaimer

The views expressed here are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the regulatory agency/agencies or organizations with which the authors are employed/affiliated.

UMC Utrecht

Systematic Reviews and Meta-Analysis involving Individual Participant Data: IPD Reviews

Valentijn de Jong[1,2], PhD

1. Julius Center for Health Sciences and Primary Care, UMCU
2. Data Analytics and Methods Task Force, European Medicines Agency

Why systematic reviews (in general)?

- 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

Outline

- Why IPD reviews?
- What is an IPD review
- Benefits & Challenges
- Running an IPD review
- Reporting & Appraising an IPD review
- Impact of IPD

UMC Utrecht

IPD review: what is it?

Universitair Medisch Centrum Utrecht

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 an individual patient with his/her outcomes, patient characteristics (like in the original study), and added study characteristics like design, intervention features
- Data from different studies are stacked

Why IPD reviews?

- 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

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)

Similarities IPD and AD review

- 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

- IPD requires an International collaborative effort

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

Data structure 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]

UMC Utrecht

IPD Reviews: Overview of Potential Benefits

Potential benefits IPD review [3]

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

Why not IPD: Drawbacks

- Obtaining the data (ethical and privacy issues), cleaning and recoding takes time and effort
- 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?

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

UMC Utrecht

IPD Reviews: Potential drawbacks & Challenges

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

Running an IPD review

- International collaborative effort:
  - small management group
  - advisory group
  - trialists who provide data
- Project leader / initiator:
  - expert in the field
  - performed at least one relevant trial
- Most effort is required to establish and maintain collaboration and process data
- Least problematic area might be the analysis itself

AD vs IPD: when results different?

- 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

UMC Utrecht

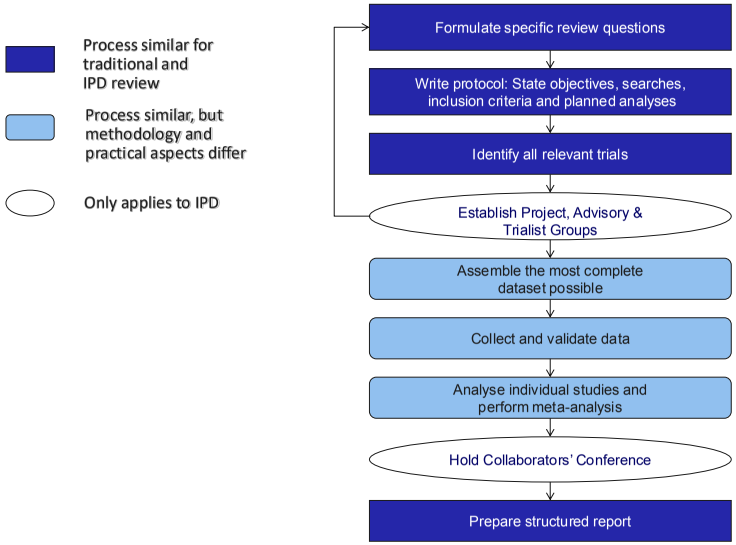
Running an IPD review

Establishing & maintaining collaboration

- Initial letter inviting collaboration should explain:
  - main aims and objectives
  - importance of the collaborative group
  - publication policy
  - confidentiality of data
  - offer an official agreement
- Ask for trial protocol, questionnaires etc.
- If necessary, arrange a meeting

Which trial level data to collect

- Data to adequately describe the trial:
  - trial ID and title
  - randomisation method
  - method of allocation concealment
  - planned treatments
  - recruitment and stopping information
  - information that is not clear from trial report



Formal protocol

- Design a review (IPD meta-analysis) with the same rigour as a primary study
- Write a protocol:
  - Specify rationale & main review questions
  - Specify a priori(?) hypotheses and methods
  - Register protocol (PROSPERO, but also see osf.io)
  - Increase transparency & streamline discussions

Which IPD to collect: all patients

- Investigators in primary studies frequently exclude patients from analyses:
  - legitimate reasons to exclude certain participants
- Collect data on excluded patients and reasons:
  - ineligibility, protocol violation, missing outcome data, withdrawal, 'early' outcome
- Allows analyses:
  - as done in original studies
  - all participants by intention to treat
  - applying exclusion criteria consistently across studies

UMC Utrecht

Reporting & Appraising an IPD review

Universitair Medisch Centrum Utrecht

Example form

META-ANALYSIS OF CONCOMITANT CHEMORADIOTHERAPY FOR LOCALLY ADVANCED CANCER OF THE UTERINE CERVIX

Name: _____ Your trial/protocol number: _____

Name of trial: _____

Are you willing to take part in this meta-analysis? Yes ☐ No ☐

If yes, please can you supply a copy of the trial protocol and forms when you return this form.

Trial Design

Was informed consent obtained from each patient? Yes ☐ No ☐

Date trial opened to accrual: dd mm yy Date trial closed to accrual: dd mm yy

What method of randomisation was used?

Simple ☐ Permuted blocks ☐ Minimisation ☐ Other _____

What method was used to conceal randomisation:

Sealed envelope ☐ Central telephone ☐ Other _____

What, if any, stratification factors were used? _____

What proportions was the trial designed to have in each arm (e.g. 1:1)? _____

Early Stopping

	Yes	No		Yes	No
Did the trial have a target for patient accrual?	☐	☐	Did the trial stop early?	☐	☐
Did the trial reach its target accrual?	☐	☐	Was a formal stopping rule used?	☐	☐

If a formal stopping rule was not used, what was the reason for stopping the trial? _____

Data Transfer

Please provide data on all patients randomised. You may complete the data forms provided or supply your data as a computer printout, on floppy disk (formatted for PC) or by e-mail. Data can be in almost any format (ASCII, Excel, Dbase, FoxPro, etc.), but please indicate which format has been used. Data files should be encrypted. It would be helpful if you used the coding suggested. However, you may code the data in the way that is most convenient to you. Please supply us with full details of the data coding system used.

Are you able to use the suggested coding? Yes ☐ No ☐

Which method of data encryption would you prefer? (e.g. WinZip etc) _____

Guarantee of Confidentiality of Individual Trial Results

Data will remain the property of the trial investigator who supplied it and will not be used, circulated or distributed in any way that allows access to individual trial data, without first seeking the permission of the trial investigator.

I want my data to remain confidential Yes ☐ No ☐

Which IPD to collect: variables

- What variables are required for your analysis?
- What do you need to adequately describe trials?
- Publications can indicate:
  - which variables will be present
  - but more data may be collected than reported
- Provide a provisional list of planned variables in protocol/form to establish feasibility

Reporting IPD review

- PRISMA checklist +
  - if trialists identified extra studies
  - inclusion criteria applied at trial or patient level
  - if data on unreported outcomes were obtained
  - methods for checking the integrity of IPD and reporting of findings (might be sensitive)
  - exploring variation in treatment effect
  - many modifications in wording
- Leading to a specific extension: PRISMA-IPD

Stewart et al. Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data The PRISMA-IPD Statement. JAMA 2015

UMC Utrecht

Impact of IPD

Universitair Medisch Centrum Utrecht

Presenting and publishing results

- Project management group draft presentation / report with input from Advisory Group
- Circulate to all collaborators for comment once, twice, …
- Summarise and respond to comments
- Achieve consensus
- On behalf of collaborative group:
  - Present at conference
  - Submit to journal

Appraisal of IPD review: key questions

AMSTAR 2: critical appraisal tool for systematic intervention reviews (Not specific to IPD) *BMJ 2017;358:j4008*

Tierney et al. Individual Participant Data (IPD) Meta-analyses of Randomised Controlled Trials: Guidance on Their Use. PLOS Medicine 2015 :

1. Is the IPD meta-analysis part of a systematic review?
2. Were all eligible trials identified?
3. Were IPD obtained for most trials?
4. Was the integrity of the IPD checked?
5. Were the analyses pre-specified in detail?
6. Was the risk of bias of included trials assessed?
7. Were the methods of analysis appropriate?
8. Does the report adhere to the PRISMA-IPD statement?

Impact IPD review on trial design & analysis

- Trials design:
  - collaboration IPD group continues into new trial
  - choice of comparator
  - defining the population
  - determining sample size & further recruitment
- Trial analysis:
  - prognostic model from IPD to stratify new patients
  - choice of subgroup analysis
  - stopping ongoing trials

Tierney J et al. How individual participant data meta-analyses have influenced trial design, conduct, and analysis. J Clin Epidemiol 2015

UMC Utrecht

Summary

Universitair Medisch Centrum Utrecht

IPD use and uptake

- Descriptive study of uptake of 33 IPD reviews in 177 matching clinical guidelines
- Findings:
  - 37% of the guidelines cited the IPD review
  - reasons for not citing unclear for the vast majority of guidelines
  - if used, one third of these guidelines critically appraised the IPD review

Vale et al. Uptake of systematic reviews and meta-analyses based on individual participant data in clinical practice guidelines: descriptive study. BMJ 2016

Prospective meta-analysis (PMA)

- PMA is a meta-analysis of studies identified and determined to be eligible before the results of any of those trials became known

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

John Ioannidis

- Benefits:
  - hypotheses to be specified really a priori
  - a priori statements of intended (subgroup) analyses before looking at the data
  - prospective application of selection criteria
  - opportunities to standardise
  - often collect individual participant data

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
- IPD no cure for poorly designed studies

Indirect benefits IPD

- 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)