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Meta-analysis of individual patient data from randomized trials: a review of methods used in practice

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Background Meta-analyses based on individual patient data (IPD) are regarded as the gold standard for systematic reviews. However, the methods used for analysing and presenting results from IPD meta-analyses have received little discussion.

Methods We review 44 IPD meta-analyses published during the years 1999–2001. We summarize whether they obtained all the data they sought, what types of approaches were used in the analysis, including assumptions of common or random effects, and how they examined the effects of covariates.

Results Twenty-four out of 44 analyses focused on time-to-event outcomes, and most analyses (28) estimated treatment effects within each trial and then combined the results assuming a common treatment effect across trials. Three analyses failed to stratify by trial, analysing the data is if they came from a single mega-trial. Only nine analyses used random effects methods. Covariate-treatment interactions were generally investigated by subgrouping patients. Seven of the meta-analyses included data from less than 80% of the randomized patients sought, but did not address the resulting potential biases.

Conclusions Although IPD meta-analyses have many advantages in assessing the effects of health care, there are several aspects that could be further developed to make fuller use of the potential of these time-consuming projects. In particular, IPD could be used to more fully investigate the influence of covariates on heterogeneity of treatment effects, both within and between trials. The impact of heterogeneity, or use of random effects, are seldom discussed. There is thus considerable scope for enhancing the methods of analysis and presentation of IPD meta-analysis. *Clinical Trials* 2005; **2**: 209–217. www.SCTjournal.com

Introduction

Systematic reviews have become increasingly used as a means of assessing and interpreting the results from medical research, enabling comprehensive and powerful investigation of the effects of healthcare interventions. Such reviews aim to comprehensively identify and appraise all studies relevant to a given question and, if appropriate, to quantitatively combine their results. Consequently the quantitative synthesis of results, or meta-analysis, has become common. Many methods for meta-analysis are available, but the most commonly applied in the evaluation of interventions focus on the combination of published summary statistics, usually in some form of weighted average [1–3]. As an alternative, the reanalysis of all the individual patients' data (IPD) from the studies is widely considered the gold standard [4]. This approach has several advantages: the ability to examine the data in detail; to produce consistent analyses across studies; use of up-to-date data; the ability to avoid biases associated with use of aggregate data in meta-regression [5–7]; and the possibility of investigating additional hypotheses, particularly related to individual patient characteristics where the data would be lacking in published

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results [8]. However, obtaining and analysing IPD can be both costly and time consuming.

The methodology of meta-analyses of summary data is well developed, with fixed-effect approaches such as inverse-variance weighting [3], the Mantel–Haenszel [9] or Peto [10] methods, and random effects approaches such as that of DerSimonian and Laird [2]. Meta-analysis of IPD offers an even wider choice of analysis methods. For the purposes of this paper we distinguish between two general approaches to IPD meta-analysis. The first we call a one-stage analysis. This combines all the IPD from all studies to perform a single analysis. This could be in a "mega-trial" analysis, where distinctions between studies are ignored and the data are analysed as if they belong to a single trial, or a stratified analysis where the trial identities are included in a model. The second we call the two-stage approach. Here studies are analysed separately, and then summary statistics combined using standard summary data meta-analysis techniques.

There is little discussion of methodology for IPD meta-analysis in the statistical literature, much of which concentrates either on general practicalities of IPD reviews [8], or on more advanced multilevel modelling techniques [11–13]. This lack of guidance may have led to the wide variation in methods we have noticed from casual observation. To identify areas in need of guidance or further research, we performed a review of the methods used in practice in recent IPD meta-analyses of randomized trials in health care.

Methods

Identification of meta-analyses

We sought recently published meta-analyses of randomized trials of health care interventions that sought individual patient data, whether or not they were performed as part of a systematic review. The following five electronic databases were searched from 1990 to 2001: MEDLINE, The Scientific Citation Index, Embase, the Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects; the latter two form part of The Cochrane Library.

The search strategy had three parts: a standard search strategy to identify randomized trials [14], a sensitive search to identify meta-analyses and systematic reviews and a simple sensitive search to identify papers concerned with individual patient data. These three searches were combined to provide a sensitive search for IPD meta-analyses of controlled trials. The results of the searches from the five databases were combined in reference management software and obvious duplicates removed. Two independent reviewers examined all titles and abstracts to remove those clearly not related to IPD meta-analysis. An agreed shortlist of potentially relevant papers was further checked and duplications combined or removed as appropriate.

Data extraction and analysis

For the detailed study of the methodology used in the IPD meta-analyses we extracted information from the full text of the papers from the three years 1999–2001 (the most recent years prior to the start of the study). The following information was extracted by two independent reviewers using a form designed and agreed in advance. Discrepancies were resolved by discussion to reach a consensus. Information on statistical methods was collected only for the analysis of the primary outcome, as defined by the authors, or that outcome which was considered most extensively in the paper.

- Medical field and type of intervention.
- Context of meta-analysis (e.g., a systematic review, or a meta-analysis of readily available trials).
- Numbers of trials from which IPD were sought, and obtained.
- Numbers of patients for whom IPD were sought, and obtained.
- The outcomes studied and their data type (e.g., binary data, time-to-event data).
- Whether the analysis was on an intention-to-treat basis.
- Method of analysis of the primary treatment effect: whether by a one- or two-stage method; assumptions of common effect or random effects across studies; use of covariate adjustment; and details of method(s) used.
- Method of analysis of any covariates: whether by one- or two-stage method; methods for trial- or patient-level covariates; assumptions of common effects or random effects; and details of method(s) used.
- Considerations of missing data (both whole studies or missing participants within studies), use of software and other interesting methodological issues.

Results

The electronic search yielded a total of 3800 papers, which were reduced to 231 after obviously irrelevant papers were discarded. A further assessment and removal of duplicates reduced this to 144, for which we obtained the full papers. Ninety-eight fulfilled the inclusion criteria. IPD meta-analyses were rare before 1993, with only six publications identified

in 1991–1992, after which time they have gradually increased in number, with 16 publications during 1993–1995, 33 during 1996–1998 and 43 during 1999–2001. A further publication from 2001 was brought to our attention by a referee [15]. Based on subsequent searches, we estimate that the current publication rate is about 20 per year.

The 44 published during 1999–2001 were the subject of further study [15–58]. These were concentrated in major areas of public health concern, with cancer and cardiovascular conditions dominating. Of the 44 publications, 16 were meta-analyses of cancer trials, including colorectal, breast and lung cancer and leukaemia [18,22–24,30–32, 35,39,45–50,52,56]; 10 publications studied cardiovascular conditions including cardiac arrest, hypertension and stroke [21,25,36,38,40–42, 44,49,51]; six publications studied areas of mental health including epilepsy and depression [28,33,43,54,55,57]. The remaining 12 publications were in other areas. Thirty-seven publications were systematic reviews which aimed to obtain all the trials in the given medical field, five were "opportunistic" analyses, where an analysis was conducted on data readily available to the investigator [21,25,28,33,54], and two were a reanalysis of a previous meta-analysis [15,56]. Two of the opportunistic analyses were supported by, and used data provided by, pharmaceutical companies [33,54].

Numbers of trials and patients

Figure 1 illustrates the variation in the number of trials from which IPD were obtained in each of the 44 meta-analyses. These range from six meta-analyses of only two or three trials [21,22,25,36,38,52], to four with more than 40 trials [30,32,47,48]. The number of patients

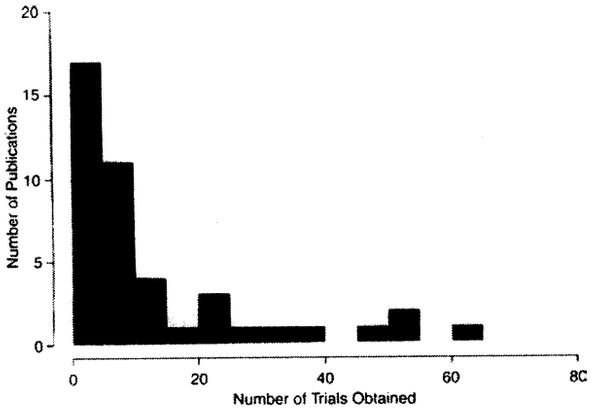

Figure 1 Number of trials from which IPD were obtained in 44 IPD meta-analyses published during 1999–2001 (unclear in one meta-analysis)

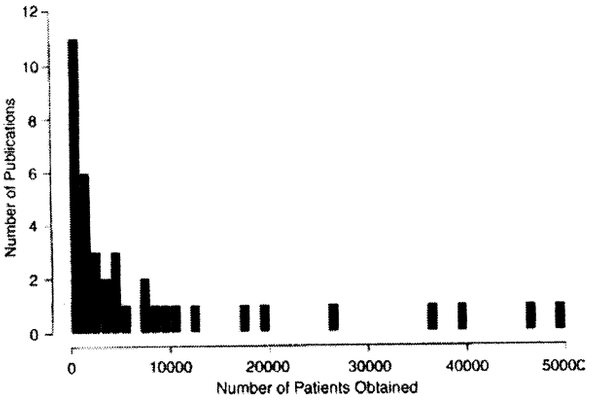

Figure 2 Number of patients from which IPD were obtained in 44 IPD meta-analyses published during 1999–2001 (unclear in four meta-analyses)

obtained also shows the wide variation in the size of the meta-analyses (Figure 2). Five meta-analyses had fewer than 500 patients, and five had more than 20 000. Four papers did not state how many patients were included in the analysis [20,23,28,34].

IPD meta-analyses may not be able to obtain data on all the trials sought or all of the patients relevant to the question posed. Figure 3 shows the percentage of randomized patients sought whose data were obtained. Eighteen meta-analyses obtained 90% or more of the total number of randomized patients, but 11 obtained less than this. Fifteen gave no clear indication of the proportion of patients sought that were obtained.

Statistical methods

Although most papers considered more than one outcome we focus on the methods used to analyse

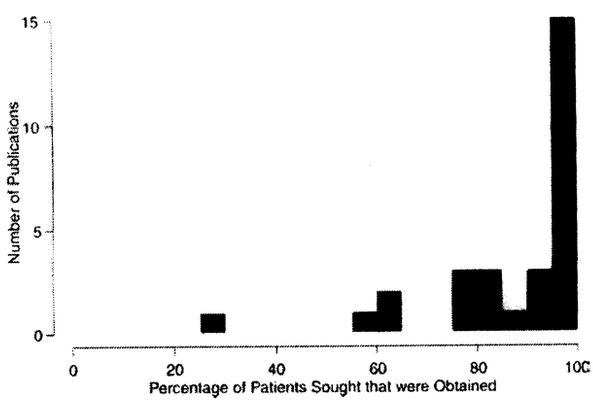

Figure 3 Percentage of randomized patients sought that were included in 44 IPD meta-analyses published during 1999–2001 (unclear in 15 meta-analyses)

Table 1 Types of data analysed as the primary outcome in IPD meta-analyses published during 1999–2001

Time-to-event	*N*	Binary	*N*	Continuous	*N*
Mortality	16	Mortality	4	Continuous scale	4
Disease-free survival	4	Other negative event	3	Rating scale	1
End of treatment	2	Positive response	6	Proportion	1
Others	2	Dichotomized scale	1		
Total	24	Total	14	Total	6

the primary outcome. The data types of the primary outcomes are given in Table 1. Time-to-event analyses predominated, although binary data analyses were also common. We did not identify any meta-analyses that included ordinal outcomes, even as a secondary outcome. A majority of analyses concentrate on mortality. All but one of the IPD meta-analyses of cancer trials analysed time-to-event data. Meta-analyses of cardiovascular conditions, and of mental health conditions, were split between time-to-event and binary data analyses.

The treatment effect

In the introduction we distinguished between one-stage and two-stage methods. For the estimate of an overall treatment effect, Table 2 shows that two-stage analyses, where trials were analysed individually and then summary statistics pooled, were by far the most common, with two-thirds of the meta-analyses using only these. Fourteen meta-analyses used one-stage modelling methods, in which all the data were analysed simultaneously.

Among those papers that used a two-stage analysis, Table 3 shows that a simple approach based on comparing observed and expected numbers of events, commonly known as the Peto method [10], was used in more than half of these analyses. There are variants of this method for analysing binary data [10], time-to-event data stratified by year [59] and time-to-event data using a log-rank approach [60]. The resulting log odds or

Table 2 General strategies used for estimating treatment effect in 44 IPD meta-analyses published during 1999–2001

Two-stage method	28 (64%)
One-stage method	6 (14%)
Both methods	8 (18%)
Unclear	1 (2%)
Not performed	1 (2%)

Table 3 Analysis method and treatment effect among 36 two-stage analyses

Analysis method		Treatment effect	
Peto	22 (61%)	Common effect	29 (81%)
Inverse-variance	6 (17%)	Random effect	4 (11%)
Mante–Haenszel	2 (6%)	Both	3 (8%)
DerSimonian–Laird	4 (11%)		
Cox (two-stage)	1 (3%)		
ANOVA	1 (3%)		

log hazard ratios are combined in a standard weighted meta-analysis. Of the 24 time-to-event analyses 20 used a form of Peto method, with eight apparently using the stratified version and 12 the log-rank version; one applied a Cox proportional hazards model to each trial and meta-analysed those results.

In the remaining meta-analyses all used a standard inverse-variance approach, adapted to the DerSimonian–Laird method if random effects were used. Overall, very few analyses used random effects methods, seven of the 36 two-stage analyses [16,25,34,35,37,44,51] (Table 3), but 29 papers presented some form of explicit test for heterogeneity across trials.

Among the one-stage methods (Table 4), regression modelling (either Cox models or logistic models) was the standard technique. Most studies used fixed trial effects; a stratified approach which allows each trial to have a different baseline. Three used the "mega-trial" approach [28,33,38], thus ignoring potential baseline differences between trials. Random effects models were very rarely used. Treatment effects (Table 4) were usually taken to be a single, common effect. Only two analyses used random effects for the treatment effect. Four analyses used fixed effects, where a distinct treatment effect is estimated for each trial.

The effects of covariates

Since most IPD analyses have both prognostic and outcome information on individuals, most also aim to explore whether the treatment effect varies

Table 4 Trial effects and treatment effects in 14 one-stage analyses

Trial effects		Treatment effect	
Fixed effects (stratified trials)	10 (71%)	Common effect	10 (71%)
Common effect (mega-trial)	3 (21%)	Random effect	1 (7%)
Unclear	1 (7%)	Common and random	1 (7%)
		Fixed effects	2 (14%)

according to baseline covariates. As with treatment effects, examinations of covariates may be divided into one and two-stage strategies. One-stage methods include covariate adjustment and inclusion of interaction terms in a model. Two-stage methods include subgroup analyses, meta-regression of treatment effects on study-level covariate summaries [61], or meta-analysis of interaction estimates from each trial [62]. Subgroup analyses may divide trials by study-level covariates, or divide patients within each trial into groups, say by sex, and estimate the treatment effect across trials. This results in separate meta-analyses, for example, among men and among women. A meta-analysis of interaction estimates fits a model, including an interaction term, to each trial independently. The interaction estimates from each trial are combined as in a standard meta-analysis of summary estimates. As for treatment effect, two-stage analyses were most common for estimating covariate effects (Table 5). Most papers used the same strategy for both treatment and covariate effects. Three papers did not consider covariates, restricting their analyses to the overall treatment effect.

Two-stage analyses may examine either study-level covariates – that is, factors that are fixed within trials and vary across trials – or patient-level covariates, which can vary among patients within trials. Study-level covariates might be different treatment regimens or types of control groups; patient-level covariates include age, sex and specific type of disease. Subgroup analysis was by far the most common approach used for both types of covariate (Table 6), whether by combining treatment estimates within subgroups of trials in the study-level case, or by combining within-trial subgroups of patients across trials for the patient-level case. Meta-regression was used in only one analysis [36].

Meta-analyses that used one-stage analyses for covariates did so by adding covariate adjustments and treatment-covariate interaction terms to the model used to estimate the overall treatment effect. As a result they had the same structure of fixed and common effects for study and treatment as before. All these models used common effect terms for adjustments and interactions. Two papers did not include any interaction terms [35,55]. Random effects were not used in any analysis.

Table 5 Analysis method for covariates in 44 IPD meta-analyses

Two-stage methods	26 (59%)
One-stae methods	9 (20%)
Both methods	4 (9%)
No covariate analyses	3 (7%)
Unclear	2 (5%)

Table 6 Types of two-stage analyses for study-level and patient-level covariates in 30 IPD meta-analyses

Study-level covariates		Patient-level covariates	
Subgroups of trials	16 (53%)	By-patient subgroups	24 (80%)
Meta-regression	1 (3%)	By-trial subgroups	1 (3%)
None performed	13 (44%)	Meta-regression	1 (3%)
		None performed	4 (13%)

Discussion

The number of individual patient data meta-analyses is growing steadily, although even recently this probably represents less than 5% of the total meta-analysis literature. These publications vary substantially in their size, aims, presentation and statistical methodology. This review clarifies some strengths and weaknesses of IPD meta-analyses, and where there is a need or scope for further research.

The medical fields considered in the meta-analyses we identified were primarily those of major public health concern, such as cancer and heart disease. These are fields with substantial funding and in which time-to-event analyses, describing the extent to which treatment may prolong life or prevent recurrent events, are the norm. Since meta-analyses of time-to-event data are problematic if based on published results [63] it is perhaps not surprising to find that the majority of IPD analyses were found in these areas.

Most papers reported basic information relevant to the meta-analysis, such as numbers of trials and patients, but some did not. Several failed to make a clear distinction between the number of trials from which IPD were sought and the number from which IPD were obtained. A large proportion (16 out of 44) failed to report what proportion of the total number of randomized patients were included in the analysis. Systematic reviews and meta-analyses of published data may also omit patients when these are excluded from reports of primary studies. Such omissions leave these publications open to selection bias, and the validity of their results might be questioned. These fundamental quantities should always be presented in reports of IPD and other types of meta-analysis.

Clear reporting of the statistical methods used was rare. In many papers we had to infer the precise methods used from the results presented rather than extracting them from methods sections. Phrases such as "a logistic regression was performed" or "the method of Peto was used" were frequently the only

indication in the text of the statistical methods implemented. For two-stage methods a limited selection of approaches has led to a few common standards in the meta-analysis literature. For one-stage modelling many more options exist and a one-line description is usually insufficient to describe what was done. In only one of the analyses that included one-stage models did we consider the modelling strategy to be well explained. Two could not be reviewed fully because the paper had too little detail.

Little discussion was reported on why particular methods were used, particularly in choosing between one- and two-stage approaches and using common or random effects. We suspect many choices were made largely by following the example of others. Six of the 44 meta-analyses reviewed were produced by the Clinical Trial Service Unit in Oxford, UK, and four by the UK Medical Research Council Clinical Trials Unit. Both of these groups produce large numbers of IPD meta-analyses, mostly using time-to-event analyses based on comparing observed and expected numbers of events, and both use subgroup analyses as part of their standard toolkit. Other investigators may be unaware of the availability of other approaches, or may, for consistency or from their own convictions, always perform analyses in a particular way.

In common with systematic reviews of published literature, meta-analyses of IPD should follow a specific protocol. The protocol determines which outcomes and baseline characteristics are to be collected from trialists and thence subject to meta-analysis and subgroup analysis. Few publications in our review referred to such protocols, although we are aware that they existed for some of them. Many papers had several outcomes or performed five or more subgroup analyses. Without justification (and prespecification) of outcomes and covariates chosen there is the possibility of selection bias or data dredging problems [64]. In some fields, such as cancer and heart disease, the outcomes are largely standardized. In others, outcomes reported may be based on availability of data, or even statistical significance of results. When only significant results are selected for publication papers may overestimate the importance of the results presented.

Two-stage analysis methods that mimic published data meta-analyses are by far the most common method of analysing IPD. These are comparatively straightforward to perform, and are familiar to most readers. From a purely statistical perspective two-stage methods for analysing treatment effect require full IPD only if the appropriate trial summary results are not available in the publication, or direct from the trialist. However, there are many other benefits to collecting IPD, including detailed data checking, consistency in dealing with missing data, and possible longer term follow-up of participants. For these reasons, results from IPD analyses and equivalent summary data meta-analyses can be very different [65,66].

One-stage models are considerably more flexible than two-stage approaches, since the latter may be obtained as special cases of the former. Interpretation of a one-stage model from a clinical perspective may be difficult since the methods, terminology and presentation of results may be unfamiliar. Furthermore, selection of an appropriate model to analyse the full data set is difficult. It is unclear how many studies or participants are required before multiple random effects can reliably be included in a model. One-stage models share with two-stage models the difficulty of determining whether the usual normal assumption for random effects is valid when there are few studies. Few of those papers that used one-stage models gave a clear account of their model selection procedures.

Those papers that declared any modelling strategy were largely limited to dropping covariates that were deemed non-significant. No papers considered detailed model fit criteria. Three papers failed to distinguish between trials in their model, performing a pooled, rather than a stratified, analysis, which could be seriously biased if randomization is not balanced in each trial. Stratification by trial ensures that like is compared with like [67,68] in that the inference is based on the randomization of patients within each trial.

The majority of analyses assumed common effects for treatment and also for covariates. In particular, almost all one-stage analyses assumed common effects, including two cases where random effects had been used in a two-stage analysis. The reason for this reluctance to use random effects is unclear. It may stem from ideology, from a limited knowledge of the flexibility in the statistical methods, or due to limited availability of suitable software. Multilevel modelling is technically and computationally more complicated, especially for time-to-event data, and perhaps this has deterred some authors from using random effects in one-stage models.

Random effects were even used infrequently in two-stage methods, although in this case random effects analyses are straightforward to implement. As in meta-analyses of published data [69] we observed a lack of concern for heterogeneity in general. Although 29 papers performed a test for heterogeneity of treatment effect, none quantified the impact of heterogeneity [70]. This may be because the results did not merit the use of random effects, or through belief that random effects approach is inappropriate [67]. As IPD are commonly collected precisely so covariate effects on treatment can be considered, using random effects,

or quantifying heterogeneity, may be valuable in demonstrating differences between trials that covariate effects may be able to explain. Any such *post hoc* investigations should be reported as such and should generally be interpreted with more caution than analyses of covariates that are listed *a priori*. Furthermore, a lack of clear overall heterogeneity of treatment effects does not rule out the presence of important covariate-treatment interactions.

IPD give considerable scope for investigating whether patient and trial characteristics influence the overall treatment effect, offering considerable advantages over meta-regression in this regard. The investigation of such covariate-treatment interactions was rather limited in the meta-analyses we reviewed, being almost always by performing separate meta-analyses in subgroups. Combining such subgroups (and hence patients) across trials, rather than comparing patients only within trials, may lead to inferences that are biased by confounding due to differences between trials [61]. IPD give more scope for investigating treatment covariate interactions: for example, in the consideration of continuous covariates, of multiple covariates simultaneously, and in whether covariates explain heterogeneity in treatment effect among trials. To ensure that covariate-treatment interactions are not confounded by between-trial differences, either a two-stage approach should combine trial-specific interaction terms across trials [62], or a one stage approach must allow for differences between trials in an appropriate multilevel model [12,15,71].

Our review highlighted problems with limited availability of data, with many publications obtaining IPD from less than 90% of the randomized patients. This mirrors a common problem in meta-analyses of summary data from published papers, where incomplete data may be reported, data may be reported in a form unsuitable for meta-analysis, or trials may not be published at all [72]. IPD allow more elaborate techniques for addressing missing participants' outcomes than do meta-analyses of summary data, since methods may be used that incorporate correlations between covariates and the likelihood of a missing outcome. When IPD are unavailable for whole studies, it would seem sensible to compare analyses based on published data with IPD analyses based on trials that provided IPD [73]. Requesting summary data when full IPD are unavailable could also overcome the problem. This is particularly the case if unpublished studies have been identified, but even if summary data are available in trial reports, updated summary data may be more complete, up-to-date and free of biases introduced in the publication process. There is always the possibility that IPD, and even summary data, are unavailable for reasons other than an unwillingness on behalf of the trialists (for example due to deletion of data files or corporate policies).

Few attempts were made to consider the impact of missing data. Only two papers presented a meta-analysis of published data as a comparison [19,44]. No papers reported taking the option of seeking summary results from trialists, despite the concern that ignoring missing data may lead to selection bias. Clear strategies are needed for dealing with trials from which IPD are unavailable.

Conclusion

There are many advantages of using IPD in meta-analysis: consistent analysis across studies, which is particularly important for survival data; the consideration of covariates to examine differences in treatment effectiveness across patients and trials; and the possibility of using advanced modelling strategies. Yet this review has shown that there are many areas in which IPD meta-analyses can be developed and improved, particularly in how to make best use of the data available and in how to report methods and findings. There is still much scope for developing modelling methods that incorporate heterogeneity, for example by using random effects, that are accessible and understandable. More consideration needs to be given as to how trials where IPD are not available can be included in the analysis to avoid problems of bias. When we should include random effects, and how to choose covariates for an appropriate model, also remain open questions.

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