Identifying Predictors of Response Using an Individual Patient Data Meta-Analysis

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Abstract

Osteoarthritis is a common painful condition affecting the joints. Currently, there is no cure for osteoarthritis, only the management of its symptoms. To personalize pain relief to an individual, we need to first identify predictors of treatment response. We undertook two individual patient data (IPD) meta-analyses conducted as part of the OA Trial Bank. One aim was to identify predictors of response to two topical treatments: topical non-steroidal anti-inflammatory drugs and capsaicin. The other aim was to identify placebo responders and predictors of response in osteoarthritis. IPD meta-analysis requires the original trial authors to share the data on all the individual patients in their trial. The raw data are then re-analyzed centrally while preserving the clustering of participants within their original trials. Obtaining the IPD from randomized controlled trials is the most important step in conducting an IPD meta-analysis. However, collecting IPD is a long process and a flexible approach to data collection is needed. The advantages of an IPD meta-analysis includes an increased study sample size, while allowing both individual patient-level and study-level predictors of response to be taken into account. Meanwhile, being restricted only to variables previously measured within the trials is a limitation. In this case study, we report on some of the challenges we experienced, and lessons learnt from undertaking two different IPD meta-analyses to identify predictors of response in patients with osteoarthritis.

Learning Outcomes

By the end of this case, students should be able to

- Describe the steps required to conduct an individual patient data (IPD) meta-analysis
- Define the benefits of an IPD meta-analysis
- Give an overview of a one-stage IPD meta-analysis approach
- List factors to consider as a primary researcher to optimize the use of your data in subsequent IPD analysis

Project Overview and Context

Osteoarthritis (OA) is a common condition that can affect any moveable joint in the body causing pain and disability. Pain is the most troubling issue for people with OA, and treatment is most often aimed at providing pain relief. Unfortunately, current treatments only provide mild to moderate pain relief overall. Treatment guidelines have therefore emphasized the need to tailor treatments to the individual, thereby moving away from a “one size fits all” approach and toward more individualized care (National Collaborating Centre for Chronic Conditions [NCCCC], 2008). A prerequisite for this to occur is for clinical biomarkers, or predictors, to be identified. These are defined as any diagnostic test or clinical observation that, because of superior efficacy, indicates a preferred treatment for a patient subpopulation (Trusheim et al., 2007).

Several approaches can be used to identify these predictors of treatment response. One approach is to

identify subgroups with different responses to treatments within a randomized controlled trial (RCT), usually in the form of post hoc or predefined analyses (Bierma-Zeinstra & Verhagen, 2011). However, these are often inadequately powered and subject to a high risk of error (Bierma-Zeinstra & Verhagen, 2011). On one hand, by dividing the trial population into smaller subgroups, there is reduced power to detect the treatment effect of interest. Subgroup analyses are therefore subject to type II error (false negative results). On the other hand, performing analyses on several different subgroups can be likened to multiple testing and is therefore subject to type I error (false positive results). A better approach would be to combine data from multiple studies, using a meta-analysis. One could relate the average treatment effect in trials to the patient characteristics within the trial, in a meta-regression (Bierma-Zeinstra & Verhagen, 2011). However, this is subject to study-level confounding and may lead to spurious results affected by ecological bias (Hingorani et al., 2013). Ecological bias, or ecological fallacy, arises when inferences are made about the individual based on aggregate, or study-level, results. Alternatively, one could do a meta-analysis of subgroup effects, but these are rarely presented in publications (Koopman et al., 2008). A more robust method is to conduct an individual patient data (IPD) meta-analysis.

IPD meta-analysis requires the original trial authors to share the data on all the individual patients in their trial. The raw data are then re-analyzed centrally while preserving the clustering of participants within their original trials. It has many advantages over other commonly used methods. First, it increases the study sample size, thereby minimizing the problems associated with inadequate power (Bierma-Zeinstra & Verhagen, 2011). Second, while subgroup factors are rarely presented in published reports of RCTs, these are often measured at an individual level so are readily available (Koopman et al., 2008). Finally, IPD meta-analysis permits both individual patient-level and study-level predictors of response to be taken into account. Predictors of a treatment or placebo response may be person-specific (e.g., age and gender) or study-specific (e.g., sample size and allocation concealment), and both person- and study-level characteristics therefore need to be considered.

To pool resources and overcome difficulties associated with obtaining raw patient-level data from RCTs, IPD meta-analyses are often conducted as collaborative projects. Our work was undertaken as part of the OA Trial Bank, an ongoing international consortium aiming to collect IPD from existing RCTs for all treatments of OA. The Bank has completed IPD meta-analysis for intra-articular (IA) glucocorticoid injection, glucosamine tablet, and topical non-steroidal anti-inflammatory drug (NSAIDs) trials.

Within this case, we describe two projects conducted as part of the OA Trial Bank— one aiming to identify predictors of response to two topical treatments: topical NSAIDs and capsaicin, and the other aiming to use IPD available within the OA Trial Bank to identify placebo responders and predictors of response in OA.

Section Summary

- Currently there is no cure for osteoarthritis, only the management of its painful symptoms, and in order to tailor pain relief to an individual, we need to first identify predictors of treatment response.
- Advantages of an IPD meta-analysis includes an increased study sample size, while allowing both

individual patient-level and study-level predictors of response to be taken into account.

Research Design

We conducted a systematic literature search to identify all (published and unpublished) RCTs that had assessed a topical NSAID or capsaicin in people with OA. In parallel, we identified the pharmaceutical companies that manufacture the drugs for the United Kingdom, in case these had unpublished RCT data available. We contacted the study authors, institutions, and pharmaceutical companies asking them to collaborate on the project by sharing the raw de-identified IPD from their RCTs. Contact was made via email, telephone, letter, and online (clinicalstudydatarequest.com).

The IPD were cleaned, variables were standardized, and data were pooled across studies. Trial participants maintained their original patient identifier, and RCTs were allocated trial identifiers. We analyzed the data using a one-stage IPD meta-analysis, which involves analyzing all data from the trials simultaneously, while maintaining participant clustering within trials. Ensuring that patients are kept clustered within their original trials is very important, and this is done using a multilevel model. For continuous outcomes, such as pain, the models are often an extension of analysis of covariance (ANCOVA) models. We conducted our analyses using Stata (*Stata Statistical Software: Release 15*) as this was the package we were most familiar with, although any statistical package that allows multilevel modeling to be conducted could have been used (Debray et al., 2015). When running the analyses, we developed our models based on the IPD meta-analysis literature (Burke et al., 2017; Debray et al., 2015).

Predictors of response to topical NSAIDs were identified by determining whether a significant interaction between the treatment (topical NSAID or placebo) and the characteristic of interest existed. The characteristics we examined were age, gender, baseline pain, body mass index, evidence of inflammation, duration of complaints, and radiographic severity.

We then combined the IPD from the topical NSAIDs trials with data available in the OA Trial Bank from glucosamine and steroid injection studies to look at placebo predictors. As we analyzed only patients in the placebo arm, our analysis did not include a treatment term. Each characteristic was therefore entered into the model individually as a covariate, and those that were significant were determined to be predictors of placebo response.

The studies were registered on PROSPERO (2016: CRD42016033212) and (2016: CRD42016035254) and the protocols published (Fu et al., 2016; Persson et al., 2016).

Section Summary

- Maximize the number of study data obtained by conducting a systematic review of all RCTs and contact pharmaceutical companies for unpublished study data.
- The benefit of one-stage IPD meta-analysis is that all data from the trials are analyzed simultaneously, while maintaining participant clustering within trials.

Research Practicalities

In the early stages of the IPD meta-analysis, much of the focus was on obtaining the IPD from RCTs. This is the most important step in conducting an IPD meta-analysis, as the work cannot go ahead if no data are received. To obtain the IPD, the most appropriate method of contact with the study data custodian had to be determined. Phrasing the initial contact email and determining the amount and type of content to be shared at the initial stage were difficult. Investigators may, naturally, be skeptical of an email arriving out of the blue asking them to share their raw data. With the increasing number of predatory journal email requests, it is difficult to select a subject line which will encourage recipients to open the email and it not to be filtered out as spam or junk mail. We used a dedicated OA Trial bank email account to make initial contact and hope that as the consortium publishes more IPD meta-analyses, researchers will be aware of the name when they see email from this account in the future and will respond. Publications which may help guide the approach used are available, but these were not published when we were drafting our emails (Nevitt et al., 2017; Polanin & Terzian, 2019).

Another important consideration was the formulation of the data transfer agreements used for the collaborations. We used a version pre-drafted by the OA Trial Bank, but also decided to be flexible and accept agreements drafted by the collaborators themselves. A commonly held misbelief is that IPD cannot be shared unless explicit consent for this is obtained from all original trial participants. However, this mistakenly disregards an important concept, which is that the data shared are de-identified or anonymized. An agreement was therefore only required between us and the trial data custodian, who could share the data as long as it were de-identified. Further information and practical guidance on de-identifying data sets are available from Keerie et al. (2018).

The next decisions we had to make were which analysis approach to use. Our primary approach was to conduct a one-stage IPD meta-analysis (described earlier), but its application required more statistical expertise than using the two-stage approach. It was unclear if the benefits (more power and flexibility) would outweigh the challenges posed by adopting a more complex statistical model. We therefore chose to apply both, for comparison, while keeping the one-stage method as our a priori defined primary approach.

It was anticipated that undertaking the combined placebo IPD study would be much easier than for the topical treatment IPD study. Some data custodians had been interested in contributing their data to the topical NSAID, glucosamine, or steroid IPD meta-analyses, but were unable to locate the raw data or did not have staff available to extract the relevant data for us. This was not a concern for the placebo study as the raw data were already held by the OA Trial Bank. Data were therefore easier to share, as long as the data custodian was happy to collaborate. However, it was still necessary to obtain consent from the original data custodians for data already held within OA Trial to be used for the placebo analysis. This involved attempting to make contact with the original authors again, and this was a lengthy process. In some cases, pharmaceutical companies had changed hands since last collaborating with the OA Trial Bank, so it was difficult to identify the name of the new data custodian, or previous staff members who had agreed to the data sharing had left the

company and the agreement had to be approved again with the new custodian. For academic studies with clinicians as corresponding authors, problems arose when they moved institutions and no longer had publicly available contact details. Many authors who had previously shared their data questioned why the original IPD meta-analysis had not been published yet.

As with many papers, criteria for authorship of an IPD meta-analysis raise some discussion. When contacting the data custodians, we offered the opportunity of acknowledgment or authorship for this new analysis. There was some debate regarding how many authors could be suggested per contributing study. Often the corresponding author of a study was not the lead author, leading to discussions about how many researchers could be included as co-authors. Making clear the criteria for authorship and how many authors could be included from each contributing study should have been decided in advance and clearly spelled out in the initial correspondence.

Section Summary

- Obtaining the IPD from RCTs is the most important step in conducting an IPD meta-analysis.
- Making contact, data transfer and negotiating agreements between data custodians and researchers is a lengthy process which needs to be accounted for in study planning.

Method in Action

In practice, we experienced a lot of difficulties when trying to obtain the IPD from relevant trials. Of 73 topical NSAID and capsaicin RCTs identified, we only obtained the IPD for 15 topical NSAID RCTs. No data were received for any of the capsaicin RCTs, and we were simply not able to conduct an IPD meta-analysis for capsaicin. In the initial stages, we had also wanted to examine the two treatments for a different disease (neuropathic pain), but also failed to get the necessary IPD to do this. Although it was disheartening to only receive the data for a modest proportion of topical NSAID RCTs, the data actually covered over 3,100 participants. This sample size is much larger than any individual trial ever conducted for topical NSAIDs in OA. Although methods are available for combining IPD and aggregate data in a meta-analysis (Riley et al., 2008), we did not apply them because the data required were not reported in the publications of the eligible trials. Our main interest was predictors of response rather than mean treatment effects, and no such data were available to extract from published reports. However, comparison of patient and trial characteristics, including mean treatment effects, between trials that did and did not share the raw data indicated that the subset of trials for which data were received were broadly representative of the wider research body. We received data from a variety of pharmaceutical companies and non-industry funded institutions, covering several different kinds of topical NSAIDs, and reporting treatment effects that varied from large to not statistically superior to placebo.

The largest challenges experienced were therefore related to data acquisition. The major difficulties experienced were making contact with data custodians and identifying the data. Trials dated back to over 30 years ago, and this made it difficult to contact data custodians. Investigator contact details were

often unavailable or out of date, or they were no longer working at the same institution. Sometimes the pharmaceutical companies that had conducted the RCTs no longer existed, or had transferred ownership of the data elsewhere. Other data custodians were interested in collaborating, but could not find the data or had destroyed the data after passing the data retention period. Identifying and preparing the data for sharing represented an increased workload for data custodians, and some were not interested for this reason. We conducted the work as part of the OA Trial Bank, whose membership includes world-leaders in the field of OA research, and this may have helped convince data custodians to collaborate. Using clinicalstudydatarequest.com to request data from pharmaceutical companies worked very well. We received almost half our data in this way. This is an invaluable resource if much of the data identified for the IPD meta-analysis are held by pharmaceutical companies.

As we had expected when planning the work, the data were received in various formats (from PDF documents to SAS files). Although cleaning and merging the data sets was cumbersome, it minimized the workload required from the data custodians. We found that this approach worked well. When looking into the data, we found that there were data available for characteristics which had not been available in the publication. Although this was beneficial for our analyses, it does make it difficult to determine what variables you will be able to analyze from the publication alone. Many of the potential characteristics that we had wanted to examine (e.g., the nature of the pain) were not measured in the RCTs, so our analyses were restricted to relatively basic characteristics. Although all trials reported pain as the outcome, these were measured on different scales. To account for this, we standardized the different pain test scores accordingly, but in our analysis the pain test used still ended up being a study-level predictor of placebo response. We rescaled the different pain test scores to a 0–100 scale, while accepting the caveat that the instruments may have different measurement properties or sensitivities which could impact this approach. Where trials had reported pain outcomes on different measurement scales, we used a predetermined hierarchy to ensure a consistent approach to which pain scales were pooled.

A further difficulty encountered was that some studies were not conducted or recorded in English. This meant that we had to spend a considerable time translating the variable headings in the database using a combination of Google translate software or trying to decipher abbreviations adopted by the original study team, through using secondary language skills of the IPD researcher and other colleagues. Some researchers provided only data on characteristics they thought relevant to our study while others provided over 50 individual folders of data which we needed to extract data from. An additional challenge was deciding which data time point to analyze from each respective study. For example, one study reported they would collect data at 3-month intervals over 2 years. This would provide an expected 9 data collection points for each participant (8 + the final data collection at 2 years). However, some participants had 13 data points (12 + final data collection at 2 years), while others only had 3 (2 + final data collection at 2 years). We therefore decided to calculate the actual visit week using the visit date from baseline. Often these dates did not clearly fall around a 3-month visit period, so using data at or nearest to a predefined time point was difficult.

As well as the primary study team who undertake the IPD meta-analysis, members of the consortium who

initiated the OA Trial bank were also included as co-authors. Having more than 20 authors makes it difficult to receive feedback in a timely manner and achieve conclusions everyone agrees with. It is also awkward to assess the quality of a particular study, when that study lead is also a co-author of the IPD meta-analysis manuscript.

Another difficulty occurred while going through the data to check that the coding matched the results in the published manuscript or other analysis. The data custodians trust you are going to use the data only as agreed in the data transfer agreement; however, this involves data checks to ensure that all data are received and the coding is interpreted correctly. Challenges therefore arose when dealing with discrepancies and how to discuss these with the data custodian. We chose to use the raw data as provided to us, even if it did not accurately correspond with results published in the original peer reviewed study.

Using the one-stage IPD meta-analysis method resulted in more precise estimates than the two-stage method, but the approach was more statistically complex. In the future, we would continue to use the one-stage approach over the two-stage, due to the increased precision and flexibility it provides, but with the understanding that its implementation requires greater statistical knowledge.

Learning to run multi-level models and getting a deeper understanding of the assumptions to make for an IPD meta-analysis, and how to translate these into statistical code, was a steep learning curve. However, with the input from a statistician and attending a course on IPD meta-analysis, it was achievable within a few months.

Section Summary

- Data acquisition and maintaining contact with the primary data custodian is one of the greatest challenges in undertaking an IPD study.
- **Accurately formatting, interpreting, and standardizing data is essential for merging IPD from all studies**
- One-stage IPD meta-analysis method resulted in more precise estimates than the two-stage method, but the approach was more statistically complex.

Practical Lessons Learned

The main lesson learned is the absolute importance of maximizing your chance of receiving IPD. Perseverance and a flexible approach are needed, and it may be useful to conduct the work as part of a collaboration. Data collection took approximately two years, and this should be factored into the planning stages. Applying strict inclusion criteria, perhaps coupled with author contact to determine if the variables of interest are measured with the trial, may facilitate the process. We used the original study authors' definition for recruitment so some had lower pain scores, for example, zero at baseline, as pain was not an inclusion criterion for the original study, others only had self-reported osteoarthritis as a recruitment criteria rather than radiographically diagnosed OA. We decided to include all studies which provided data in our primary analysis, but then undertook sub-analyses, for example with pain scores of 3 out of 10 or above, on the standardized

pain scale, on the day of randomization.

Many of our initial variables of interest were also missing from the data collected by the studies. For example, not all used recommend OARSI (Osteoarthritis Research Society International) and OMERACT (Outcome Measures in Rheumatology) core outcome measures to assess pain and function in people with osteoarthritis. We ended up amending our original protocol as variables and timepoints we had intended to investigate were missing when we received some of the studies' data.

Contact with the data custodian is important throughout the IPD meta-analysis to get clarification on how variables were collected and to explain any possible outliers. Also, once data have been shared, it is important to get in contact again for additional subsequent studies utilizing different variables. Therefore, it would be useful to collect additional forms of communication on initial contact. Examples include personal and work email addresses, phone numbers, contact details of department administrator, as well as making contact on professional social media accounts such as ResearchGate or LinkedIn. This would ensure that it is still possible to make contact with someone who can authorize the use of the data if the data custodian moves position, or the place of employment changes name. When the manuscript is finally drafted it is also important to get input from the data custodians who had requested authorship alongside their data sharing, a further reason to maintain contact throughout the study.

Section Summary

- Collecting IPD is a long process, and a flexible approach to data collection is needed.
- Maintaining contact with the data custodian is essential to maximize the use of all data in future IPD meta-analyses.

Conclusion

The greatest advantage of IPD meta-analyses is likely to be the opportunity to conduct analyses with a large sample size. For this reason, they are extremely useful for looking at predictors of response. However, a prerequisite is that the variables of interest need to be measured within the trials. Careful application of inclusion and exclusion criteria in the screening phases would indicate the utility of an IPD meta-analysis for the approach.

Obtaining the IPD from RCTs is the most important step in conducting an IPD meta-analysis and also provides the greatest challenges. Primary data custodians should be encouraged to make their data available to researchers undertaking IPDs, especially if funded through charities or public grants. The United Kingdom's National Institute for Health Research (NIHR) supports the fundamental principle that "ideas and knowledge derived from publicly funded research must be made available and accessible for public use, interrogation and scrutiny as widely, rapidly and effectively as possible." NIHR also require that NIHR-funded researchers publish their main study findings in a peer-reviewed, open access journal. These policies could be expanded globally, that raw data from publicly funded research should be accessible to approved researchers for IPD

analysis once the original researchers have published their findings. Developing consortia or management teams, such as OA Trial Bank, with whom the primary researcher can deposit data once the study is published, will enhance occurrence and the success of future IPD meta-analyses.

Section Summary

- The opportunity to undertake large sample size analyses makes IPD meta-analyses extremely useful for looking at predictors of response.
- Obtaining the IPD from RCTs is the most important step in conducting an IPD meta-analysis while also providing the greatest challenges.

Classroom Discussion Questions

Classroom Discussion Questions

1. What approaches could be adopted by researchers to maximize the number of both pharmaceutical and academic investigators that decide to share the IPD from their trials?
2. What approaches could funders or publishers adopt to require investigators to share the IPD from their trials?
3. As a primary researcher, what factors should you consider to optimize the use of your data in subsequent IPD analysis?
4. What are the benefits and drawbacks of an IPD meta-analysis over other approaches for identifying predictors of response?

Declaration of Conflicting Interests

The Authors declare that there is no conflict of interest.

Further Reading

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Web Resources

https://www.oatrialbank.com/

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