

# EFFICIENT / INNOVATIVE DELIVERY OF NIHR RESEARCH – 2019 PROJECTS

## FINAL REPORT

**Word count (sections 1-6):** 1949

### 1) Title of Project

Supporting **E**ffective and **E**fficient Initiation and **D**elivery of Individual Participant Data  
Meta-analyses (SEED: IPD Meta-analysis)

### 2) Abstract

**Background:** Individual Participant Data (IPD) meta-analyses have become increasingly common over the past decade. Despite the many benefits of IPD over aggregate data in meta-analyses, it poses important challenges and uncertainties with regards to initiation and delivery. To enhance effective and efficient initiation and delivery of IPD meta-analyses, we aimed to develop a suite of practical resources for use within the national CTU Network and beyond. These included:

1. A two-day workshop to equip participants with knowledge and skills about how to effectively and efficiently initiate and deliver IPD meta-analyses.
2. An online 'IPD Meta-Analysis Tool Box' containing freely available resources that can be accessed and utilised to facilitate effective and efficient delivery of IPD meta-analyses.
3. Software (as part of the Tool Box) that can be used to perform power calculations (before each IPD project is embarked upon), based on published (or provided) aggregate information from existing studies, to inform the extent of data collection required to ensure an IPD meta-analysis project is worth doing.

**Results and conclusion:** We successfully developed and delivered all planned resources. Our workshop ran virtually in October 2021. It was attended by 30 participants from across the UK and internationally, with varying backgrounds and experience in IPD meta-analysis delivery. The workshop received positive feedback and as such is planned to run annually. The Tool Box was launched in October 2020. Since July 2021 (after which date, metrics are available), its landing page has had 455 views in total, and 298 unique page views. Prototype testing received very positive feedback about its usefulness and clarity. The software (online power calculation) was launched in October 2021 and has been accessed over 700 times. Overall therefore, this suite of resources will provide lasting benefit to the NIHR and wider research community about effective and efficient initiation and delivery of IPD meta-analyses.

**Dissemination:** The IPD meta-analysis Tool Box and power calculation software are freely and publicly available, with IP owned by Keele University. All resources have been widely disseminated and will continue to be advertised and updated on an annual basis, to coincide with the ongoing running of the 2-day workshop. The Tool Box and software for power calculation can be found here:

<https://www.keele.ac.uk/ipdmatoolbox/>

### **3) Introduction**

Individual Participant Data (IPD) meta-analyses have become increasingly common over the past decade, due to an increased willingness (and expectation) to share IPD in order to answer questions previously unconsidered or not powered in primary studies [1-6]. Many of the limitations seen in traditional aggregate data meta-analysis (including poor reporting, and different approaches to derivation and presentation of aggregate data across studies) can be addressed using an IPD meta-analysis [3,7,8]. Having IPD allows re-analysis of data using consistent choices for analysis in each study, including choice of adjustment variables and cut-offs for continuous variables, handling of missing data, length of follow-up, examination of non-linear trends, and assessment of modelling assumptions. Importantly, having IPD allows greater investigation of the causes of between-study heterogeneity, and potential effect-modifiers (interactions) by avoiding ecological (aggregation) bias [9].

Despite the many benefits of IPD over aggregate data in meta-analyses, it poses important challenges and uncertainties with regards to initiation and delivery. Lack of trained staff makes it difficult for funders and researchers to judge when an IPD project is needed, as does limited Patient and Public Involvement and Engagement (PPIE). IPD meta-analyses are difficult to deliver, being time-consuming and expensive, and require significant expertise and resource to obtain, clean, and harmonise IPD prior to data synthesis [10,11]. Despite extensive efforts to obtain IPD, it may still be unavailable for some studies leading to availability bias [12].

Given these challenges, before embarking on an IPD project, researchers and funders should ensure that a) staff have the appropriate expertise and resource to

deliver it effectively and efficiently; and b) it is likely to be worth the effort and investment. Power calculations and sample size justifications are rarely reported in IPD meta-analysis protocols or publications. This may be because they are complex and depend on many factors [13-17]. If power calculations are made more accessible, they could also reveal which studies contribute most to the power, and thus direct how much IPD is needed and from which studies, making future IPD meta-analyses more efficient.

We aimed to enhance effective and efficient initiation and delivery of IPD meta-analyses by developing a suite of practical resources for use within the national CTU Network and beyond. These included:

1. A two-day workshop to equip participants with knowledge and skills about how to effectively and efficiently initiate and deliver IPD meta-analyses.
2. An online 'IPD Meta-Analysis Tool Box' containing freely available resources that can be accessed and utilised to facilitate effective and efficient delivery of IPD meta-analyses.
3. Software (as part of the Tool Box) that can be used to perform power calculations (before each IPD project is embarked upon), based on published (or provided) aggregate information from existing studies, to inform the extent of data collection required to ensure an IPD meta-analysis project is worth doing.

## **4) Methods**

### **i. Workshop**

Our 2-day workshop considered all steps within IPD meta-analysis projects, from initial rationale and conception to dissemination. It aimed to equip participants with the necessary knowledge and skills to effectively and efficiently initiate and deliver IPD meta-analysis projects. Whilst we originally planned to run the workshop face-to-face, in response to the COVID-19 pandemic we ran the workshop remotely using different strategies. These included pre-recorded lectures, live lectures delivered by two guest speakers (Professor Shakila Thangaratinam (University of Birmingham); Professor Catrin Tudur Smith (University of Liverpool)), live question and answer sessions, and interactive sessions including group discussion, problem solving, case studies, and critical appraisal. There was also the opportunity to gain individual advice during a one-to-one 'expert consultation' session.

To ensure relevance to a wide audience, the workshop drew on different study types from a number of different fields (e.g. musculoskeletal, cancer, cardiovascular, pregnancy). It was applicable to a broad range of staff, including healthcare researchers, statisticians and non-statisticians, study managers, data managers, funders, journal editors, and clinicians involved in the funding, delivery, appraisal, and/or interpretation of IPD meta-analyses in healthcare.

Please see Appendix 1 for an overview of the final workshop programme and its learning objectives.

## **ii. The IPD Meta-analysis Tool Box**

A freely available online 'IPD Meta-Analysis Tool Box' containing resources to facilitate effective and efficient delivery of IPD meta-analyses was developed and housed on Keele CTU's website. It includes step-by-step information and recommendations for each phase of an IPD meta-analysis project, with practical resources necessary to complete an IPD meta-analysis (e.g. copies of data sharing agreements, exemplar IPD meta-analysis protocols, exemplar software code in Stata and R, reporting guidelines, and PPIE engagement principles). Steps covered include:

- What, why and when (when to undertake an IPD meta-analysis rather than a traditional meta-analysis)
- Planning
- Data harmonisation
- Quality and generalisability
- Analyses
- Power/ sample size
- Engaging the public
- Critical appraisal and reporting
- Further training and information

To ensure that the Tool Box is useful and understandable, we sought feedback on a prototype from 13 potential future users, including clinical academics, statisticians, and study managers. Suggestions for improvement were incorporated into the final version.

### **iii. Software for IPD meta-analysis power calculation**

We developed methodology and software for the calculation of power of prospective IPD meta-analyses. Our previous research [17] developed simulation-based power calculation methods for continuous and binary outcomes, using a two-stage IPD meta-analysis framework. This project enabled development of computationally efficient closed-form analytical solutions for the potential power of an IPD MA to detect an interaction effect. User-friendly software was developed in both R and Stata. These methods will improve competing options based on approximate closed-form solutions [13-15]. The software was also developed into an interactive web application and included in the online 'IPD Meta-Analysis Tool Box' described above. This will allow users to interrogate the potential power of a prospective IPD meta-analysis given various parameters and using data visualisation.

## **5) Results and Conclusion**

### **i. Workshop**

We successfully ran the workshop in October 2021. It was attended by 30 participants from various institutions from across the UK, and internationally (including from the Netherlands, Norway, and Australia). Participants had a range of backgrounds (including Clinical Trials Unit study managers, statisticians and clinical academics) and different levels of experience with regards to conducting IPD meta-analyses. We received post-workshop feedback from 12 participants. On the whole was very positive with regards to its organisation, content and online platform. For example, one participant stated: *"I think the course was great for someone with little*

*knowledge of IPD meta-analysis. It was really helpful and explained all the various different aspects to undertaking it, to give you a really good overall feel for what it would be like and the time and processes involved if you were to undertake one”.*

Areas for improvement included allowing more time for breaks and increasing time for interactive group sessions. This feedback has been incorporated into the workshop programme, which, due to its success, is being planned annually (next one 13<sup>th</sup>-14<sup>th</sup> October 2022).

## **ii. The IPD Meta-analysis Tool Box**

The Tool Box launched in October 2020. Since July 2021 (from which date metrics are available), its landing page has had 455 total views, and 298 unique page views. Feedback on its prototype testing was very positive, with users finding it easy to navigate, and including clear and concise information. For example, one user stated *“Overall this is very impressive! Clearly much work has gone into this, it covers so many different angles and provides a wealth of information necessary for IPD meta-analysis. It is well presented and easy to follow too, with many links for further information, and a good combination of different ways of displaying information (text, graphs, images, videos etc)”.*

## **iii. Software for IPD meta-analysis power calculation**

We developed several new methods, calculating analytical solutions to derive the potential power of an IPD MA to detect interaction effects with both binary and continuous patient level covariates, when analysing both binary and continuous outcomes. We have published a book chapter and peer-reviewed manuscript



discussing one of these methods [18-19] and have two further manuscripts currently under review covering new methodologies developed through this funding [20-21]. We have also written user-friendly software in both R and Stata to implement these approaches which will facilitate the rapid uptake of these methods. The analytical solutions developed are quick and efficient, making them very appealing as approaches to assessing the potential power of IPD MA projects quickly and easily. We also developed an interactive web tool which implements these methods and has been accessed over 700 times to date, with new methods to be added over time.

Overall therefore our aim and objectives have been achieved and the development of this suite of resources will provide lasting benefit to the NIHR and wider research community about effective and efficient initiation and delivery of IPD meta-analyses.

## **6) Dissemination**

The IPD meta-analysis Tool Box and online power calculator are freely and publicly available, with IP owned by Keele University. The presence of our resources has been widely disseminated, including via: social media, personal contacts, clinical trials units (UKCRC), Cochrane, Allstat, NIHR methodology hubs, NIHR West Midlands Clinical Research Network, and the NIHR School for Primary Care Research. They will continue to be advertised and updated on an annual basis, to coincide with the ongoing running of the 2-day workshop.

The Tool Box, software for sample size calculation, and information about the workshop can be found here:

<https://www.keele.ac.uk/ipdmatoolbox/>

## 7) Acknowledgements

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workshop, namely: Professor Shakila Thangaratinam, Professor Catrin Tudur Smith Dr Steven Blackburn, Christine Walker (patient representative) and John Maddison (patient representative). We would also like to thank the events team at Keele University for supporting the online delivery of the workshop.

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## 9) Conflict of interest declaration

There are no competing interests to declare.

## **10) Appendices**

### **Appendix 1: Workshop Overview and Learning objectives**

#### **Workshop Programme**

##### **Workshop title:**

Individual Participant Data Meta-Analysis Projects: A Practical Introduction

##### **Target audience:**

This workshop is intended for a broad audience, including: healthcare researchers; statisticians and non-statisticians; study managers and data managers; funders; journal editors; and clinicians or other staff involved in the funding, delivery, appraisal, and/or interpretation of IPD meta-analyses in healthcare.

##### **Learning objectives:**

By the end of the two-day workshop, participants will:

- Have a deep understanding of what an IPD meta-analysis is, and the types of research questions it can address.
- Know when and why to conduct an IPD meta-analysis rather than a traditional systematic review and meta-analysis of (published) aggregate data, or a primary study with new data collection.
- Be fully aware of the ethical and governance issues involved in IPD meta-analyses.
- Understand the fundamental steps involved in completion of an IPD meta-analysis project, including: identification of relevant studies; selection of IPD and variables for analyses; obtaining IPD; examining data quality and risk of bias; data cleaning and checking; harmonising IPD; and merging data for analyses.
- Know how to calculate the potential power of an IPD meta-analysis to address the research question(s) of interest, and how to use that to ensure that data collection is targeted and as efficient as possible.

- Understand the basic principles of fundamental approaches to IPD meta-analysis; specifically, differences in 1-stage and 2-stage approaches, why they may differ, and when each should be used.
- Understand how to achieve active PPIE throughout the IPD project.
- Ensure timely dissemination of IPD meta-analyses and adherence to reporting guidelines.
- Critically appraise published IPD meta-analyses.
- Gain individual advice during a one-to-one 'expert consultation' session.

### **Optional reading and resources:**

LEVIS B, HOLDEN MA, HATTLE M, ET AL. The Keele Toolbox for IPD Meta-analyses. 1st January 2021.

<https://www.keele.ac.uk/pcsc/research/ctu/whatweoffer/educationandtraining/ipdmatoolbox/>

LEVIS B, HATTLE M, RILEY RD. 2021. PRIME-IPD Series Part 2. Retrieving, checking, and harmonizing data are underappreciated challenges in individual participant data meta-analyses. *J Clin Epi*, 136:221-223.

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## Day 1: Thursday 14<sup>th</sup> October 2021

*Please note that sessions will be delivered using different strategies including lectures, interactive elements, group discussion, problem solving and case studies*

<b>Time UK</b>	<b>Session focus</b>	<b>Presenter(s)</b>	<b>Session Chair</b>	<b>Format</b> <i>(pre-recorded lecture, live lecture, small group work)</i>
9:00-9:30	Logging into the system, virtual meet and greet	-	-	-
9:30-9:45	Welcome and introductions	All	BL	Live
9:45-10:30	<b>Lecture 1:</b> IPD meta-analysis: The 'what', 'why' and 'when'	RR	-	45 mins pre-recorded lecture
10:30-11:15	<b>Practical 1</b>	Group A: RR/BL Group B: JE/MeH Group C: MiH/DvdW		45 mins live interactive groups
11:15-11:30	Coffee break	-	-	-
11:30-12:30	<b>Guest speaker:</b> Prof. Shakila Thangaratinam. Initiating and managing IPD projects – example from the pregnancy field, followed by Q and A	ST	DVdW	Live lecture
12:30-1:00	Questions and answers	All (and ST)	DVdW	Live
1:00-1:30	Lunch	-	-	-
1:30-2:30	<b>Lecture 2:</b> Identification of relevant studies; selection, obtaining and sharing of IPD	BL DvdW MeH	-	55 mins pre-recorded lecture 5 mins break
2:30-3:15	<b>Practical 2</b>	Group A: BL/RR Group B: MeH/JE Group C: DvdW/MiH		45 mins live interactive groups
3:15-3:30	Break	-	-	-
3:30-5:00	<b>Lecture 3:</b> Data handling and harmonisation including resolving missing data	MiH	BL	80 mins pre-recorded lecture 10 mins live Q and A

**Day 2: Friday 15<sup>th</sup> October 2021**

<b>Time UK</b>	<b>Session</b>	<b>Presenter(s)</b>	<b>Session Chair</b>	<b>Format</b> <i>(pre-recorded lecture, live lecture, small group work)</i>
8:45-9:00	Log on	-	-	-
9:00-9:20	<b>Lecture 4:</b> Examining the quality and risk of bias in IPD obtained Group work / partner work	BL	-	20 mins pre-recorded lecture
9:20-9:50	<b>Practical 3</b>	Group A: BL/RR Group B: MeH/JE Group C: DvdW/MiH		30 min live interactive groups
9:50-11:00	<b>Lecture 5:</b> Approaches to IPD meta-analysis (1 stage or 2 stage)	RR	JE	60 mins pre-recorded lecture 10 mins live Q and A
11:00-11:15	Break	-	-	-
11:15-12:15	<b>Lecture 6:</b> How much IPD is enough? Power calculations for IPD projects and the online calculator	JE	RR	50 mins pre-recorded lecture 10 mins live Q and A
12:15-12:45	Lunch	-	-	-
12:45-2:00	<b>Guest speaker:</b> Prof. Catrin Tudur Smith. The benefits and impact of IPD over aggregate data – the example in the field of epilepsy	CTS	MiH	Live lecture followed by live Q and A
2:00-2:15	Break	-	-	-
2:15-3:05	<b>Lecture 7:</b> The role of PPIE in research and IPD meta-analyses	SB JM MeH CW	MeH	40 mins pre-recorded lecture 10 mins live Q and A
3:05-3:45	<b>Lecture 8:</b> Critical appraisal of IPD projects in small groups	RR	-	40 mins pre recorded
3:45-4:15	<b>Practical 4</b>	Group A: RR/BL Group B: JE/MeH Group C: MiH/DvdW		30 mins live interactive groups
4:15-4:30	Close	All	BL	Live
4:30-5:00	Optional - Meet the Expert session – opportunity for one-to-one advice	Room A: RR/BL Room B: JE/MeH Room C: MiH/DvdW		Drop in to one of the 3 rooms