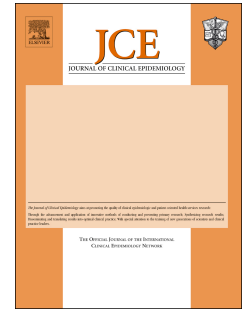


# Accepted Manuscript

How individual participant data meta-analyses have influenced trial design, conduct and analysis

Jayne F. Tierney, Jean-Pierre Pignon, Francois Gueffier, Mike Clarke, Lisa Askie, Claire L. Vale, Sarah Burdett



PII: S0895-4356(15)00268-1

DOI: [10.1016/j.jclinepi.2015.05.024](https://doi.org/10.1016/j.jclinepi.2015.05.024)

Reference: JCE 8898

To appear in: *Journal of Clinical Epidemiology*

Received Date: 10 October 2014

Revised Date: 15 April 2015

Accepted Date: 27 May 2015

Please cite this article as: Tierney JF, Pignon J-P, Gueffier F, Clarke M, Askie L, Vale CL, Burdett S, On behalf of the Cochrane IPD Meta-analysis Methods Group, How individual participant data meta-analyses have influenced trial design, conduct and analysis, *Journal of Clinical Epidemiology* (2015), doi: 10.1016/j.jclinepi.2015.05.024.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Jayne F Tierney<sup>1</sup>, Jean-Pierre Pignon<sup>2</sup>, Francois Gueffier<sup>3</sup>, Mike Clarke<sup>4</sup>, Lisa Askie<sup>5</sup>, Claire L Vale<sup>1</sup>, Sarah Burdett<sup>1</sup>

On behalf of the Cochrane IPD Meta-analysis Methods Group

<sup>1</sup> MRC Clinical Trials Unit at UCL, Aviation House, 125 Kingsway, London WC2B 6NH, UK

<sup>2</sup> LNCC plateforme de méta-analyse en oncologie, Service de Biostatistique et d'Epidemiologie, Gustave-Roussy, Villejuif, France

<sup>3</sup> Université Claude Bernard Lyon I / Université de Lyon, 69365 LYON CEDEX 07, Lyon, France; Hospices Civils de Lyon, Service de Pharmacologie Clinique, Bron cedex, France

<sup>4</sup> All-Ireland Hub for Trials Methodology Research, Queen's University Belfast, University Road, Belfast, BT7 1NN, Northern Ireland, UK

<sup>5</sup> NHMRC Clinical Trials Centre, ABN 15 211 513 464, Locked Bag 77, Camperdown, NSW 1450 Australia

Corresponding Author  
Jayne F Tierney

Email: [jayne.tierney@ucl.ac.uk](mailto:jayne.tierney@ucl.ac.uk)

Tel: 0207 670 4724

Keywords: Individual participant data (IPD), Systematic review. Meta-analysis, Trial conduct, Trial Design

Word count: 3701

## Objective

To demonstrate how individual participant data (IPD) meta-analyses have impacted directly on the design and conduct of trials and highlight other advantages IPD might offer.

## Study design and setting

Potential examples of the impact of IPD meta-analyses on trials were identified at an international workshop, attended by individuals with experience in the conduct of IPD meta-analyses and knowledge of trials in their respective clinical areas. Experts in the field, who did not attend were asked to provide any further examples. We then examined relevant trial protocols, publications and websites to verify the impacts of the IPD meta-analyses. A subgroup of workshop attendees sought further examples and identified other aspects of trial design and conduct that may inform IPD meta-analyses.

## Results

We identified 52 examples of IPD meta-analyses thought to have had a direct impact on the design or conduct of trials. After screening relevant trial protocols and publications we identified 28 instances where IPD meta-analyses had clearly impacted on trials. They have influenced the selection of comparators and participants, sample size calculations, analysis and interpretation of subsequent trials, and the conduct and analysis of ongoing trials, sometimes in ways that would not possible with systematic reviews of aggregate data. We identified additional potential ways that IPD meta-analyses could be used to influence trials.

## Conclusions

IPD meta-analysis could be better utilised to inform the design, conduct analysis and interpretation of trials.

## What is new

- Systematic reviews and meta-analyses based on aggregate data can inform subsequent clinical trials, but empirical evidence of this happening is limited.

- ACCEPTED MANUSCRIPT
- Systematic reviews and meta-analyses based on IPD are international collaborative projects that often provide more detailed and reliable results, and so have greater potential to inform trials.
  - To our knowledge, this is the first attempt to explore the impact of IPD meta-analyses on ongoing and subsequent trials
  - We identified examples of IPD meta-analyses having a direct impact on trial design, conduct and analysis and interpretation, sometimes in ways that would not be possible with aggregate data.
  - IPD meta-analysis could be better utilised to inform additional aspects of design and conduct.

## Background

Systematic reviews, are recognised as the optimal way to resolve or confirm uncertainty about the effects of interventions, both informing clinical practice and providing the scientific and ethical justification for the design of new trials(1). However, empirical evidence suggests that they are still used infrequently to explain the rationale for(2-4), or directly influence the design of trials(3, 4). Systematic reviews can also be used to take account of external evidence that accumulates during the conduct of a trial, thereby ensuring that participant recruitment and any protocol amendments are informed by the accumulating external evidence, however it is not clear how often this actually happens. When a trial is completed, systematic reviews can also help place the results in the context of the results of other related trials, but this is far from standard practice(3, 5, 6).

Most commonly, systematic reviews are based on aggregate data extracted from publications or obtained from trial investigators, which can limit the availability and quality of such data. Furthermore, the range of analyses possible with aggregate data is limited and they may lack power. Instead, systematic reviews and meta-analyses that involve individual participant data (usually called IPD meta-analyses) tend to be larger scale, international projects in which researchers collaborate to collect and analyse the original data from all the studies relevant to the review question(7-9). A well-conducted IPD meta-analysis(10) can bring about substantial improvements to the quantity and quality of the data, for example, by including more eligible trials and participants, and to the analysis, by allowing the investigation of whether treatment effects vary by participant characteristics (8, 9). Thus, they often provide more detailed and reliable results, and a greater depth of understanding than is possible from aggregate data. This has led to them being coined the 'gold standard' of systematic review(11). Collated IPD also represents a unique resource for secondary hypothesis testing and exploratory analyses, which can provide further clinical insight. Thus, IPD meta-analyses have the potential to inform the design, conduct, analysis and interpretation of subsequent trials in ways that are IPD-specific, as well as in ways that would also be possible with aggregate data. This paper aims to provide verified examples of both. Given that IPD meta-analyses can take longer and be more resource-intensive than standard systematic reviews based on aggregate data, we also want to highlight how IPD meta-analyses might be better utilised to inform ongoing or new trials.

## Methods

Funders of randomised trials often require that relevant systematic reviews are cited and used in the trial funding application, and this direct linkage has allowed researchers to use cohorts of such applications to assess the impact of aggregate data systematic reviews on trial design and conduct(4).

It would not be possible to define a similar cohort of trials and trace the impact of IPD meta-analyses on these, as IPD meta-analyses are not a requirement for trial funding and remain relatively few in number. Therefore, rather than comprehensively identifying the effects of IPD meta-analyses on trials, rather we aim to provide a range of illustrative examples. Initially, we sought examples at an international workshop of 31 members of the Cochrane IPD Meta-analysis Methods Group, which took place in London in September 2012. Not only did the attendees have considerable experience in the conduct of IPD meta-analyses, but also actively collaborate with trialists as part of the IPD approach, and have valuable knowledge of trials in their respective clinical areas. In March 2015, we also surveyed the entire membership of the Methods Group to solicit further examples. Two authors (JT, SB) screened relevant trial protocols, publications and websites to verify those IPD meta-analyses that were used to support trial design and conduct (Boxes 1-3 and Table 1). A subgroup of workshop attendees (the authors) sought further examples of impact from their own experience and identified aspects of trial design and conduct that might better informed by IPD meta-analyses.

## Results

We identified 52 IPD meta-analyses thought to have had direct impacts on the design and conduct of trials. On further investigation, we could find no direct evidence of a link between 24 IPD meta-analyses and trials, but that is not to say that such a link does not exist. For five of these examples, we suspect that it was too soon after the publication of the IPD meta-analysis for a trial to have credited it. Therefore, we found 28 IPD meta-analyses giving 29 instances where the trial protocol, publication or website explicitly described how an IPD meta-analysis had influenced the trial. Sometimes more than one IPD meta-analysis contributed to an impact or more than one impact was derived from a single IPD meta-analysis. In 19 cases, these impacts would only be possible with IPD, either because the results or other aspects of their were IPD-specific (Box 1-3, Table 1). For the remaining 10, the impacts we identified might also have been possible with an equivalent aggregate data meta-analyses (Box 1, Table 1). This cohort of examples also helped highlight the ways in which IPD meta-analyses might be under-utilised in trial design and conduct.

## Impact on trial design

### *Choosing comparators*

Systematic reviews and meta-analyses based on aggregate data have the potential to influence the choice of comparators in a subsequent trial, and there is already some evidence of this(4). We found too that IPD meta-analyses showing a clear, robust and clinically relevant effect of an intervention, have been used to justify its use as a control group comparator in subsequent randomised trials

(Breast Cancer I, Table I). Even when results of an IPD meta-analysis were less definitive, but suggested that an intervention might be beneficial, we saw that this can maintain or generate interest in particular therapeutic comparisons, giving the impetus both for ongoing trials to continue and for confirmatory or trials to be conducted (NSCLC I, Table I). Instead, an IPD meta-analysis that fails to show any benefit, or shows that a therapy is harmful could provide the rationale for discontinuing its further investigation, and for the current standard therapy to remain as a control against which emerging therapies should be compared, but we did not find evidence of the overall results of a meta-analysis being used in this way. While we suspect that it is easier to justify maintaining the status quo, without explicit reference to a systematic review, ideally the current evidence should be cited.

#### *Promoting consensus and collaboration*

The collaborative group needed to conduct IPD meta-analysis often includes those investigators who have supplied their trial data, and we have found that this can facilitate consensus being reached on the design of subsequent trials (Box I). It is common practice to bring together such a group of individuals, from different clinical specialties and disciplines to discuss the preliminary results of an IPD meta-analysis and their implications. As this is often in advance of formal presentation or publication of the results, it can also help speed up the design and launch of a new trial (Box I), or even refine the design of one still in development (Soft-tissue sarcoma I, Table I). Moreover, a group of trialists are well placed to judge how a new trial might be achieved and by whom. In one example, where large-scale international collaboration was needed to achieve a trial of sufficient size (to detect a small predicted treatment effect), it was drawn from the meta-analyses collaborative group (Box I); an advantage likely restricted to the IPD approach.

#### *Determining sample size*

A new trial can draw on estimates of control group or baseline risk provided by a meta-analysis to give a good indication of the approximate effect size to target in trials of new or confirmatory comparisons. Examples of these sorts of impact are evident for both IPD (NSCLC I, Cervix I, Table I) and aggregate data reviews(4). It would be possible to interrogate the IPD further to provide estimates of baseline risk for particular types of participant, such as those who might be expected to benefit most from a new therapy, thereby helping to refine or improve the reliability of sample size calculations. Although, IPD could be used to inform predictions of trial duration and follow-up and hence, resourcing, we did not find examples of IPD meta-analyses being exploited to this extent.

#### *Defining the population*

Pooling IPD from multiple trials provides considerably more power than any individual trial to investigate how participant or disease characteristics interact with treatment effects, and uniquely, the IPD also allows the relative influence of multiple trial and participant characteristics to be considered simultaneously, which can help deal with confounding(12). Not surprisingly then, IPD meta-analyses showing interactions between treatment effects and particular participant or disease characteristics, have been used to justify focussing on particular subgroups or characteristics in subsequent trials (e.g. Hypertension I, Head and Neck I, Table I). While, being able to establish with confidence that an effect is not modified by participant or disease characteristics can reassure trialists that the inclusion criteria should remain broad for the next trial, we did not find evidence of IPD meta-analyses being used in this way.

IPD collected for a meta-analysis also provides a resource for assessing the prognostic effects of individual characteristics or for defining risk groups based on multiple prognostic factors. In particular, detailed IPD from multiple studies offers the possibility to both generate and validate prognostic models within the same meta-analysis, or to validate already established prognostic standards (Box 2), which could be used to inform the stratified randomisation procedures in subsequent trials, although we haven't found any examples of this. As aggregate data meta-analyses usually cannot be used to determine appropriately prognostic effects or interactions between treatment effects and individual participant characteristics (13, 14), we would not expect them to affect trials in these ways.

### *Choosing outcomes*

There is certainly evidence that aggregate data reviews have helped inform the choice of outcomes in new trials(4). However, a major advantage of making such decisions based on an IPD meta-analysis is that it often will include data on more outcomes per trial, and more complete information on those outcomes, and therefore, results are less likely to be skewed by the biases associated with selective reporting of outcomes(15). For example, when IPD meta-analyses establish that benefits of treatments are consistent across related outcomes, we found that it can provide extra re-assurance that a certain intervention should be used in subsequent trials (Head and Neck I, NSCLC I, Table I). In contrast, the identification of differential effects of an intervention across related outcomes, with IPD, can give a clearer picture of its mode of action and more specifically inform trial design (Head and Neck I, Table I). As under-reporting of harms of interventions is particularly prevalent in RCTs(16), it may be that an IPD meta-analysis including comprehensive data on such outcomes and so properly ascribing the risks of a therapy, is needed properly inform the design of subsequent trials. Less obvious perhaps is that the process of seeking data from multiple trials for an IPD meta-analysis can highlight not only those outcomes that were under-reported, but also those that that



ACCEPTED MANUSCRIPT  
were not collected routinely, so providing evidence on where there is room for improvement(17). However, we did not find examples of IPD meta-analyses being used to inform these sorts of decisions in new trials.

While aggregate data can be used to determine whether the effects of an intervention on a proposed surrogate and final outcome are correlated, associations between these outcomes using participant level data are considered necessary for proper surrogate validation(18). Thus, data from one or more IPD meta-analyses can be used as a resource to identify reliable surrogate outcomes, as well as those that are clearly unsuitable. In principle, this might identify shorter-term surrogates with the potential to speed up the evaluation of therapies in new trials. Alternatively, finding a reliable surrogate outcome that is more practical to measure could facilitate outcome data collection, and so improve data quality in subsequent trials. While IPD meta-analyses have been utilised to validate surrogate outcomes(19, 20), in our cohort, we did not find evidence of trials adopting such surrogate outcomes on the basis of these analyses. One possible explanation is that the treatments investigated in the new trials are different to those evaluated in prior meta-analysis, such that further validation would be necessary.

#### *Defining and collecting outcome data*

If outcomes have been defined and analysed very differently in individual trials, it may be necessary to make assumptions about their comparability or use standardised effect measures in aggregate data meta-analysis, whereas IPD offers the opportunity to translate varying outcome definitions into an agreed common scale or to generate standardised definitions from other data items(21). Thus, if an IPD meta-analysis can demonstrate the effects of a therapy based on such a common or standardised outcome definition, it provides trialists with both the rationale and motivation for adopting a standard definition in future trials. Moreover, the process of collecting IPD can reveal outcomes or outcome definitions that generate better or poorer quality data, which could also help optimise how data are defined and collected in the next generation of trials. To our knowledge, however, these advantages of IPD have not been explicitly described in the design of RCTs.

For time-to-event outcomes, a major advantage of collecting IPD is the ability to obtain additional follow-up from investigators, sometimes substantially beyond the aggregate data results reported in trial publications. While the primary aim is to provide more events and greater power for the analysis, importantly, this practice can help reveal the pattern of events over time. In particular, any benefits or harms of interventions that take a long time to accrue, such as late side effects of treatment or late recurrence of disease, can become apparent. We did find an example, where the

IPD meta-analysis highlighted the need to collect long term outcome data in subsequent trials, as well as informing the appropriate duration of data collection (Breast Cancer I Table I).

## **Impacts on trial conduct**

### *Informing the conduct of ongoing trials*

For trials that are ongoing, a prospective approach to IPD meta-analysis can offer greater collective power to produce definitive results when, for example, it has not been possible to adequately power individual trials for all of the outcomes of interest and/or there are practical or other barriers to adhering to a single trial protocol. We found the approach being adopted, when sufficiently-powered trials recruited less well than expected (Box 3, Colon cancer I, Table I), or the prognosis of the participants' was more favourable than predicted at the design stage (Box 3), so that events accrue more slowly than expected. In one example, these issues would have affected the timely completion of the individual trials, reduced their power to detect effects of therapies reliably, and jeopardised their continuation (Box 3), and the prospective decision to pool the trials has been used to encourage continued recruitment into the individual trials and justify their ongoing follow-up and funding (Box 3). Prospective meta-analysis hypotheses, inclusion criteria and analyses are defined prior to, and without influence from, the results of individual trials, which is a potential source of bias for retrospectively-designed IPD meta-analyses(22). Although individual trials often run according to their own protocols and timetables, there is also the potential for the proposed meta-analysis to directly influence the day-to-day running of the individual studies. For example, we found investigators aligned trial materials and procedures (Stroke I, Pre-term neonates I, Table I). A clear challenge of this approach, however, is being able to respond to the accumulating results of the individual trials, and managing their impact on the remaining ongoing trials, the collaboration and subsequent meta-analysis results.

### *Stopping ongoing trials*

In a similar way to any standard systematic review, an IPD meta-analysis that shows that an intervention is inferior to standard treatment, or harmful, should discourage further use of that intervention both in practice and in future trials. Of course, a comprehensive IPD meta-analysis may show this more definitively and reliably, or, importantly, for a certain subgroup of participants (NSCLC I, Table I).

## **Impacts on trial analysis and interpretation**

### *Informing the analyses*

Prognostic factors or risk groups identified via IPD have been used to adjust or stratify trial analyses (Box 2), as well as being used to define the population to be studied in a new trial. In addition, where an IPD meta-analysis has identified participants or disease characteristics that modify treatment effects and these are regarded as hypothesis generating, this has led to further exploration and testing in subsequent trials, for example by stratifying the analysis by these characteristics (Box 2).

### *Interpreting and reporting results*

Trial results can be readily placed in the context of the results of an existing meta-analysis using standard two-stage meta-analysis techniques, and so this is possible both with aggregate data(3, 5) and IPD. The latter does not necessarily require access to the full IPD, but rather the reported results of the IPD meta-analysis. In fact, in the examples we identified, in the trial report the trial results were combined both with the results of an existing IPD meta-analysis, and results of other trials published subsequently, to provide the totality of evidence about the effects of an intervention. Anecdotal evidence also suggests that participation in an IPD meta-analysis encourages trialists to publish previously unreported trials, or publish updated analyses.

## **Potential negative impacts on trials**

As IPD meta-analyses can take years from inception to final publication, awaiting the final results can delay the start of a new trial by a similar time frame. Moreover, if the results are in favour of or against a particular intervention, even if not definitively, they can jeopardise recruitment to ongoing trials investigating that intervention.

## **Discussion**

Through consultation with experts in the field we have identified a cohort of 29 examples of IPD meta-analyses impacting directly on trials. They have influenced the selection of comparators and sample size calculations of subsequent trials, and also been used to place trial results in context in a similar fashion to aggregate data reviews(4). In addition, we found evidence of IPD meta-analyses playing a role in the selection of participants, and the conduct, analysis and interpretation of trials, particularly in relation to subgroup or prognostic factor analyses, which would not have been

possible with aggregate data. This study also highlights that IPD meta-analyses generate information, for example, on the natural history of a disease or on the definition of outcomes that could be used to inform trials, but we have yet to find evidence of this.

To our knowledge, this is the first attempt to explore how IPD meta-analyses can impact on subsequent trials. By considering relevant trial protocols, publications and websites, we have ensured that the examples presented here are evidence based. That does not mean that other IPD meta-analyses we examined have not had an impact on trials, but rather that no direct evidence of this could be found. Having targeted a selected group of individuals with experience in the conduct of IPD meta-analyses, many with knowledge of related trials, means that the study represents only a small subset of potential impacts. Indeed many of the examples are in the cancer and cardiovascular fields, where there is a long history of using the IPD approach. In other clinical areas, the collection of IPD for meta-analysis has been a more recent phenomenon, and so it could take some time before any influence on trials becomes apparent. While the our list of examples is illustrative rather than exhaustive, it does emphasise potential missed opportunities to use retrospective or prospective IPD meta-analysis in trial design, conduct, analysis and interpretation.

Those undertaking IPD meta-analyses might maximise their impact on trials by publishing as speedily as possible, following an open access model, in order to ensure widespread availability of results. Making full use of journal online facilities and using reporting guidelines for systematic reviews based on IPD(23) should ensure such reports are sufficiently detailed and help trialists to select those IPD meta-analyses that are well-conducted(10). The outputs and recommendations in IPD meta-analysis reports tend to be focused on clinical practice, so perhaps there is a need to regard IPD meta-analyses as playing an equally important role in informing subsequent clinical research. Structuring recommendations on the direction of new research around the quality of the existing evidence, and the interventions, comparisons and outcomes(23, 24), would highlight gaps and areas for improvement. Ideally, such recommendations would draw on the spectrum of expertise found among trialists in an IPD collaborative group, who will often be key players in the next generation of trials. Further, if these collaborations could also be harnessed to plan and conduct future studies more strategically, it might avoid the duplication of effort and inadequately powered trials that remain a feature of some areas of clinical research. Greater involvement of patients and the public in IPD meta-analyses(25) could provide extra insight on which questions are important. Obviously, if the results of an IPD meta-analysis are not definitive, research recommendations should explicitly encourage recruitment to existing relevant trials, so that their continuation is not jeopardised.

Secondary analyses of the IPD, to address additional clinical questions could be potentially very informative to trialists, as well as making maximum use of the IPD collected, so making it a natural part of the process would be desirable. Certainly those conducting trials might be able to help direct this kind of research by highlighting, for example, that surrogate outcomes or potential prognostic factors need evaluating. Also, where possible, IPD meta-analysts should be amenable to requests for extra information or analyses that might help trialists refine the study design and conduct further trials.

Many trials do not appear to take prior trials(26) or systematic reviews(4) into account, so we encourage more widespread use of evidence synthesis to inform all stages of trials. Although we identified examples of IPD meta-analyses having a direct impact on trials, sometimes in ways not possible with aggregate data, the richness of the results and the underlying data, and the collaborative advantages seem to be under-utilised. The potential benefits of both retrospective and prospective IPD meta-analyses to clinical research need to be more widely recognised, especially as these projects are likely to benefit from a drive for greater sharing of data held within trials(27). Thus, wherever available, well-conducted IPD meta-analyses should be utilised to inform trials.

### **Competing interests**

The authors declare that they have no competing interests

### **Authors' contributions**

JT, JPP, FG, MC, LA, CV and SB contributed to the conception of the study. JT and SB extracted and collated the data, and wrote the first draft of the manuscript. JPP, FG, MC, LA and CV contributed to the interpretation of the results and revising of the article for important intellectual content. All authors read and approved the final manuscript.

### **Acknowledgements**

The project was funded by the UK Medical Research Council.

We thank the attendees of the Workshop on the use of IPD in systematic reviews, London, UK, 25th September 2012. Attendees were drawn from members of the Cochrane IPD Meta-analysis Methods Group and those listed contributed to discussion at the workshop and provided examples of impact of IPD systematic reviews on trials.

P Alderson, Oxford, UK; L Askie, Sydney, Australia; D Bennett, Oxford, UK; S Burdett, London, UK; M Clarke, Belfast, UK; S Dias, Bristol, UK; J Emberson, Oxford, UK; F Gueyffier, Lyon, France; A

lorio, Ontario, Canada; M Macleod, Edinburgh, UK; BW Mol, Amsterdam, The Netherlands; C Moons, Utrecht, The Netherlands; M Parmar, London, UK; R Perera, Oxford, UK; R Phillips, York, UK; JP Pignon, Villejuif, France; J Rees, Bristol, UK; H Reitsma, Amsterdam, The Netherlands; R Riley, Birmingham, UK; M Rovers, Nijmegen, The Netherlands; L Rydzewska, London, UK; C Schmid, Boston, USA; S Shepperd, Oxford, UK; S Stenning, London, UK; L Stewart, York, UK; J Tierney, London, UK; C Tudur Smith, Liverpool, UK; C Vale, London, UK; J Welge, Cincinnati, USA; I White, Cambridge, UK; W Whiteley, Edinburgh, UK

We thank the remaining members of the Cochrane IPD Meta-analysis Methods Groups for providing further examples.

We also thank the referees for their very helpful comments and suggestions, which have improved the manuscript considerably.

**Impact on trial design: Choice of comparators, and reaching consensus and collaboration on the next trial**

## The IPD meta-analyses

- Five meta-analyses comparing the effects of different types of chemotherapy for advanced ovarian cancer(28)
- One related meta-analysis comparing CAP (cyclophosphamide, doxorubicin and cisplatin) with CP (cyclophosphamide, cisplatin) chemotherapy(29)
- Together included ~50 trials, ~10 000 women
- Provided the first comprehensive synthesis of the effects of chemotherapy for advanced ovarian cancer

## The pertinent results

- Platinum-based chemotherapy better than non-platinum chemotherapy(28)
- Platinum-based combination chemotherapy better than single-agent platinum-based chemotherapy(28)
- No clear difference between the effects of carboplatin and cisplatin when used as single agents or when substituted for one another in combination regimens(28)
- CAP better than CP, but dose of cisplatin in CAP regimen sub-optimal because of toxicity(29)

## Impact on new trials

*(1) Informed choice of comparators in new trial*

- International Collaborative Ovarian Neoplasm 2 trial (ICON2) compared CAP with optimal dose carboplatin(30); the latter being less toxic than cisplatin
- In its time, ICON2 was the largest trial to be conducted in ovarian cancer and it showed definitely that carboplatin was an effective, but less toxic treatment than CAP for women with advanced ovarian cancer.
- Carboplatin was the control group comparator in the subsequent ICON3 trial(31)
- Impact may have been possible using aggregate data

*(2) Collaboration*

- Large-scale collaboration was needed to achieve a trial of sufficient size and was formed from the meta-analyses collaborative groups

- ACCEPTED MANUSCRIPT
- 1 526 patients in ICON2 were recruited by 132 centres in nine countries.
  - Collaborations and strategic planning of ovarian cancer trials (ICON 1-8) have continued long after the original meta-analysis
  - Impact only possible because of the individual participant data approach

ACCEPTED MANUSCRIPT



**Impact on trial analysis and interpretation: Validated prognostic factor used to stratify new trial analysis, which formed part of the final report**

The IPD meta-analyses

- 11 acute stroke trials, 5 843 participants fitting entry criteria(32) from the Virtual International Stroke Archive (VISTA, [www.gla.ac.uk](http://www.gla.ac.uk))

Pertinent results

- Prognostic model developed and validated using IPD
- Provided the predicted probability of a poor outcome at six months(32)

Impact on new trials

*(1) Prognostic factor analysis informed trial analysis stratification*

- Predicted probability of a poor outcome used to stratify the analysis of IST-3 trial of thrombolysis versus control
- Larger benefit of thrombolysis was seen with higher probability of a poor outcome(33)
- Impact only possible because individual participant data was used

**Impact on trial conduct: Designed prospective IPD meta-analysis of ongoing trials to achieve power and encourage continued recruitment**

The IPD meta-analysis

- Adjuvant versus salvage radiotherapy after radical prostatectomy for locally advanced prostate cancer

Three trials and ~2 000 patients

RADICALS (ISRCTN40814031), RAVES (NCT00860652), GETUG-17 (NCT00667069)

Impact on ongoing trials

*(1) To achieve power for key outcomes*

- Trials are recruiting slowly and the prognosis of participants is better than expected, so a meta-analysis will help achieve sufficient power to detect an effect on survival
- Impact only possible because of individual participant data approach

*(2) Informing the conduct*

- Used to justify and encourage continued recruitment, follow-up and funding of ongoing trials(34)

*(3) Informing the analysis*

Deciding on definition and analysis of intermediate outcomes

## References

1. Clarke M. Doing new research? Don't forget the old. *PLoS medicine*. 2004;1(2):e35.
2. Cooper NJ, Jones DR, Sutton AJ. The use of systematic reviews when designing studies. *Clin Trials*. 2005;2(3):260-4.
3. Clarke M, Hopewell S, Chalmers I. Clinical trials should begin and end with systematic reviews of relevant evidence: 12 years and waiting. *Lancet*. 2010;376(9734):20-1.
4. Jones AP, Conroy E, Williamson PR, Clarke M, Gamble C. The use of systematic reviews in the planning, design and conduct of randomised trials: a retrospective cohort of NIHR HTA funded trials. *BMC medical research methodology*. 2013;13:50.
5. Clarke M, Hopewell S, Chalmers I. Reports of clinical trials should begin and end with up-to-date systematic reviews of other relevant evidence: a status report. *J R Soc Med*. 2007;100(4):187-90.
6. Chalmers I, Altman DG. How can medical journals help prevent poor medical research? Some opportunities presented by electronic publishing. *Lancet*. 1999;353:490-3.
7. Stewart LA, Clarke MJ, on behalf of the Cochrane Working Party Group on Meta-analysis using Individual Patient Data. Practical methodology of meta-analyses (overviews) using updated individual patient data. *Stat Med*. 1995;14:2057-79.
8. Stewart LA, Tierney JF. To IPD or Not to IPD? Advantages and disadvantages of systematic reviews using individual patient data. *Eval Health Prof*. 2002;25(1):76-97.
9. Stewart LA, Tierney JF, Clarke M, on behalf of the Cochrane Individual Patient Data Meta-analysis Methods Group. Reviews of individual patient data. In: Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions* 2008. p. 547-58.
10. Tierney JF, Vale CL, Riley R, Tudur Smith C, Stewart LA, Clarke M, et al. Appraising individual participant data (IPD) meta-analyses of randomised controlled trials. *PLoS medicine*. Submitted.
11. Chalmers I. The Cochrane Collaboration: preparing, maintaining and disseminating systematic reviews of the effects of health care. *Annals of New York Academy of Sciences*. 1993;703:156-65.
12. Groenwold RH, Donders AR, van der Heijden GJ, Hoes AW, Rovers MM. Confounding of subgroup analyses in randomized data. *Arch Intern Med*. 2009;169(16):1532-4.
13. Berlin JA, Santanna J, Schmid CH, Szczech LA, Feldman HI, Anti-Lymphocyte Antibody Induction Therapy Study G. Individual patient- versus group-level data meta-regressions for the investigation of treatment effect modifiers: ecological bias rears its ugly head. *Stat Med*. 2002;21(3):371-87.
14. Fisher DJ, Copas AJ, Tierney JF, Parmar MKB. A critical review of methods for the assessment of patient-level interactions in individual patient data (IPD) meta-analysis of randomised trials, and guidance for practitioners. *J Clin Epidemiol*. 2011;64:949-67.
15. Kirkham JJ, Dwan KM, Altman DG, Gamble C, Dodd S, Smyth R, et al. The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews. *BMJ*. 2010;340:c365.
16. Ioannidis JP, Lau J. Completeness of safety reporting in randomized trials: an evaluation of 7 medical areas. *JAMA*. 2001;285(4):437-43.
17. Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. *J Clin Oncol*. 2008;26(35):5802-12.
18. Buyse M, Molenberghs G, Burzykowski T, Renard D, Geys H. The validation of surrogate endpoints in meta-analyses of randomized experiments. *Biostatistics*. 2000;1(1):49-67.

19. Michiels S, Le Maître A, Buyse M, Burzykowski T, Maillard E, Bogaerts J, et al. Surrogate endpoints for overall survival in locally advanced head and neck cancer: meta-analyses of individual patient data. *Lancet Oncology*. 2009;10(4):341-50.
20. Mauguen A, Pignon JP, Burdett S, Domerg C, Fisher D, Paulus R, et al. Surrogate endpoints for overall survival in chemotherapy and radiotherapy trials in operable and locally advanced lung cancer: a re-analysis of meta-analyses of individual patients' data. *The lancet oncology*. 2013;14(7):619-26.
21. Askie LM, Duley L, Henderson-Smart D, Stewart LA, on behalf of the PARIS Collaborative Group. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. *Lancet*. 2007;369(9575):1791-8.
22. Ghera D, Berlin J, Askie L, on behalf of the Prospective Meta-analysis Methods Group. Prospective meta-analysis. In: Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions* 2008. p. 559-70.
23. Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, et al. PRISMA-IPD: An extension to the PRISMA statement for systematic review and meta-analysis of individual participant data. *Journal of the American Medical Association*. In Press.
24. Brown P, Brunnhuber K, Chalkidou K, Chalmers I, Clarke M, Fenton M, et al. How to formulate research recommendations. *BMJ*. 2006;333:804-6.
25. Vale CL, Tierney JF, Spera N, Whelan A, Nightingale A, Hanley B. Evaluation of patient involvement in a systematic review and meta-analysis of individual patient data in cervical cancer treatment. *Systematic reviews*. 2012;1(1):23.
26. Robinson KA, Goodman SN. A systematic evaluation of the citation of prior research in reports of randomized, controlled trials. *Ann Intern Med*. 2011;154:50-5.
27. Godlee F, Groves T. The new BMJ policy on sharing data from drug and device trials. *BMJ*. 2012;345(20th November):e7888.
28. Advanced Ovarian Cancer Trialists Group. Chemotherapy in advanced ovarian cancer: an overview of randomised clinical trials. *BMJ*. 1991;303:884-93.
29. Ovarian Cancer Meta-analysis Project. Cyclophosphamide plus cisplatin versus cyclophosphamide, doxorubicin and cisplatin chemotherapy of ovarian carcinoma: A meta-analysis. *J Clin Oncol*. 1991;9(9):1668-74.
30. The ICON Collaborators. ICON2: randomised trial of single-agent carboplatin against three-drug combination of CAP (cyclophosphamide, doxorubicin and cisplatin) in women with ovarian cancer. *Lancet*. 1998;352:1571-6.
31. The International Collaborative Ovarian Neoplasm (ICON) Group. Paclitaxel plus carboplatin versus standard chemotherapy with either single-agent carboplatin or cyclophosphamide, doxorubicin, and cisplatin in women with ovarian cancer: the ICON3 randomised trial. *Lancet*. 2002;360(9332):505-15.
32. König IR, Ziegler A, Bluhmki E, Hacke W, Bath PM, Sacco RL, et al. Predicting long-term outcome after acute ischemic stroke: a simple index works in patients from controlled clinical trials. *Stroke*. 2008;39(6):1821-6.
33. The IST-3 Collaborative Group. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. *Lancet*. 2012;379:2352-63.
34. Sydes MR, Vale C, Kneebone A, Pearse M, Richaud P, Tierney JF, et al. Re: Postoperative Radiation Therapy for Pathologically Advanced Prostate Cancer After Radical Prostatectomy. *Eur Urol*. 2012;62:e99.
35. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview on the randomised trials. *Lancet*. 2005;365:1687-717.
36. Davies C, Pan H, Godwin J, Gray R, Arriagada R, Raina V, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet*. 2013;381:805-16.

37. ATLAS. Adjuvant Tamoxifen Longer Against Shorter  
<http://www.ctsu.ox.ac.uk/research/mega-trials/atlas/atlas-website>.
38. Non-small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. *BMJ*. 1995;311:899-909.
39. Fournel P, Robinet G, Thomas P. Randomized phase III trial of sequential chemoradiotherapy compared with concurrent chemoradiotherapy in locally advanced non-small cell lung cancer: Groupe Lyon Saint Etienne d'Oncologie Thoracique-Groupe Francais de Pneumo-Cancerologie NPC 95-01 study. *Journal of Clinical Oncology*. 2005;23:5910-7.
40. Belderbos J, Uitterhoeve L, van Zandwijk N. Randomised trial of sequential versus concurrent chemo-radiotherapy in patients with inoperable non-small cell lung cancer (EORTC 08972-22973). *Eur J Cancer*. 2007;43:114-21.
41. Scagliotti GV, Fossati R, Torri V, Crinò L, Giaccone G, Silvano G, et al. Randomized study of adjuvant chemotherapy for completely resected stage I, II or IIIa non-small cell lung cancer. *J Natl Cancer Inst*. 2003;95(19):1453-61.
42. Douillard JY, Rosell R, De Lena M, Carpagnano F, Ramlau R, Gonzales-Larriba JL, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIa non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. *Lancet Oncology*. 2006;7:719-27.
43. The International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small cell lung cancer. *N Engl J Med*. 2004;350:351-60.
44. Waller D, Fairlamb DJ, Gower N, Milroy R, Peake MD, Rudd R, et al. The Big Lung Trial (BLT): Determining the value of cisplatin-based chemotherapy for all patients with non-small cell lung cancer (NSCLC). Preliminary results in the surgical setting. *Proceedings of the American Society of Clinical Oncology*. 2003;22:632.
45. Sarcoma Meta-analysis Collaboration. Adjuvant chemotherapy for localised resectable soft tissue sarcoma in adults: meta-analysis of individual patient data. *Lancet*. 1997;350:1647-54.
46. Kraybill WG, Harris J, Spiro IJ, Ettinger DS, DeLaney TF, Blum RH, et al. Phase II study of neoadjuvant chemotherapy and radiation therapy in the management of high-risk, high-grade, soft tissue sarcomas of the extremities and body wall: Radiation Therapy Oncology Group Trial 9514. *J Clin Oncol*. 2006;24(4):619-25.
47. Gueyffier F, Bulpitt C, Boissel JP, Schron E, Ekbom T, Fagard R, et al. Antihypertensive drugs in very old people: a subgroup meta-analysis of randomised controlled trials. *Lancet*. 1999;353(9199):793-6.
48. Bulpitt CJ, Beckett NS, Cooke J, Dumitrascu DL, Gil-Extremiera B, Nachev C, et al. Results of the pilot study for the Hypertension in the Very Elderly Trial. *J Hypertens*. 2003;21:2409-17.
49. Beckett NS, Peters R, Fletcher AE, J.A. S, Liu L, Dumitrascu DL, et al. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med*. 2008;358:?
50. Gueyffier F, Boissier JP, Boutitie F, Pocock S, Coope J, Cutler J, et al. Effect of antihypertensive treatment in patients having already suffered from stroke. *Stroke*. 1997;28:2557-62.
51. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. *Lancet*. 2001;358:1033-41.
52. Lievre M, Gueyffier F, Ekbom T, Fagard R, Cutler J, Schron E, et al. Efficacy of diuretics and beta-blockers in diabetic hypertensive patients: results from a meta-analysis. *Diabetes Care*. 2000;23(Suppl 2):B65-B71.
53. Advance Collaborative Group. ADVANCE - Action in diabetes and vascular disease: patient recruitment and characteristics of the study population at baseline. *Diabet Med*. 2005;22:882-8.
54. ADVANCE Management Committee. Study Rationale and design of ADVANCE: Action in diabetes and vascular disease - preterax and diamicon MR controlled evaluation. *Diabetologia*. 2001;44:1118-20.

55. Bourhis J, Overgaard J, Audry H, Ang KK, Saunders M, Bernier J, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: an individual patient data meta-analysis of 15 randomized trials. *Lancet*. 2006;368:843-54.
56. Aupérin A, Arriagada R, Pignon J-P, Le Péchoux C, Gregor A, Stephens RJ, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. *N Engl J Med*. 1999;341(476-484).
57. Le Pechoux C, Dunant A, Senan S, Wolfson A, Quoix E, Faivre-Finn C, et al. Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): a randomised clinical trial. *Lancet Oncology*. 2009;10:467-74.
58. Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. *Lancet*. 2000;355(9217):1757-70.
59. Burdett S, Rydzewska L, Tierney JF, Fisher DJ. A closer look at the effects of postoperative radiotherapy by stage and nodal status: Updated results of an individual participant data meta-analysis in non-small-cell lung cancer. *Lung Cancer*. 2013;80:350-2.
60. Askie LM, Brocklehurst P, Darlow BA, Finer N, Schmidt B, Tarnow-Mordi W, et al. NeOProm: Neonatal Oxygenation Prospective Meta-analysis Collaboration study protocol. *BMC pediatrics*. 2011;11:6.
61. IMPACT Investigators. Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. *Lancet*. 1995;345:939-44.
62. Friboulet L, Olausson KA, Pignon J-P, Shepherd FA, Tsao M-S, Graziano S, et al. ERCC1 isoform expression and DNA repair in non-small cell lung cancer. *N Engl J Med*. 2013;368(11):101-10.
63. Soria JC, Barlesi F, Besse B, Mazieres J, Merle P, Cadranet J, et al. Results of the prospective, randomized, and customized NSCLC adjuvant phase II trial (IFCT-0801, TASTE trial) from the French Collaborative Intergroup. *J Clin Oncol*. 2013;31:Suppl Abstr 7505.
64. Wislez M, Barlesi F, Besse B, Mazieres J, Merle P, Cadranet J, et al. Customized adjuvant phase II trial in patients with non-small cell lung cancer: IFCT-0801 TASTE. *J Clin Oncol*. 2014;32(12):1256-61.
65. Woll PJ, Reichardt P, Le Cesne A, Bonvalot S, Azzarelli A, Hoekstra HJ, et al. Adjuvant chemotherapy with doxorubicin, ifosfamide, and lenograstim for resected soft-tissue sarcoma (EORTC 62931): a multicentre randomised controlled trial. *The lancet oncology*. 2012;13(10):1045-54.
66. Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Adjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis of individual patient data. *Eur Urol*. 2005;48(2):189-201.
67. Sternberg CN, Skoneczna I, Kerst JM, Albers P, Fossa SD, Agerbaek M, et al. Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994): an intergroup, open label, randomised phase 3 trial. *Lancet Oncology*. 2015;16:76-86.



Example	Description of IPD meta-analyses	What was the impact?	Impact IPD specific
Trial design			
Breast cancer(1)	<ul style="list-style-type: none"> <li>• 3 IPD meta-analyses comparing effects of hormonal therapy vs. non or two durations of this treatment for early breast cancer(35)</li> <li>• 71 trials, 80 273 patients</li> </ul>	<ul style="list-style-type: none"> <li>• Informed choice of comparators in the ATLAS trial (36, 37)</li> </ul>	<ul style="list-style-type: none"> <li>• No</li> </ul>
Non-small cell lung cancer(1)	<ul style="list-style-type: none"> <li>• 4 IPD meta-analyses investigating effects of adding chemotherapy to surgery; surgery and radiotherapy; radiotherapy and supportive care (38)</li> <li>• 52 trials, 9 387 patients</li> </ul>	<ul style="list-style-type: none"> <li>• Informed the choice of comparators in new trials in locally advanced disease (39, 40)</li> <li>• Renewed enthusiasm for chemotherapy led to collaborations on new trials from IPD collaborative group (41-44)</li> <li>• Control group survival and absolute survival benefits used as the basis for sample size calculation(43, 44)</li> </ul>	<ul style="list-style-type: none"> <li>• No</li> <li>• Yes</li> <li>• No</li> </ul>
Soft tissue sarcoma(1)	<ul style="list-style-type: none"> <li>• 1 IPD meta-analysis investigating the effects of adding doxorubicin-based chemotherapy after local treatment(45)</li> <li>• 14 trials, 1 568 patients</li> </ul>	<ul style="list-style-type: none"> <li>• Subgroup results helped define population in trial RTOG 95-14(46),</li> </ul>	<ul style="list-style-type: none"> <li>• Yes</li> </ul>
Cervical cancer(1)	<ul style="list-style-type: none"> <li>• 1 IPD meta-analysis investigating concomitant chemoradiotherapy (CTRT) vs. the same radiotherapy(17)</li> <li>• 18 trials, 4 818 patients</li> </ul>	<ul style="list-style-type: none"> <li>• IPD meta-analysis and another trial together informed choice of comparators in the OUTBACK trial (ANZGOG 0902/GOG-0274/RTOG 1174)</li> <li>• Control group survival used as the basis for sample size calculation</li> </ul>	<ul style="list-style-type: none"> <li>• No</li> <li>• No</li> </ul>

Hypertension (1)	<ul style="list-style-type: none"> <li>• 1 IPD meta-analysis investigating anti-hypertensive drugs in very elderly patients (47)</li> <li>• 7 trials, 1 670 patients</li> </ul>	<ul style="list-style-type: none"> <li>• Subgroup results helped define the population in the HYVET trial(48, 49)</li> </ul>	<ul style="list-style-type: none"> <li>• Yes</li> </ul>
Hypertension (2)	<ul style="list-style-type: none"> <li>• 1 IPD meta-analysis investigating the effect of anti-hypertensive treatment in patients having already suffered a stroke(50)</li> <li>• 9 trials, 6 752 patients</li> </ul>	<ul style="list-style-type: none"> <li>• Subgroup results helped define population for the PROGRESS trial(51)</li> </ul>	<ul style="list-style-type: none"> <li>• Yes</li> </ul>
Hypertension (3)	<ul style="list-style-type: none"> <li>• 1 IPD meta-analysis investigating diuretic vs. placebo based treatment of hypertension for diabetes(52)</li> <li>• 4 trials, 18 097 patients</li> </ul>	<ul style="list-style-type: none"> <li>• Subgroup results helped define population for the ADVANCE trial(53, 54)</li> </ul>	<ul style="list-style-type: none"> <li>• Yes</li> </ul>
Head and Neck (1)	<ul style="list-style-type: none"> <li>• 1 IPD meta-analysis comparing conventional radiotherapy vs. altered fractionated radiotherapy for head and neck cancer(55)</li> <li>• 15 trials, 6 515 patients</li> </ul>	<ul style="list-style-type: none"> <li>• Subgroup results helped define population of GORTEC-ELAN-RT (NCT01864850) trial</li> </ul>	<ul style="list-style-type: none"> <li>• Yes</li> </ul>
Small-cell lung cancer (1)	<ul style="list-style-type: none"> <li>• 1 IPD meta-analysis comparing prophylactic cranial irradiation (PCI) vs. none in patients with small cell lung cancer</li> </ul>	<ul style="list-style-type: none"> <li>• Informed choice of comparators in trial PCI 99-01/EORTC 22003-08004/RTOG 0212/IFCT 99-01(57)</li> </ul>	<ul style="list-style-type: none"> <li>• No</li> </ul>



	<p>(SCLC)(56)</p> <ul style="list-style-type: none"> <li>• 7 trials, 987 patients</li> </ul>		
Breast cancer (2)	<ul style="list-style-type: none"> <li>• 1 IPD meta-analysis comparing radiotherapy and other treatments vs. the same other treatment with no radiotherapy(58)</li> <li>• 40 RCTs, 19 582 patients</li> </ul>	<ul style="list-style-type: none"> <li>• Informed choice of comparators in SUPREMO trial (ISRCTN 61145589),</li> </ul>	<ul style="list-style-type: none"> <li>• No</li> </ul>
Non-small cell lung cancer (2)	<ul style="list-style-type: none"> <li>• 1 IPD meta-analysis of post-operative radiotherapy (PORT) vs. none(59)</li> <li>• 11 RCTs, 2 343 patients</li> </ul>	<ul style="list-style-type: none"> <li>• Subgroup results helped define population in the Lung ART trial (NCT00410683)</li> </ul>	<ul style="list-style-type: none"> <li>• Yes</li> </ul>
Stroke(1)	<ul style="list-style-type: none"> <li>• Prospective IPD meta-analysis comparing anti-depressants vs. none in recovering stroke patients</li> <li>• 2 trials, 4 600 patients (approx.)</li> </ul>	<ul style="list-style-type: none"> <li>• Prospective IPD MA led to common trial design of the 2 included trials <ul style="list-style-type: none"> <li>○ Affinity – <a href="http://www.affinitytrial.org">www.affinitytrial.org</a></li> <li>○ FOCUS - <a href="http://www.focustrial.org.uk">www.focustrial.org.uk</a></li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Yes</li> </ul>
Preterm neonates	<ul style="list-style-type: none"> <li>• Prospective IPD meta-analysis comparing oxygen saturation given to extremely premature babies(60)</li> <li>• 5 trials, 5 000 patients (approx)</li> </ul>	<ul style="list-style-type: none"> <li>• Prospective IPD MA to achieve power for key outcomes</li> </ul>	<ul style="list-style-type: none"> <li>• Yes</li> </ul>
Trial conduct			
Colon cancer (1)	<ul style="list-style-type: none"> <li>• Prospective IPD meta-analysis comparing adjuvant fluorouracil and folinic acid vs. control for Dukes B and C</li> </ul>	<ul style="list-style-type: none"> <li>• Prospective IPD MA used to achieve power for key outcome</li> </ul>	<ul style="list-style-type: none"> <li>• Yes</li> </ul>

	colon cancer (61)		
	<ul style="list-style-type: none"> <li>3 trials, 1 493 patients</li> </ul>		
Stroke(1)	<ul style="list-style-type: none"> <li>As above</li> </ul>	<ul style="list-style-type: none"> <li>Collaborative design of prospective IPD MA study materials in the 2 included trials</li> </ul>	<ul style="list-style-type: none"> <li>Yes</li> </ul>
Non-small cell lung cancer(3)	<ul style="list-style-type: none"> <li>1 IPD meta-analysis of post-operative platinum-based chemotherapy vs. none for NSCLC(62)</li> <li>2 trials, 494 patients</li> </ul>	<ul style="list-style-type: none"> <li>Subgroup results used as rationale for trial stopping (IFCT 0801, TASTE (NCT00775385(63, 64)</li> </ul>	<ul style="list-style-type: none"> <li>Yes</li> </ul>
Preterm neonates	<ul style="list-style-type: none"> <li>As above</li> </ul>	<ul style="list-style-type: none"> <li>Prospective IPD MA influenced aspects of the individual trials e.g. data collection and study materials</li> </ul>	<ul style="list-style-type: none"> <li>Yes</li> </ul>
Trial analysis and interpretation			
Soft tissue sarcoma(2)	<ul style="list-style-type: none"> <li>IPD meta-analysis investigating the effects of adding doxorubicin based chemotherapy after local treatment(45)</li> <li>14 trials, 1 568 patients</li> </ul>	<ul style="list-style-type: none"> <li>EORTC 62931 trial report uses results of meta-analysis and subsequent trials to places trial results in context (65)</li> </ul>	<ul style="list-style-type: none"> <li>No</li> </ul>
Stroke(1)	<ul style="list-style-type: none"> <li>As above</li> </ul>	<ul style="list-style-type: none"> <li>Prospective IPD MA influenced planned analysis of 2 included trials</li> </ul>	<ul style="list-style-type: none"> <li>Yes</li> </ul>
Bladder cancer	<ul style="list-style-type: none"> <li>IPD MA of adjuvant chemotherapy versus none in bladder(66)</li> <li>6 trials, 491 patients</li> </ul>	<ul style="list-style-type: none"> <li>EORTC 30994 trial report (67) uses results of IPD meta-analyses and subsequent results to places trial results in context.</li> </ul>	<ul style="list-style-type: none"> <li>No</li> </ul>

**Table 1: Further examples of the impact of IPD meta-analyses on trial design, conduct, and analysis and interpretation**