Identifying back pain subgroups: developing and applying approaches using individual patient data collected within clinical trials

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Scientific summary

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Background

Identifying subgroups of people living with low back pain (LBP) who may do better, or worse, with different treatment choices is a high research priority internationally. Many randomised controlled trials (RCTs) could be designed to address individual components of this problem. High-quality trials in this area are very costly and time-consuming (typically requiring a minimum of 700 participants, at a cost of £1M to £2M, and taking at least 6 years from design to implementation); each will address only one small part of this complex problem.

Alternative methods can provide complementary information that could add value to our knowledge. Approaches, that make the best possible use of existing data might produce timely answers to a range of important research questions and provide substantial added value to the money that is already invested in this area.

We present a programme of work – using systematic reviews, methodological development, and secondary analyses of existing data sets – to identify strategies to improve outcomes for people who are seeking treatment for back pain by improving how patients, clinicians and purchasers choose treatments. Our programme of work ensures that the maximum information is gleaned from existing substantial trial data sets. The analysis plan for these data and the modelling of clinical effectiveness and cost-effectiveness are informed by our literature reviews.

Aims and objectives

The overall aim of this programme grant was to improve the clinical effectiveness and cost-effectiveness of therapist-delivered treatments for LBP by providing patients, their clinical advisors and health service purchasers with better information about which patients are most likely to benefit from which treatment choices. Our objectives were to:

1. synthesise what is already known about the validity, reliability and predictive value of possible treatment moderators (patient factors that predict response to treatment)
2. develop a repository of individual participant data from RCTs testing therapist-delivered interventions for LBP
3. determine which participant characteristics, if any, predict clinical response to different treatments for LBP
4. determine which participant characteristics, if any, predict the most cost-effective treatments for LBP.

Seeking to achieve these objectives required substantial methodological work, including the development and evaluation of some novel statistical approaches. This programme of work was not designed to analyse the main effect of interventions and no such interpretations should be made.

Method and results

To synthesise what is already known about the validity, reliability and predictive value of possible treatment moderators

We carried out two systematic reviews: one to identify potential moderators of treatment effect from studies of therapist-delivered interventions to inform our analyses, and, the second, to review the quality of subgroup analyses in LBP trials.

As the purpose of moderator identification was for future application in our analyses, we identified potential moderators with strong evidence ($p < 0.05$) and potential moderators with weaker evidence in one or more studies ($0.05 < p \leq 0.20$). Data from four trials were included in the review. Potential moderators with strong evidence included age, employment status and type, back pain status, narcotic medication use, treatment expectations and education. Potential moderators with weaker evidence included gender, psychological distress, pain/disability and quality of life. Although the overall data were weak and lacking in rigour to inform clinical practice, they provided a starting point for application in our analyses.

The second review looked at the quality and reporting of subgroup analyses in LBP. Thirty-nine papers were included in the final review. The majority of papers provided only exploratory or insufficient findings. Only three trials provided confirmatory findings (i.e. subgroup analyses were hypothesis driven and grounded in existing theory or empirical data). The overall quality of reporting was poor and, generally, the subgroup analyses have been severely underpowered. We concluded the need to develop new approaches to subgroup identification to identify multiple participant characteristics or clusters of moderators that would identify who is most or least likely to benefit.

To develop a repository of individual participant data from randomised controlled trials testing therapist-delivered interventions for low back pain

To allow the identification of subgroups in appropriately powered data sets, we developed a repository of data from completed trials. We used a systematic approach in identifying trials and approached chief investigators for their data. Our pool of potential trials came from the search results that were generated in our review of moderators. As a starting point, we were interested only in RCTs of therapist-delivered interventions with a sample size of > 179. We were offered data from three smaller trials, which we also included.

The final repository comprises 19 trials, with 9328 participants. No two trials had identical interventions or controls. Despite the large initial sample, we had to broadly pool interventions into groups for our analyses in order to draw any meaningful comparisons. As a first step, we identified the control interventions and classified these as either usual care or as a sham control; furthermore, we have specified the type of sham, as there may be qualitative differences between sham treatments. To cluster the interventions we first classified them into core groups (individual physiotherapy, exercise, manipulation, advice/education, psychological therapy, graded activity, acupuncture, combination therapy, mock transcutaneous electrical nerve stimulation, sham acupuncture and control). We later looked at the data to explore the scope for direct and indirect comparisons, and the data available for these comparisons. This indicated that, without grouping these interventions, it would be difficult to make any meaningful comparisons; therefore, the collaborative team decided on broader categories: active physical (exercise and graded activity), passive physical (individual physiotherapy, manipulation and acupuncture) and psychological (advice/education and psychological therapy). In this programme of work we are not seeking to estimate the true effect size of any individual intervention. Rather, we are seeking to identify predictors of treatment response making it reasonable to pool in this manner.

In addition to the challenges of pooling multiple data sets using multiple interventions, there was careful consideration of how to most accurately map multiple participant-reported outcome measures that measure the same domain, to a common scale. We concluded that, because of the lack of correlation and responsiveness in outcomes from two measures in the same individual, it would not be appropriate to map any physical disability outcome measures to another.

To determine which participant characteristics, if any, predict clinical response to different treatments for low back pain

We undertook analysis of covariance analyses comparing all of the intervention groups with all controls to identify potential moderators to take forward for our main analyses. We were able to take forward the Hannover Functional Ability score, the Roland–Morris Disability questionnaire (RMDQ), the Short Form questionnaire-12 items (SF-12)/ Short Form questionnaire-36 items (SF-36) physical and mental component scores, age, gender, pain, fear avoidance and coping as variables, with a possible signal in one or more analysis.

In this programme grant we have explored, in considerable detail, new and novel methods for subgroup identification. We have presented three core methods in this report: recursive partitioning (interaction trees and subgroup identification based on a differential effect search), adaptive risk group refinement and individual participant data indirect network meta-analysis (NWMA).

Our prespecified analytical approaches – recursive partitioning and adaptive risk group refinement – produced identifiable subgroups, the parameter definitions of which were grounded in the data. The differences in effect sizes, between groups, however, were small, and unlikely to be clinically meaningful. The effect sizes in the groups who did less well would still justify the use of these interventions. The overall results point to larger treatment responses in those with higher levels of the outcome of interest at baseline. The results also suggest that those with greater psychological distress, as measured by the SF-12/36 mental component score, do not have a greater treatment effect on physical outcomes from any of the therapist-delivered interventions tested. Targeting low-intensity interventions at those with higher levels of psychological distress for treatment might not be justified.

We undertook a post hoc exploratory individual participant data indirect NWMA to identify subgroups. This does not identify subgroups in the traditional manner but rather uses the available data to work out the probability that a particular treatment choice is most likely to be effective. The outputs from this method have the potential to inform clinical decision-making but requires further testing and application.

To determine which participant characteristics, if any, predict the most cost-effective treatments for low back pain

We applied the directed peeling algorithm to the economic and resource-use data. When exploring interventions compared with control, subgroups were identified. These subgroups comprised patients who were older, with relatively worse physical functioning at baseline. The gain in treatment effect for the subgroup was small, therefore, given the relatively low cost of the intervention treatment it is likely to be cost-effective for the whole patient group. No convincing subgroups were found for active and passive physical treatment. This may be as a result of lack of power or simply that there is no subgroup to be found.

Age, SF-12/36 physical component score and RMDQ score were the three potential moderators identified from the economic analysis. However, the relationship of the quality-adjusted life-years (QALYs) with the moderators differed in some cases to that of the clinical outcome measures. Subgroups were identified only in the comparison of treatment with control. Our interpretation is that those who are older, with worse RMDQ score and SF12/36 physical component score are likely to gain a greater benefit on QALY outcomes from treatment. Doing this, however, will not improve overall QALY gain and is very unlikely to be seen as a cost-effective choice if the National Institute for Health and Care Excellence threshold of £20,000–30,000 per QALY is used to inform treatment choices.

Conclusions and recommendations

In this programme of work we have developed advances in methodological developments for subgroup analyses. We have developed different approaches to the identification of differential subgroup effects that provide considerable added value compared with conventional analyses that simply test for interactions between single baseline parameters and treatment allocation. In addition, we have developed advanced systems for pooling and storing large data sets, highlighted that it is not possible to map different outcome measures for a meta-analysis, and, finally, we have developed an important resource for back pain researchers who wish to undertake further analyses on data from multiple trials.

Clinically, the application of the different frequentist methods (recursive partitioning and adaptive design) has not allowed us to identify subgroups of patients who might benefit from different back pain treatments. Some of the core outputs and recommendations from this work include:

- application of these methods for the identification of subgroups in other clinical areas
- reanalysis of existing meta-analyses of back pain treatments to separate out results from trials with different outcome measures
- further development of methods and application to the data that we already have
- making the data set available to other researchers
- adding additional trial data sets to the repository
- developing and testing a web portal to help inform choice of treatments based on our NWMA.

Overall, our results do not provide sufficient clinical effectiveness or cost-effectiveness justification for the use of baseline characteristics in the development of subgroups for LBP. We would, however, suggest that such methods should be applied in other clinical areas where subgroups may be important.
The exploratory outputs from our Bayesian NWMA provide some scope for deciding on optimal therapies. This, however, would need empirical testing before clinical recommendation.

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