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Review

A decade of individual participant data meta-analyses: A review of current practice

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ABSTRACT

Introduction: Individual participant data (IPD) systematic reviews and meta-analyses are often considered to be the gold standard for meta-analysis. In the ten years since the first review into the methodology and reporting practice of IPD reviews was published much has changed in the field. This paper investigates current reporting and statistical practice in IPD systematic reviews.
Methods: A systematic review was performed to identify systematic reviews that collected and analysed IPD. Data were extracted from each included publication on a variety of issues related to the reporting of IPD review process, and the statistical methods used.
Results: There has been considerable growth in the use of "one-stage" methods to perform IPD meta-analyses. The majority of reviews consider at least one covariate other than the primary intervention, either using subgroup analysis or including covariates in one-stage regression models. Random-effects analyses, however, are not often used.
Reporting of review methods was often limited, with few reviews presenting a risk-of-bias assessment. Details on issues specific to the use of IPD were little reported, including how IPD were obtained; how data was managed and checked for consistency and errors; and for how many studies and participants IPD were sought and obtained.
Conclusion: While the last ten years have seen substantial changes in how IPD meta-analyses are performed there remains considerable scope for improving the quality of reporting for both the process of IPD systematic reviews, and the statistical methods employed in them. It is to be hoped that the publication of the PRISMA-IPD guidelines specific to IPD reviews will improve reporting in this area.

Contents

1. Introduction

The aim of individual participant data (IPD) systematic reviews and meta-analyses is to obtain all the original, raw participant data from all studies on a specified topic, in order to reanalyse the data and pool it across studies. While obtaining all the original data from all relevant

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studies may be time consuming and difficult, IPD meta-analysis is recognised as having many advantages over meta-analysis based on data reported in publications, and is considered the "gold standard" for meta-analysis [1–3].

Ten years ago the first review of the practice and reporting of individual participant data meta-analyses was published in Clinical Trials [4]. At that time IPD meta-analysis was still in its early stages with numbers of publications being limited before the late 1990s. The development of statistical methods in the area was also in its infancy, with key methods papers having been published only a few years before [5–7]. The review found that reporting of the processes of IPD meta-analyses was generally poor, particularly with regard to how much of the total IPD was obtained for analysis, and with poor reporting of statistical methods. Statistical analysis was also limited, with little investigation of heterogeneity, and most meta-analyses focussing on calculating overall treatment effects, with little consideration given to subgroup analyses, or how factors such as a participant's age might modify the effectiveness of a treatment. Another review performed in 2008 and published in 2010 [8] came to broadly similar conclusions.

In the ten years since that first review was published much has changed. The number of systematic reviews and meta-analyses published continues to grow, and consequently IPD meta-analysis has also grown in popularity. Advances in computing have also made meta-analyses easier to perform; most methods for IPD meta-analysis can now be implemented in all major statistical software packages. As the number of IPD meta-analyses grows there is an increased need to ensure high quality of conduct reporting of these analyses, to avoid some of the problems identified in the original review.

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [9] is widely used as guidance on how to report a systematic review and meta-analysis. Recently a new PRISMA-IPD statement has been released specifically to guide the conduct and reporting of IPD reviews and meta-analyses [10]. As part of the process of creating this statement, a review of current practice in reporting of IPD reviews was conducted to identify areas where reporting was poor to inform development of the guidance. This paper presents the results of this review, updated to 2014, and expanded to consider statistical methods used in IPD meta-analyses.

2. Methods

The aim of this review was to identify published systematic reviews of medical interventions that sought to obtain and meta-analyse IPD. It was intended to obtain a representative sample of recent reviews for analysis, rather than find all such reviews, so an exhaustive database search was not performed. A MEDLINE search was performed including terms "individual participant/patient data", "meta-analysis" and "systematic review". This search was originally performed in January 2013 and was updated in February 2015. Papers published from 2008 (when the previous review in this field by Riley et al. was performed (8)) up to the end of 2014 were sought.

Only systematic reviews of IPD were included, so we did not include "opportunistic" analyses (where the reviewers combined data to which they had access) or collaborative reviews (where data from several collaborators was combined without performing a formal systematic review). Other reasons for exclusion were: papers that did not consider a medical treatment (e.g. epidemiologic reviews of the causes of a disease, diagnostic test accuracy reviews and reviews of disease prognosis), and papers not published in English. One reviewer reviewed titles and abstracts. For those considered potentially eligible the full text was sought. Where full text could be obtained the paper was further checked for eligibility.

For all eligible papers one reviewer extracted a range of data covering the reporting of the review (such as reporting of medical field, numbers of included studies, whether quality assessment was performed); the statistical methods used (such as outcomes considered, whether one or two stage methods were used, descriptions of methods, and assessment of heterogeneity); reporting of results (how many outcomes reported, how many were statistically significant, reporting of subgroup analyses or meta-regression, use of forest plots). The data extracted from the publications was analysed by creating suitable summary tables and graphs.

3. Results

The original and updated search together identified 1371 potentially relevant records. After checking titles and abstracts 184 papers were considered for inclusion. After obtaining full texts (where readily available) and further checking, 100 systematic reviews of IPD were included in this review [11–110]. Because a specific rather than a sensitive search was used, and because we include only systematic reviews, these represent only a minority of all IPD meta-analyses performed. For comparison, in 2014 there were 68 references that matched "Individual participant/patient data meta-analysis" in MEDLINE, not all of which will be IPD meta-analyses. These remain a small minority of meta-analyses as a whole; 6020 papers were tagged as meta-analyses in MEDLINE in 2014.

In the sample considered here, the numbers of reviews per year varied from 10 to 22, but there was no evidence of a trend over time, suggesting that the use of IPD analysis has stabilised in recent years. Fig. 1 shows the medical field in which the reviews were conducted. As in the review published in 2005, cancer and cardiovascular disease predominate. IPD methods appear to be gaining popularity in other fields such as paediatrics and mental health, but numbers remain small. Fig. 2a shows the number of studies for which IPD was obtained, and Fig. 2b the total number of participants providing IPD, across the reviews. Sizes vary considerably from two studies to 78 (median 8), and from 64 to 70,528 participants (median 1879).

4. Quality of reporting

The included reviews varied considerably in how they reported aspects of the review process, such as the search strategy, and quality assessment process. The numbers of reviews reporting key aspects of the IPD review process are summarised in Table 1. In general, aspects of the review process common to all systematic reviews were well reported, with, for example, 80% of reviews reporting details of the search strategy and search process. Inclusion and exclusion criteria were also generally clearly described. One area that was not widely reported was risk-of-bias or study quality assessments, despite this being a component included in the PRISMA statement. Only 34% of reviews reported performing any risk-of-bias assessment, and only 65% (22 of 34) of those reported the findings of the assessment in any detail.

Aspects of reporting specific to IPD reviews were generally rather poorly reported. Only 48% of reviews explained why an IPD review was performed, rather than a review based on published data. Only 52% described how the IPD was obtained, and for most that did it was described simply as "by contacting the study authors" or with a similar phrase. Only 33% of reviews reported that any checking of the IPD was performed to ensure consistency or identify data errors. Just 23% of reviews described why IPD was unavailable where they could not obtain IPD from all relevant studies. The most common reasons given were inability to contact authors, non-cooperation of study authors, and loss of original data.

One aspect of IPD reviews identified as being particularly poorly reported in the 2005 paper was the numbers of studies and participants from which IPD was sought, but not necessarily obtained. As in 2005 this still appears to be poorly reported: 24% of reviews did not report how many studies were sought, and 56% did not report the total number of participants sought. Of those that did report these data, most reported that they obtained all the studies (45% of such reviews) and/or all participants (58%).

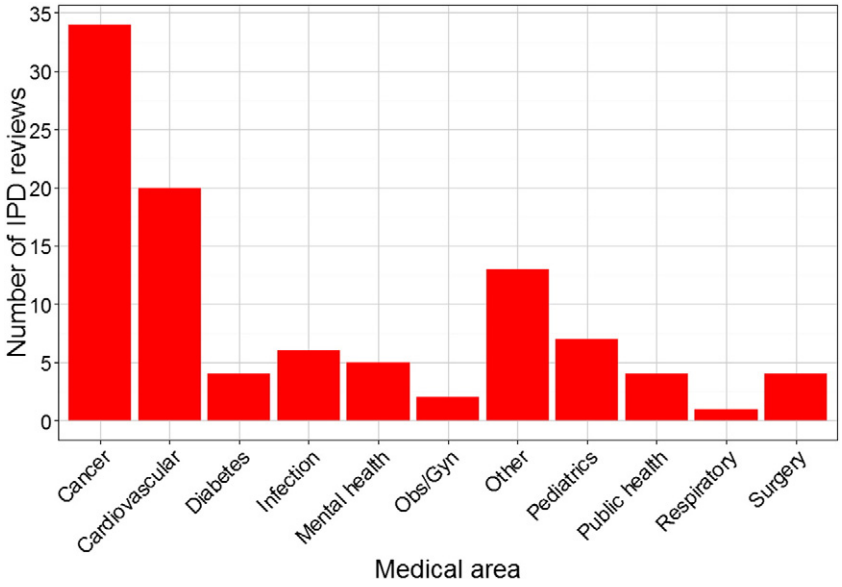

Fig. 1. Distribution across medical fields in the IPD reviews.

5. Statistical methods

The review of 2005 identified two distinct statistical approaches for IPD meta-analysis [4]. In a two-stage approach studies are analysed individually to obtain summary results for each study in the first stage, and the summary results pooled across studies as in a conventional meta-analysis in the second stage. In a one-stage approach all data from all studies are analysed simultaneously, in a single model, usually a regression model. This distinction in approaches remains in current practice.

Table 2 shows the distribution of methods used according to the type of primary outcome in each review. In the 2005 review two-stage methods predominated, being the method used in over two-thirds of reviews. The situation has changed dramatically, with just 26% of reviews using only two-stage methods. One-stage methods are now more popular, being used exclusively in 37% of reviews. This is particularly true of reviews of dichotomous or continuous outcomes, where 51% of reviews used only one-stage methods. The most commonly used one-stage approaches are the use of logistic and linear regression models to pool data across studies. This change is probably explained by growing familiarity with one-stage methods among reviewers, and improved software to perform them. Two-stage methods remain more popular in analyses of survival data; 76% of survival analyses used two-stage methods. This may be because statistical methods for one-stage analyses of survival data are less well developed and little software is available. Two-stage methods are particularly common in reviews of cancer treatment; 79% of such reviews used two stage methods. In IPD reviews of cancer trials two-stage methods based on the log rank test are well-established and remain the most commonly used statistical method [111].

Description of statistical methods was often poor, with 36% of papers deemed not to have described the statistical methods used (see Table 3); six were described so poorly it was not possible to tell what type of outcome was used or whether analyses were one or two-stage. One-stage methods were in general more poorly described, perhaps because of the greater complexity involved in describing properties of regression models. Even where the methods were judged to have been described this description may have been limited. For example, one-stage regression models were often described simply as “a logistic regression model was used…”, with no further clarification as to the

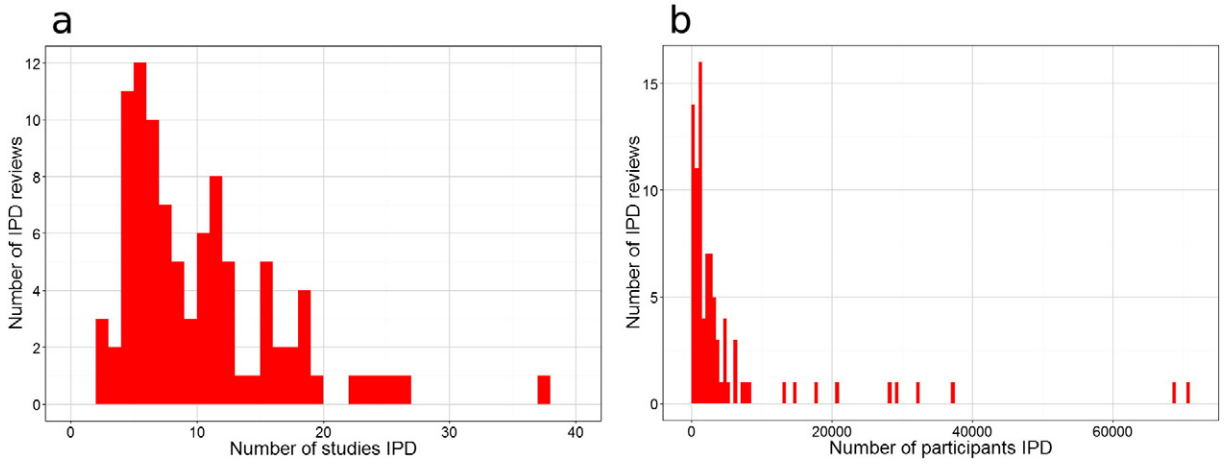

Fig. 2. Distribution of numbers of studies and participants.

Table 1
Reporting quality in the IPD reviews.

	Number reporting		Number reporting
Rationale for using IPD	48	IPD checking process	33
Details of search	80	Results of IPD checking	8
How IPD was obtained	52	Whether missing or incomplete IPD was sought	11
Risk-of-bias or quality assessment	34	Reasons for non-availability of IPD	23
Results of quality assessment	22		

structure of the model. Only in a minority of cases did we consider that a reader could readily replicate the one-stage analyses performed in the reviews. The use of the actual terms "one-stage" and "two-stage" to describe IPD methods appears to be growing in popularity, but these terms were used in only a minority of reviews.

Table 4 summarises the use of fixed and random effects and reporting of heterogeneity. Only 33% of all reviews used random-effects analyses. This is a greater proportion than in 2005, but small compared to the widespread use of random-effects methods in published data meta-analyses. Most analyses of survival data used fixed effect models (84%), because this remains conventional in analyses of cancer survival. The choice between fixed and random effects was more evenly balanced for other outcomes, across one-and two-stage methods and in medical areas other than cancer. Assessments of heterogeneity were rarely reported. Only 18% of studies reported I^2, and 24% Cochran's Q test. Heterogeneity estimates were rarely reported in papers using one-stage regression models; just four reviews using one-stage models reported the heterogeneity in these models.

IPD meta-analysis, because it provides access to full data on every participant, is often used to go beyond estimating the overall treatment effect to investigate how covariates such as participant age might modify the effect. A summary of how covariates were considered across reviews is given in Table 5. Unlike in 2005, the majority of reviews (72%) examined how covariates might influence the effect of the intervention. In two-stage analyses subgroup analysis was most commonly used, either by dividing trials into groups or dividing participants within trials into subgroups. Only three reviews used meta-regression. One review estimated interactions between treatment and covariates within each study and pooled these results across studies. In one-stage analyses, most papers reported including covariates in the one-stage regression model (21 reviews), although exactly how this was done was rarely reported.

As IPD may not be obtained for all studies combining IPD with published results may be important. However only 14 of the 66 reviews that were missing at least some IPD made any attempt to combine IPD and published data. Nearly all of these used a two-stage approach (11 reviews), pooling summary estimates from publications with summary results derived from the IPD.

When reporting results and outcomes, most papers (77%) reported more than one outcome, and of those 68% of reviews reported at least one result that was not statistically significant. Similarly, when investigating the impact covariates such as age had on the treatment effect, most papers (56%) reported results of multiple subgroup analyses, or findings from multiple covariates in one-stage models. The subgroup analyses or interaction terms were rarely statistically significant; only 25 reviews identified any statistically significant covariate effects. This suggests that there is little selective reporting bias in IPD reviews. Most reviews presented some results in forest plots, with 75% of reviews using a two-stage analysis presenting a forest plot for at least one outcome, although most reviews presented forest plots for only a subset of all the outcomes reported. Similarly 64% of reviews that used a two-stage subgroup analysis to assess the impact of covariates presented a forest plot of the subgroup analysis for at least one covariate.

6. Discussion

Much has changed in IPD systematic reviews and meta-analyses in the last ten years. The most notable change is the switch from a predominance of two-stage methods, where studies are analysed separately and summary results poled across studies; to one-stage methods where all IPD are analysed simultaneously. This is probably driven by growing familiarity with these methods, improved software, and recognition that regression models offer the greatest flexibility for IPD analysis. Another key change is the growth in analyses of covariates other than treatment. The ability to examine how factors such as age can impact on treatment effectiveness has long been recognised as a benefit of IPD analysis, but up to 2005 it was little used. Now the majority of reviews consider at least one covariate other than treatment, either using subgroup analysis or including covariates in one-stage regression models.

In other areas there has been less change. IPD reviews remain a tiny minority of systematic reviews and meta-analyses, and most are still performed on cancer or cardiovascular disease trials. This might change if IPD become more readily available as a result of current initiatives to increase access to, and sharing of, clinical trial data. Poor quality of reporting, particularly of statistical methods, remains an issue, although there have been some improvements in this.

This review found that IPD systematic reviews were generally good at reporting the basic processes of a systematic review such as searching and inclusion criteria. One area of weakness was a lack of risk-of-bias assessment, despite this being explicitly required in the PRISMA guidance. Although the analysis of IPD can reduce some risks of bias, such as selective reporting (because data on all outcomes are collected from included trials not just those that were reported in the trial publication) or poor randomisation (by adjusting for covariates which were not balanced across groups), it cannot remove all potential biases, such as a lack of blinding. Hence considering risk of bias in an IPD review is important and should be performed in all such reviews. Much of a risk-of-bias

Table 2
Type of outcomes and main statistical approach used.

Statistical approach	Primary outcome				Total
	Dichotomous	Continuous	Survival	Other	
One-stage	14	13	10	0	37
Two-stage	6	5	15	0	26
One-stage and two-stage	9	3	19	0	31
Unclear	2	1	1	2	6
Total	31	22	45	2	

Table 3
Summary of quality of description of statistical methods.

Statistical approach	Quality of description of methods	Number of reviews
One-stage	Methods described	27
	Not described	10
Two-stage	Methods described	20
	Not described	6
One-stage and two-stage	Both described	17
	One-stage not described	8
	Two-stage not described	4
	Neither described	2
Unclear		6

Table 4
Summary of heterogeneity assessment across reviews.

	Statistical approach			Total
	One-stage	Two-stage	Both	
Fixed vs random effects				
Fixed effect	23	17	21	61
Random effects	14	9	10	33
Reporting of heterogeneity				
I^2	7	6	5	18
Cochran's Q (without I^2)	4	11	9	24
From one-stage model	3	–	1	4
Other	0	1	1	2
Not reported	23	7	15	45

assessment can be performed or supplemented by examining the IPD itself, but this has not been done in practice. The IPD reviews identified often did not report much detail on issues specific to the use of IPD, including explaining the benefits of using IPD; how IPD was obtained, managed and checked for consistency and errors; and how for how many studies and participants IPD were sought and obtained. These are all issues which should be discussed in any IPD review.

Reporting of statistical methods could also be improved in many reviews. Where two-stage methods were used they were mostly described adequately, as they generally used methods familiar from meta-analyses of published data. One-stage models, however, were generally poorly described, and simply noting that a logistic regression model, or similar, was used should not be considered sufficient. Ideally, all descriptions of one-stage models should clearly state the following: how models were stratified by study to preserve distinctions between studies and to preserve randomisation; whether models were adjusted for baseline factors, and if so, which ones; how treatment was modelled; whether any interactions between treatment and other covariates were included; whether random-effects were included and, if so, on which model terms. The presentation of a formal model specification, or sample computer code, may aid substantially in understanding how one-stage models are used.

Reporting of the results of one-stage analyses could also be improved. Reporting regression coefficients from the model, as was common in the included reviews, may be difficult to interpret. Using two-stage methods for part of the analysis, for example, in order to present a forest plot of the primary outcome with an assessment of heterogeneity, may aid understanding in IPD reviews. One-stage models could then be used for the more complex modelling processes, such as for investigating the impact of covariates on efficacy.

Assessing heterogeneity and performing random-effects meta-analyses have become commonplace in meta-analyses of published results, so it perhaps surprising that they are so little used in IPD analyses, with fixed effect analyses being in the majority, although some reviews may have considered random effects methods but not reported them because no heterogeneity was identified. Where IPD reviews intend to investigate how covariates might alter the effectiveness of an intervention, assessing heterogeneity to identify differences across studies and participants should be considered a priority.

Table 5
Summary of analyses of covariates.

	Number of reviews
Any analysis of covariates	72
Any two-stage analysis	50
Subgroups of studies	29
Subgroups of participants	36
Meta-regression	3
Within-study models including covariates	1
Covariates included in one-stage models	38

There remains considerable scope for the use of more advanced statistical modelling methods in IPD meta-analysis. Multivariate meta-analysis models, for example, are widely employed in other disciplines but appear to have no uptake in the world of clinical medicine. Comparing multiple models using stepwise regression, AIC or other model fit diagnostics is not widely used. Multiple imputation methods could assist in fitting models where there is substantial missing covariate or outcome data [112].

This review has focused on IPD systematic reviews of medical treatments. IPD meta-analysis is also popular for "opportunistic" and collaborative meta-analyses where researchers analyse IPD without performing a full systematic review. We suspect that many of the issues around reporting and use of statistical methods discussed in this paper will apply equally to these non-systematic analyses. Our database searches also found that there has been growth in the use of IPD meta-analysis in other medical areas, such as in reviews of diagnostic tests, network meta-analyses, epidemiological reviews examining the causes of disease, and reviews of disease prognosis and progression. In these last two cases one-stage regression models appear to be particularly widely used as they offer considerable flexibility when analysing non-randomised data such as data from cohort studies.

7. Conclusion

The last ten years have seen substantial changes in how IPD meta-analyses are performed, particularly with the growth of the use of one-stage regression models. There remains considerable scope for improving the quality of reporting both the process of IPD systematic reviews, and the statistical methods employed in them. It is to be hoped that the publication of the PRISMA-IPD guidelines specific to IPD reviews will improve reporting in this area [10].

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