# Meta-analysis of individual participant data: rationale, conduct, and reporting

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The use of individual participant data instead of aggregate data in meta-analyses has many potential advantages, both statistically and clinically. **Richard D Riley and colleagues** describe the rationale for this and outline how to conduct this type of study

Meta-analysis methods involve combining and analysing quantitative evidence from related studies to produce results based on a whole body of research. As such, meta-analyses are an integral part of evidence based medicine. Traditional methods for meta-analysis synthesise aggregate study level data obtained from study publications or study authors, such as a treatment effect estimate (for example, an odds ratio) and its associated uncertainty (for example, a standard error or confidence interval). An alternative but increasingly popular approach is meta-analysis of individual participant data, or individual patient data, in which the raw individual level data for each study are obtained and used for synthesis.[1] In this article we describe the rationale for individual participant data meta-analysis and illustrate through applied examples why this strategy offers numerous advantages, both clinically and statistically, over the aggregate data approach.[1 2] We outline when and how to initiate an individual participant data meta-analysis, the statistical issues in conducting one, how the findings should be reported, and what challenges this approach may bring.

## What are individual participant data?

The term "individual participant data" relates to the data recorded for each participant in a study. In a hypertension trial, for example, the individual participant data could be the pre-treatment and post-treatment blood pressure, a treatment group indicator, and important baseline clinical characteristics such as age and sex, for each patient in each study (table). A set of individual participant data from multiple studies often comprises thousands of patients; this is the case in the table, so for brevity we do not show all rows of data here.

This concept is in contrast to the term "aggregate data," which relates to information averaged or estimated across all individuals in a study, such as the mean treatment effect on blood pressure, the mean age, or the proportion of participants who are male. Such aggregate data are derived from the individual participant data themselves, so individual participant data can be considered the original source material.

## What is an individual participant data meta-analysis?

As with any meta-analysis, an individual participant data meta-analysis aims to summarise the evidence on a particular clinical question from multiple related studies, such as whether a treatment is effective. The statistical implementation of an individual participant data meta-analysis crucially must preserve the clustering of patients within studies; it is inappropriate to simply analyse individual participant data as if they all came from a single study. Clusters can be retained during analysis by using a two step or a one step approach.[3] In the two step approach, the individual participant data are first analysed in each separate study independently by using a statistical method appropriate for the type of data being analysed; for example, a linear regression model might be fitted for continuous responses such as blood pressure, or Cox regression might be applied for time to event data such as mortality. This step produces aggregate data for each study, such as a mean treatment effect estimate and its standard error. These data are then synthesised in the second step using a suitable model for meta-analysis of aggregate data, such as one that weights studies by the inverse of the variance while assuming fixed or random (treatment) effects across studies. In the one step approach, the individual participant data from all studies are modelled simultaneously while accounting for the clustering of participants within studies. This approach again requires a model specific to the type of data being synthesised, alongside appropriate specification of the assumptions of the meta-analysis (for example, of fixed or random effects across studies).

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## SUMMARY POINTS

- Meta-analysis of individual participant data involves obtaining and then synthesising the raw individual level data from multiple related studies
- Increases the power to detect differential treatment effects across individuals in randomised trials and allows adjustment for confounding factors in observational studies
- Individual participant data meta-analyses should be protocol based, clearly reported, driven by clinical questions, and used when a meta-analysis of (published) aggregate data cannot reliably answer the clinical questions
- Statistical methods for meta-analysis of individual participant data must preserve the clustering of patients within studies. Either a one step or a two step approach should be used
- Individual participant data meta-analyses are often resource intensive but can be facilitated by the collaboration of research groups

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]

Detailed statistical articles regarding the implementation and merits of one step and two step individual participant data meta-analysis methods are available.[4-10] The two approaches have been shown to give very similar results, particularly when the meta-analysis aims to estimate a single treatment effect of interest.[9 11 12] One step individual participant data meta-analyses conveniently require only a single model to be specified, but this may increase complexity for non-statisticians and requires careful separation of within study and between study variability.[9] Two step individual participant data meta-analyses are clearly more laborious, but in the second step they allow the use of traditional, well known meta-analysis techniques such as those used by the Cochrane Collaboration[13] (for example, inverse variance fixed effect or random effects approach, or the Mantel-Haenszel method).[14] Importantly, both one step and two step approaches produce results that can inform evidence based practice, such as a pooled estimate of treatment effect across studies and how the treatment effect is modified by study level characteristics (for example, dose of treatment or study location) and patient level characteristics (for example, age or stage of disease).

## Incidence of individual participant data meta-analyses over time

To assess the changes in the publication frequency of applied articles using an individual participant data meta-analysis, we performed a systematic review of the published literature. We searched Medline, Embase, and the Cochrane Library up to March 2009 using a set of search terms as described elsewhere.[15] We defined an "applied individual participant data meta-analysis" article as one describing the application and findings of a meta-analysis of individual participant data from multiple healthcare studies or multiple collaborating research groups. There was no restriction on the type of studies being synthesised. Methodological articles, commentaries, or discussion articles regarding individual participant data meta-analysis were not included.

Our review identified 383 distinct, applied individual participant data meta-analysis articles published up to March 2009 (fig 1).[15] Only 57 articles (15%) were published before 2000, after which there was a considerable rise in the number of published articles, with an average of 49 articles published a year between 2005 and 2009. This growth is most likely the result of an increased awareness of why individual participant data meta-analyses are beneficial and the initiation of collaborations of research groups specifically to perform such studies. The 383 articles focused predominately on cancer, cardiovascular disease, and diabetes, and most assessed whether a treatment or intervention was effective, often in subgroups of patients. The assessment of risk factors for disease onset or prognostic factors for disease outcome was also popular, being the primary aim in 86 (22%) of the 383 articles, which signifies a recognition that individual participant data are particularly advantageous for time to event analyses.

## When do an aggregate data meta-analysis and an individual participant data meta-analysis coincide?

In an "aggregate data meta-analysis," researchers try to replicate the two step approach to meta-analysis of individual participant data. In the first step, suitable aggregate data are extracted from the study publications or obtained directly from the study authors to allow the second step to be implemented. For example, a treatment effect estimate and its standard error are sought from each study for synthesis. If the required aggregate data can be obtained, a two step individual participant data meta-analysis and an aggregate data meta-analysis will be equivalent, provided other factors are equal (for example, number of patients, follow-up length, and so on).[8 9 12] Individual participant data are not needed if all the required aggregate data can be obtained in full from authors or the published papers themselves, which may save considerable time and resources. Researchers should note that the required aggregate data to extract will depend on the clinical questions and on the

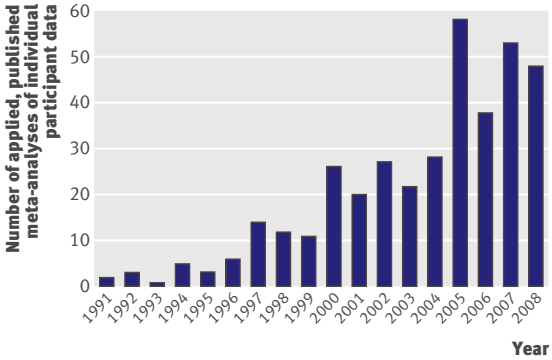


Fig 1 | Number of distinct, applied meta-analyses of individual participant data published up to March 2009,* as identified by a systematic review of Medline, Embase, and the Cochrane Library. *Six articles published in 2009 were identified up to 5 March, when the review was conducted

outcomes of interest and the most appropriate statistical measures to assess them. Thus liaison between clinicians and statisticians is crucial to identify the aggregate data needed. Also a scoping exercise, or evidence from a previous similar review, may help establish whether such aggregate data are obtainable and reliable.

### What are the advantages of a meta-analysis of individual participant data?

Meta-analysis of individual participant data has many potential advantages, both statistically and clinically, over meta-analysis of aggregate data. Aggregate data are often not available, poorly reported, derived and presented differently across studies (for example, odds ratio versus relative risk), and more likely to be reported (and in greater detail) when statistically or clinically significant, amplifying the threat of publication bias and within study selective reporting. On the contrary, having individual participant data facilitates standardisation of analyses across studies and direct derivation of the information desired, independent of significance or how it was reported. Individual participant data may also have a longer follow-up time, more participants, and more outcomes than were considered in the original study publication. This means that individual participant data meta-analyses are potentially more reliable than aggregate data meta-analyses, and the two approaches may lead to different conclusions.

### What are the disadvantages of a meta-analysis of individual participant data?

Meta-analysis of individual participant data is not without its disadvantages. In particular, this approach is resource intensive, because substantial time and costs are required to contact study authors, obtain their individual participant data, input and "clean" the provided individual participant data, resolve any data issues through dialog with the data providers, and generate a consistent data format across studies. For example, Ioannidis et al[22] undertook an individual participant data meta-analysis in 2002 that required 2088 hours for data management, with 1000 emails exchanged between study collaborators and the data managers. The required costs and time will clearly vary depending on the complexity of the analysis and the number of studies involved,[27] and such factors need serious consideration before embarking on an individual participant data meta-analysis or when applying for grant income. In particular, resource requirements must be considered for both the team conducting the individual participant data meta-analysis and the original study authors themselves. The latter group is often neglected, but cooperation of the original study authors is crucial to the success of the project and these individuals will often commit many hours "cleaning" and updating their data and resolving ongoing queries.

The individual participant data approach may also require advanced statistical expertise, and there may be ethical or confidentiality concerns about using patient level data. In our experience, individual participant data meta-analyses usually have the same objectives as the original studies, for which ethical approval should exist; however, this must be verified and, if in doubt, advice or approval must be sought from an ethics committee. When asking for individual participant data, researchers should stipulate that individuals' names and contact details must be erased from the data before they are supplied, so that participants can be identified only via a unique ID number interpretable solely by the original study authors.

Although a high proportion of the desired individual participant data can usually be obtained,[15] sometimes data are not available for all studies. Individual participant data might have been be lost or destroyed, or study authors may not be contactable or willing to collaborate. An individual participant data meta-analysis may then be biased if the provision of individual participant data is associated with the study results. In such a situation, it is important to examine any differences between studies that provided individual participant data and studies that did not provide individual participant data, and, if possible, consider whether the conclusions of the meta-analysis might change if those studies not providing individual participant data had been included. Meta-analysis methods for combining individual participant data with aggregate data are available for this purpose.[9 15] In many situations, however, such as the assessment of differential treatment effects across individuals,[9] aggregate data will add very little to an individual data meta-analysis and serve only to amplify why individual participant data was desired.

It is also important to recognise that the quality of individual participant data is dependent on the quality of the original studies themselves, and that the studies providing data are not necessarily of the highest quality. A meta-analysis of individual participant data from a set of poorly designed trials with many potential sources of bias is as deficient as a meta-analysis of aggregate data from these trials. Individual participant data meta-analyses should thus also include a quality assessment of the original studies and, if appropriate, make clear how the inclusion of lesser quality studies impacts on conclusions. If only low quality studies exist, it may be better to initiate a prospective individual participant data meta-analysis.

### How to obtain individual participant data for a meta-analysis

Two crucial steps toward undertaking an individual participant data meta-analysis are deciding how much individual participant data are needed and obtaining the individual participant data themselves. One option is to adopt a systematic review approach, where all relevant published and unpublished studies are identified through a transparent, systematic search, and then study authors are contacted to provide the individual participant data. Authors may be more willing to agree if the clinical and methodological reasons for requiring the individual participant data are clearly outlined, preferably via a face to face meeting. It may also help to promise regular updates on the results of the individual participant data meta-analysis and provide the incentive of

joint authorship on subsequent publications. Patience, politeness, and good communication are essential.

Another option is to collaborate with other research groups and agree to pool resources to answer specific clinical questions. For example, members of the receptor and biomarker group within the European Organisation for Research and Treatment of Cancer provided 18 datasets for an individual participant data meta-analysis of prognostic markers in breast cancer.[28] Such meta-analyses can also be updated prospectively as new data become available from collaborators. One concern, however, is that studies within the collaboration may not reflect the entire set of existing studies, potentially introducing bias. It is thus important for collaborations to be inclusive. For example, one individual participant data meta-analysis by the Early Breast Cancer Trialists' Collaborative Group involved over 400 named collaborators,[29] who commendably provided individual participant data for 42 000 women from 78 randomised treatment comparisons.

## Reporting individual participant data meta-analyses

A review of 33 applied individual participant data meta-analyses from between 1999 and 2001 noted that "clear reporting of the statistical methods used was rare" and that only a few studies actually referred to a protocol for their individual participant data project.[3] Clearly these shortcomings must be addressed. Like all good research, meta-analyses of individual participant data should be protocol driven and conducted with clear and prespecified objectives. Studies should also be clearly reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[30] or Meta-analysis Of Observational Studies in Epidemiology (MOOSE)[31] guidelines for meta-analyses of randomised controlled trials and observational studies, respectively.

## An applied example of an individual participant data meta-analysis of hypertension trials

An individual participant data meta-analysis of 10 hypertension trials was conducted with the objective of estimating the effect of a treatment on systolic blood pressure.[9 32] The applied one step and two step individual participant data meta-analysis models used are described fully elsewhere.[9] Briefly, they involve fitting linear regression models that estimate the treatment effect on systolic blood pressure, having adjusted for systolic blood pressure at baseline. This "analysis of covariance" approach is the most appropriate method for analysing the change from baseline in a continuous variable[33] because it gives the most precise and least biased estimate of treatment effect. It is very difficult to undertake an analysis of covariance meta-analysis without individual participant data because individual studies analyse and report a change from baseline in a heterogeneous fashion.[34]

The one step and two step individual participant data meta-analyses gave identical results. The pooled treatment effect was estimated at −10.16 (95% CI −12.27 to −8.06), indicating that hypertension treatment reduced systolic blood pressure by, on average, 10.16 mm Hg compared with controls. There was also, however, a large between study variance of 7.13, indicating that the treatment effect varied considerably across the trials. A 95% prediction interval[35] for the underlying treatment effect in a new trial was estimated as −16.69 to −3.63. This range indicates that although there is heterogeneity among trials, in any single trial hypertension treatment is effective at reducing systolic blood pressure.

Availability of individual participant data in this example also allowed a reliable and powerful assessment of how patient level characteristics modify the treatment effect. For example, a one step individual participant data analysis showed no clinically important difference in treatment effect between men and women. In contrast, if only aggregate data had been available, the analysis would have wrongly indicated a clinically important treatment effect difference in favour of women (fig 3).[9] A one step individual participant data analysis also revealed a non-linear effect of age on the treatment effect. Up to the age of 55 years, the treatment effect increased for each year increase in age; however, after 55 years there was no evidence of differential treatment effects according to age.[9] This finding was not detectable without individual participant data.

## Conclusions

The decision to undertake an individual participant data meta-analysis should be driven by the clinical questions of interest and whether a meta-analysis of (published) aggregate data can reliably answer them. In many situations an individual participant data meta-analysis will offer considerable advantages, both statistically and clinically, over a meta-analysis of aggregate data, which is why individual participant data approaches are increasingly being applied.

Important challenges remain, however, not least the task of obtaining the individual participant data itself. Detailed commentaries exist regarding the often laborious and expensive process of retrieving and processing individual participant data.[22 36] Ways of addressing this difficulty include storing individual participant data in a central repository or on the internet,[37] but perhaps most crucial is the initiation of collaborations across research groups in each field. Even when individual participant data are fully available, obstacles may still remain because studies are usually collated retrospectively. Completed studies may be of poor quality (for example, poorly designed with selection biases), may not have recorded important variables, or may have used outdated treatment strategies.[38] For such reasons prospectively planned individual participant data meta-analyses have been advocated. This technique is similar to undertaking a multicentre trial, except it allows variations in the protocols of included studies. This approach maximises the power of the meta-analysis by achieving consistency in, for example, treatments received, outcomes assessed, variables collected, and how data are recorded. Prospectively planned meta-analyses are achievable[39] but currently few have been completed, so it would be encouraging to see growth in the use of this method.

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## ENDPIECE

# Life and sex

Life is a sexually transmitted disease, and the mortality rate is one hundred percent.

R D Laing (Scottish psychiatrist, 1927-1959),In: Burston D. *The Wing of Madness: the Life and Work of R D Laing*. Cambridge, MA: Harvard University Press, 1996

Submitted by Alistair Tindall, *orthopaedic specialist registrar, London*

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