Development and validation of two clinical prediction models to inform clinical decision-making for lumbar spinal fusion surgery for degenerative disorders and rehabilitation following surgery: protocol for a prospective observational study

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ABSTRACT

Introduction Potential predictors of poor outcome will be measured at baseline: (1) preoperatively to develop a clinical prediction model to predict which patients are likely to have favourable outcome following lumbar spinal fusion surgery (LSFS) and (2) postoperatively to predict which patients are likely to have favourable long-term outcomes (to inform rehabilitation).

Methods and analysis Prospective observational study with a defined episode inception of the point of surgery. Electronic data will be collected through the British Spine Registry and will include patient-reported outcome measures (eg, Fear-Avoidance Beliefs Questionnaire) and data items (eg, smoking status). Consecutive patients (≥18 years) undergoing LSFS for back and/or leg pain of degenerative cause will be recruited. Exclusion criteria: LSFS for spinal fracture, inflammatory disease, malignancy, infection, deformity and revision surgery. 1000 participants will be recruited (n=600 prediction model development, n=400 internal validation derived model; planning 10 events per candidate prognostic factor). The study being predicted is an individual’s absolute risk of poor outcome (disability and pain) at 6 weeks (objective 1) and 12 months postsurgery (objective 2). Disability and pain will be measured using the Oswestry Disability Index (ODI), and severity of pain in the previous week with a Numerical Rating Scale (NRS 0–10), respectively. Good outcome is defined as a change of 1.7 on the NRS for pain, and a change of 14.3 on the ODI. Both linear and logistic (to dichotomise outcome into low and high risk) multivariable regression models will be fitted and mean differences or ORs for each candidate predictive factor reported. Internal validation of the derived model will use a further set of British Spine Registry data. External validation will be geographical using two spinal registries in The Netherlands and Switzerland.

Strengths and limitations of this study

- This study will enable predictions to be made regarding lumbar spinal fusion surgery and rehabilitation based on the risk of poor outcome following surgery.
- The study design is informed by the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis TRIPOD statement of items that should be included in reports of prediction model development and validation to ensure a rigorous methodology.
- A sample of n=1000 participants will ensure adequate power in the analyses (n=600 prediction model development, n=400 internal validation of derived model; planning 10 events per candidate prognostic factor).
- Statistical modelling has been planned a priori.
- Future implementation of the derived models will enable targeting surgical and rehabilitation resources at patients with the greatest clinical need and potential benefit.

Ethics and dissemination Ethical approval (University of Birmingham ERN_17-0446A). Dissemination through peer-reviewed journals and conferences.

INTRODUCTION

Surgery The recent UK National Institute for Health and Care Excellence (NICE) guideline1 is unequivocal in its recommendation regarding lumbar spinal fusion surgery (LSFS). It states that LSFS should not be offered for patients
with non-specific low back pain (NSLBP) unless LSFS is being investigated as part of a randomised controlled trial (RCT). This is coupled with a key research recommendation to investigate whether patients with NSLBP should be offered LSFS as an option for management. The NICE recommendation is noteworthy as LSFS is currently a common and increasingly used procedure aiming to decompress and stabilise the lumbar spine in degenerative presentations that encompass spinal stenosis, disc herniation, discogenic low back pain (examples of NSLBP) and spondylolisthesis (an example of specific LBP).4–5 Momentarily, the primary indication for LSFS is chronic back and/or leg pain, of degenerative or spondylolisthetic cause, resistant to conservative management; where it can potentially stabilise the spine.3 There are three aims of surgical intervention: (1) to stabilise a level(s) of the spine thought to be the pain generator; (2) to stabilise the spine at the same time as performing a lumbar decompression for radicular or stenotic leg pain where the decompression will potentially destabilise the spine or (3) a combination of aims 1 and 2.

In the UK, spinal surgery is the greatest single component of expenditure for managing LBP,6 with approximately 4500 LSFS procedures each year; although accurate National Health Service (NHS) data are difficult to ascertain with 73,000 procedures recorded as ‘other operations on the spine’. Based on current data,7 a 65% increase in LSFS over 13 years, costs the NHS £26 million annually. US data illustrate a substantial increase in hospitalisation for LSFS from 61,000 in 1993 to 451,000 in 20128 with an accompanying increase in national costs for LSFS from US$4.3 to US$33.9 billion between 1998 and 2008.9 LSFS accounted for 14% of USA spending on back surgery in 1992, increasing to 47% by 2003.10 An ageing population and surgical advancements (including anaesthetic advancements making surgery possible for elderly persons) contribute to a continued increase.11

However, data do reveal considerable regional variation in fusion rates within and between countries.10 This may reflect poor surgeon consensus and/or a range of indications for surgery; consistent with a survey from the Netherlands which found a lack of consensus between 62 surgeons regarding both prognostic factors and predictive tests for patient selection for LSFS.5 This contributes to a broad clinical heterogeneity of patients undergoing LSFS. In addition, our survey of UK current practice identified variation by surgeons regarding surgery. For example, the surgical procedure can include open or minimally invasive procedures, be instrumented or non-instrumented, employ different approaches, for example, transforaminal and fuse different numbers of levels,12 dependent on indications for surgery.

The NICE guidelines1 report their analysis of nine studies investigating clinical effectiveness of LSFS (vs usual care, conservative intervention and different surgery). An overall low/very low level of evidence does not demonstrate effectiveness of LSFS but does suggest modest benefit in some elements of pain, function and quality of life and utilisation of healthcare resources. However, only one RCT was found comparing LSFS to usual care and the included studies were extended to cohort studies and other comparators. In a follow-up of three RCTs13 that compared LSFS to multidisciplinary cognitive–behavioural therapy and exercise, no difference in patient-reported outcomes was found. Risk of bias was high across all studies (eg, large cross over bias, no data regarding interventions prior to LSFS were recorded). The guidelines call for an adequately powered multicentre RCT. However, planning for a future RCT first needs to address the clinical heterogeneity of this population, something that is acknowledged in the guidelines in that some patients responded positively to surgery with large treatment effects, thus supporting the value of being able to predict response to LSFS.

Rehabilitation

There is minimal knowledge regarding long-term outcome,6 although one recent paper15 found that after a mean of 11 years (range 8–15 years) follow-up across three RCTs, there was no difference between LSFS and multidisciplinary cognitive–behavioural therapy and exercise (mean-adjusted treatment effect was −0.7 points on the 0–100 Oswestry Disability Index (ODI)). Data from the Swedish National Spine Register revealed that 17% of their patients had no change or worsened back and/or leg pain following surgery and 28% were not satisfied regarding their outcome at 12 months.14 A high revision rate (>200 per year, in the UK12; and 13% rehospitalisation rate USA15) post-LSFS is also reported and is perhaps a sign of overutilisation. Rehabilitation (outpatient active rehabilitation programmes as distinct to normal recovery) following LSFS has also therefore been a focus within the literature. Two recent systematic reviews16 17 identified three trials that provide inconclusive, very low-quality evidence for the effectiveness of physiotherapy rehabilitation following LSFS. Our initial evaluations of current UK practice identified extensive variability in referral to and content of physiotherapy intervention due to the clinical heterogeneity of the LSFS population both presurgery and postsurgery.12 18 A key conclusion from the surveys was therefore that rehabilitation should be tailored to the individual patient.12 18

Key issue

The current evidence highlights a number of problems and a key underlying issue is the clinical heterogeneity of the LSFS population; making selection of patients for surgery, nature of the surgical procedure, selection of patients for rehabilitation and nature of intervention (eg, patients with a poor predicted outcome may require an early and more intensive intervention following surgery) key considerations. Stratified management involves targeting treatment to subgroups of patients based on their key characteristics, such as predictive factors of outcome, in order to support decision-making to maximise treatment benefit, reduce harm, and increase
healthcare efficiency and cost-effectiveness. Probability estimates are frequently based on combining data from multiple predictors to ensure reliable estimates of prognostic probabilities or risks into multivariable (risk) prediction models. Such models are mathematical equations that enable association of multiple predictors for an individual patient to their probability (or risk) of poor outcome.

**Objectives**

Potential predictors of good outcome will be measured at baseline preoperatively to develop a clinical prediction model to predict:

1. Which patients are likely to have a favourable outcome following LSFS, and potential predictors of good outcome will be measured at baseline postoperatively to develop a clinical prediction model to predict:
   2. Which patients are likely to have favourable long-term outcomes following LSFS (to inform rehabilitation).

**METHODS AND ANALYSIS**

**Source of data**

Prospective observational study with a defined episode inception of the point of surgery. The prospective design enables optimal measurement of predictors and outcome and control of unwarranted influences. Objective 1 investigating which patients should receive LSFS requires the development of a prediction model where the predictors are collected preoperatively and the outcomes of interest postoperatively. Objective 2 investigating which patients who received LSFS have a poor long-term outcome requires the development of a prediction model where the predictors are collected postoperatively and the outcomes at long-term follow-up. This protocol is written in line with the TRIPOD statement of items that should be included in reports of prediction model development and validation.

For objective 1, data will be collected electronically at baseline (preoperatively) and outcome will be assessed at 6 weeks post-surgery (to inform selection of patients for surgery). For objective 2, data will be collected electronically at baseline (6 weeks postoperatively) and outcome will be assessed at 12 months (to inform selection of patients for rehabilitation). Procedures are in place to enable data collection in the UK through the British Spine Registry (BSR) (degenerative pathway lumbar region), recruiting participants from January 2018 for approximately 24 months.

The BSR was launched in 2012 with the British Association of Spine Surgeons as the data controller. The database allows all UK spinal surgeons to record information about patient diagnosis, comorbidities (eg, smoking status), surgical procedures, complications, patient-reported outcome measures (PROMs) and patient-reported experience measures. The BSR aims to be a ‘whole practice’ registry covering lumbar degenerative, cervical degenerative, deformity, tumour, trauma, infection and intradural. The PROMs in the lumbar degenerative pathway are back and leg Numerical Rating Scale (NRS), ODI and the EuroQOL five dimensions questionnaire 5 level (ED-5D 5L). Questionnaires can be entered manually if completed on paper or electronically by patients through kiosks in clinic or email link. PROMs are completed before surgery and at 6 weeks, 6 months, 1 year, 2 years and 5 years after surgery. Reminders will be used to maximise completeness of data, in the form of electronic reminders generated by the registry on two occasions at each data collection point; with one SMS and one personal telephone reminder if required. Anonymised data will be downloaded from the BSR into SPSS V.22 and stored securely at the University of Birmingham in line with research governance procedures for a period of 10 years. Data will be checked for completeness. The PROMs data are completed by the patients and surgical data by the surgeon or a member of the clinical team. General Medical Council requirements for probity are likely to keep data accurate.

**Participants**

Eligibility criteria:

- Inclusion criteria: Adult patients (≥18 years) undergoing LSFS for back pain and/or leg pain of degenerative cause.
- Exclusion criteria: LSFS for spinal fracture, inflammatory disease, malignancy, infection, deformity and revision fusion surgery.

Patients will be recruited through the BSR. All patients who are booked in for LSFS for degenerative reasons will be invited to participate and enter their data into the registry. All consecutive eligible patients will therefore be approached for recruitment into the study. Based on feasibility data, it is estimated that 70 eligible participants will be available for recruitment in a 1-month period. Their surgeons will be invited to enter the surgical data when the procedure is complete. Registry data represent approximately 500 spinal surgeons in the UK at the start of data collection. Patients will be asked to provide separate consent through the BSR for an extended data set to be completed for this study.

**Outcome**

The outcome being predicted by the prediction model is an individual’s absolute risk of poor outcome (disability and pain). Outcome will be measured at 6 weeks postsurgery (objective 1) and 12 months postsurgery (objective 2). Disability will be measured using the ODI—a widely used and validated questionnaire to assess people with low back pain. Pain will be measured using severity of pain in the previous week with a NRS 0–10.

**Predictors**

The factors identified in our recent systematic review as being potentially indicative of poor outcome (manuscript under review), and factors identified from surveys...
of surgeons and physiotherapists will be measured at baseline.

These include factors collected from the patient:
- Age.
- Gender.
- Height and weight to obtain body mass index (BMI).
- Education (individual to each country and dichotomise).
- Smoking status.
- Duration of symptoms prior to surgery.
- Previous surgery.
- ODI.
- NRS (0–10) back pain (mean pain previous week).
- NRS (0–10) leg pain (mean pain previous week).
- Analgesia use (dichotomous scale yes/no, frequency of use, name of analgesia).
- Distribution of pain (embedded pain drawing).
- EQ5D-5L.
- Current work status-days postsurgery when returned to work/normal function.
- Pain self-efficacy—two items (items 49 and 50) from the Coping Strategies Questionnaire.
- Pain Catastrophizing Scale.
- Fear-Avoidance Beliefs Questionnaire.
- Preoperative walking capacity—estimated in metres.
- Global rating of symptom change.

Also factors collected from the surgeon:
- Indication for surgery (focused to degenerative cause).
- Number of levels fused.
- Surgical approach.
- Surgical complications.

Demographic factors and details of the operation will also be collected as our survey suggested that some factors (eg, number of levels fused) may be risk factors and are included above.12

Sample size
In predictive modelling a larger sample size enables lower bias and variance, and permits the prospective prediction of new observations. Data will be collected for an estimated n=1000 participants (initial n=600 for prediction model development and the next n=400 for internal validation of the derived model; with about 10 events per candidate prognostic factor) post-LSFS.

Methodological quality in the prediction model
Limited research has identified criteria for quality in a prediction model, but authors have identified potential quality issues to ensure methodological rigour. All issues have been addressed/planned for in this study (table 1).

Patient and public involvement
This study is coproduced by patients and healthcare professionals. It was conceived directly as a result of patients’ comments to the study team regarding their experience of LSFS. Patients have been involved since inception of this programme of research starting years ago and have contributed to our understanding of the findings from the systematic reviews informing this application. Coauthor NRH leads the Centre of Precision Rehabilitation for Spinal Pain’s Patient and Public Involvement group. A lay summary of the study report will be written for patients in collaboration with the group and disseminated through charities (eg, backcare), patient groups (eg, pain support groups) and online fora (eg, www.painsupport.co.uk) to raise awareness of the study and future research plans.

Statistical methods and management of missing data
The characteristics of the participants (demographics, clinical features, predictors) will be reported, with clarity of the number of participants with missing data for either outcome or predictors. A diagram will illustrate the flow of participants through the study, including the number of participants with and without the outcome, and capturing all time points. The correlation between candidate predictive factors will be calculated at baseline.

Statistical modelling has been planned a priori. To explore the influence of each predictive factor on poor outcome, both linear and logistic (to dichotomise the outcome score into low and high risk for the stratification tool) multivariable regression models will be fitted and mean differences or ORs including their 95% CIs for each candidate predictive factor reported. If necessary, multiple imputation will be used to deal with missing data. The characteristics of those patients with and without predictor and/or outcome data will also be compared, to inform whether patients with no predictor and/or outcome data were missing completely at random or not. Multivariable analysis will initially include all candidate predictive factors, and full results reported. Reduced multivariable analyses will be considered if necessary (eg, removing one of two candidate predictive factors that were highly correlated at baseline), to examine robustness of conclusions. Selection of items for the model will include those factors which are statistically significantly (p<0.05) associated with poor outcome according to the full multivariable regression analysis using backward stepwise selection, and those deemed clinically important to retain (regardless of statistical significance) to improve face validity for clinicians. The regression model with included predictive factors will be fitted to the cohort data to obtain a final set of parameter estimates (ie, alpha and beta terms) to form the model.

Risk groups
Good outcome is based on the best current evidence regarding change scores and the largest study to date. It is defined as a change of 1.7 on the NRS for pain, and a change of 14.3 on the ODI.

Development versus validation
For validation of the models, a comparison with the development data will enable analysis of the distribution of important variables; inclusive of demographic, predictor
Table 1  Methodological decisions to improve quality in prediction models

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Methodological decisions to improve quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td></td>
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<tr>
<td>Inception cohort</td>
<td>▶ Clear description of population.</td>
</tr>
<tr>
<td></td>
<td>▶ Clear description of the participants at baseline.</td>
</tr>
<tr>
<td>Source population</td>
<td>▶ Clear description of population.</td>
</tr>
<tr>
<td></td>
<td>▶ Clear description of sampling frame and recruitment (method and timing).</td>
</tr>
<tr>
<td>Inclusion and exclusion criteria</td>
<td>▶ Clarity of eligibility criteria.</td>
</tr>
<tr>
<td>Prospective design</td>
<td>▶ Clarity of study design.</td>
</tr>
<tr>
<td>Study attrition</td>
<td></td>
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<tr>
<td>No of drop-outs</td>
<td>▶ Adequate participation rate.</td>
</tr>
<tr>
<td></td>
<td>▶ Clear description of attempts to collect information on participants who dropped out.</td>
</tr>
<tr>
<td></td>
<td>▶ Reporting numbers and reasons for loss to follow-up.</td>
</tr>
<tr>
<td>Information provided on method of management of missing data</td>
<td>▶ Appropriate methods of imputation of missing data.</td>
</tr>
<tr>
<td>Predictive factors</td>
<td></td>
</tr>
<tr>
<td>All predictive factors described used to develop the model</td>
<td>▶ Clear definition of predictive factors.</td>
</tr>
<tr>
<td></td>
<td>▶ An adequate proportion of participants has completed data for the predictive factor.</td>
</tr>
<tr>
<td>Standardised or valid measurements</td>
<td>▶ The measurement of the predictive factor is reliable and valid.</td>
</tr>
<tr>
<td></td>
<td>▶ The measurement of the predictive factor is the same for all participants.</td>
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<tr>
<td>Linearity assumption studied</td>
<td>▶ Linearity of data will be reported.</td>
</tr>
<tr>
<td>No dichotomisation of predictive variables</td>
<td>▶ Continuous variables will be reported.</td>
</tr>
<tr>
<td>Data presentation all predictive factors</td>
<td>▶ Complete data will be presented.</td>
</tr>
<tr>
<td>Outcome measures</td>
<td></td>
</tr>
<tr>
<td>Description of outcome measures</td>
<td>▶ The outcome is clearly defined.</td>
</tr>
<tr>
<td>Standardised or valid measurements</td>
<td>▶ The measurement of the outcome is reliable and valid.</td>
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<tr>
<td></td>
<td>▶ The measurement of the outcome is the same for all participants.</td>
</tr>
<tr>
<td>Data presentation of most important outcome measures</td>
<td>▶ Complete data will be presented.</td>
</tr>
<tr>
<td>Analysis</td>
<td></td>
</tr>
<tr>
<td>Presentation of univariate crude estimates</td>
<td>▶ An appropriate strategy for model building is described.</td>
</tr>
<tr>
<td></td>
<td>▶ An adequate statistical model described.</td>
</tr>
<tr>
<td>Sufficient numbers of subjects per variable</td>
<td>▶ Adequate data will be presented.</td>
</tr>
<tr>
<td>Selection method of variables explained</td>
<td>▶ Sufficient data will be presented to enable assessment of the adequacy of the analytic strategy.</td>
</tr>
<tr>
<td></td>
<td>▶ All results will be reported.</td>
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<tr>
<td>Presentation of multivariate estimates</td>
<td>▶ An appropriate strategy for model building is described.</td>
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<td></td>
<td>▶ An adequate statistical model described.</td>
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<tr>
<td>Clinical performance/validity</td>
<td></td>
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<tr>
<td>Clinical performance</td>
<td>▶ Clinical performance of the model will be reported.</td>
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<tr>
<td>Internal validation</td>
<td>▶ Internal validation will be reported.</td>
</tr>
<tr>
<td>External validation</td>
<td>▶ Geographical external validation will be reported.</td>
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</table>

and outcome variables. Internal validation of the derived model will use a further set of BSR patient data (n=400) not used in the development process. External validation of the model will be geographical in nature and will use two further sets of patient data from similar spinal registries in The Netherlands and Switzerland. Validation will provide estimates of the ability of the model to discriminate between patients with different outcomes as well as the agreement between the observed and predicted risks (calibration).

DISCUSSION
Study data will be used to develop and internally validate two clinical prediction models to inform clinical
decision-making. First, about which patients are likely to have a favourable outcome following LSFS to inform selection of patients for surgery. Second, about which patients are likely to have favourable long-term outcomes following LSFS to inform selection of patients for rehabilitation and nature of intervention, for example, patients with a poor predicted outcome may require an early and more intensive intervention following surgery. An important requirement of the prediction model is that it should be brief to facilitate use in clinical practice. Thus, we will look to simplify the model where possible to facilitate its use, but without important reduction in its predictive ability in terms of calibration and discrimination. For example, if multi-item questionnaire scores are included in the model, then we will evaluate whether just one of the questionnaire questions is sufficient. This process will result in ideal full and simplified models if possible.

Data will be collected in parallel to this study in The Netherlands and Switzerland using this same protocol to enable external validation of the prediction models. Procedures are already in place to enable data collection through the Dutch Spine Registry and Swiss Spine Registry.

Implications of results
This study will enable predictions to be made regarding surgery and rehabilitation based on the risk of poor outcome following surgery. The resulting estimates of risk will be used to inform clinical decision-making regarding LSFS and rehabilitation interventions in line with guidelines, and future research investigating effectiveness of surgical and rehabilitation interventions. Future implementation of the models will enable targeting surgical and rehabilitation resources at patients with the greatest clinical need and potential benefit. This will therefore enable improved effectiveness (clinical and cost) as it will identify which patients to target with surgery, and post-LSFS which patients to target with rehabilitation.

ETHICS AND DISSEMINATION
Findings will be disseminated through peer-reviewed journals and conferences.

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Contributors ABR is the chief investigator leading protocol development, analyses and dissemination. ABR, JBS and MLV have led on design and are overseeing data analysis plans. ABR, JBS, MLV, AAC, PW, LB and MH have contributed to methodological decisions. MH is the study statistician. ABR, JBS, MLV, AAC, PW, LB, AE, MR, NRH and DF have contributed subject-specific expertise (rehabilitation and surgical). AAC, DS and MWH have enabled British Spine Registry collaboration and modification. All authors will contribute to data interpretation, conclusions and dissemination. ABR drafted the initial manuscript. All reviewers have read, contributed to and agreed the final manuscript. ABR is the guarantor.

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Competing interests None declared.

Patient consent Not required.

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Provenance and peer review Not commissioned; externally peer reviewed.

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