

# BMJ Open Do sensorimotor cortex activity, an individual's capacity for neuroplasticity, and psychological features during an episode of acute low back pain predict outcome at 6 months? A protocol for an Australian, multisite prospective, longitudinal cohort study

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## ABSTRACT

**Introduction** Low back pain (LBP) is the leading cause of disability worldwide, with prevalence doubling in the past 14 years. To date, prognostic screening tools display poor discrimination and offer no net benefit of screening over and above a 'treat all' approach. Characteristics of the sensory (S1) and motor (M1) cortices may predict the development of chronic LBP, yet the prognostic potential of these variables remains unknown. The Understanding persistent Pain Where it ResiDes Trial aims to determine whether sensorimotor cortex activity, an individual's capacity for plasticity and psychosocial factors in the acute stage of pain, predict LBP outcome at 6 months. This paper describes the methods and analysis plan for the development of the prediction model.

**Methods and analysis** The study uses a multicentre prospective longitudinal cohort design with 6-month follow-up. 120 participants, aged 18 years or older, experiencing an acute episode of LBP (less than 6 weeks duration) will be included. Primary outcomes are pain and disability.

**Ethics and dissemination** Ethical approval has been obtained from Western Sydney University Human Research Ethics Committee (H10465) and from Neuroscience Research Australia (SSA: 16/002). Dissemination will occur through presentations at national and international conferences and publications in international peer-reviewed journals.

**Trial registration number** ACTRN1261900002189.

## INTRODUCTION

Low back pain (LBP) is the leading cause of disability worldwide, with prevalence doubling in the past 14 years.<sup>1,2</sup> Twelve weeks after an acute episode of LBP, up to two-thirds of individuals continue to experience pain,<sup>3</sup>

## Strengths and limitations of this study

- The Understanding persistent Pain Where it ResiDes (UPWARD) study is the first adequately powered, longitudinal investigation of candidate predictors related to sensorimotor cortex activity and neuroplasticity in acute low back pain (LBP).
- The UPWARD study includes assessment of both biological and psychosocial candidate predictor variables.
- Assessment of candidate predictors is performed using standardised, robust methodology.
- The statistical analysis plan and candidate predictor variables are prespecified as recommended by the Prognosis Research Strategy framework and the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis reporting guidelines for prognostic research.
- Although classification of recovery from LBP is defined in this study based on cut-offs used in previous literature, there is no universal definition of recovery from an episode of LBP.

and the condition is defined as 'chronic' LBP.<sup>4,5</sup> For some individuals, chronic LBP is self-limiting, but for others, chronic LBP is persistent, is disabling and negatively impacts on daily life.<sup>6</sup> Chronic LBP is resistant to treatment, with current therapies failing to reduce the associated individual and socioeconomic burden.<sup>7,8</sup>

There is increasing interest in the potential for stratified care approaches that enhance the efficiency and benefits of health services.<sup>9-11</sup> In chronic LBP, self-reported

screening instruments that predominantly assess self-reported psychosocial variables such as the five-item instrument for 'Predicting the Inception of Chronic Pain' Tool (PICKUP)<sup>12</sup>; the nine-item The STarT Back Screening Tool<sup>13</sup>; and the short-form Orebro Musculoskeletal Pain Screening Questionnaire<sup>14</sup> have discrimination performance values of 0.61, 0.69 and 0.66, respectively (area under the curve [AUC]).<sup>15</sup> An AUC statistic of <0.7 represents poor discrimination,<sup>16</sup> increasing the potential for misclassification of a large proportion of patients.<sup>12</sup> Further analysis of these prediction models using decision curve analysis suggests no net benefit of screening over and above a 'treat all' approach when considering the likelihood of poor outcome at 4-month follow-up.<sup>15</sup> Consequently, there is limited consensus regarding variables most likely to predict poor outcome following an episode of acute LBP.<sup>17</sup>

Emerging evidence suggests measures of brain structure and function may help identify individuals with subacute pain who are at risk of developing chronic pain.<sup>16 17</sup> For example, altered activity in the primary sensory (S1) and motor (M1) cortices ('maladaptive plasticity') is hypothesised to be associated with the development and maintenance of chronic LBP.<sup>18 19</sup> Data from cross-sectional studies demonstrate that people with chronic LBP have enlarged and shifted M1 representations of the back muscles that show greater overlap and have less discrete boundaries (termed 'smudging') compared with pain-free individuals.<sup>20 21</sup> Similarly, chronic LBP is associated with increased activity and a medial shift of the cortical representation of the back in S1 compared with healthy, pain-free individuals.<sup>22</sup> Positive correlations exist between the magnitude of change in S1 and M1 activity and pain, functional impairment and symptom chronicity.<sup>20 22-25</sup> However, there have been no prognostic longitudinal studies of S1 and M1 activity in any pain condition and it is therefore not possible to determine whether these variables predict pain persistence following an episode of acute LBP.

One additional factor yet to be investigated within prognostic, longitudinal research in pain conditions is brain-derived neurotrophic factor (BDNF). BDNF acts as an important central modulator of neuroplasticity and is upregulated in response to activation of nociceptors during an acute pain episode.<sup>26 27</sup> Further, carriers of the VAL<sub>66</sub>MET allele of the BDNF gene exhibit a decreased capacity for neuroplasticity observed as a reduced potential for cortical reorganisation during motor learning.<sup>28-30</sup> No study has explored whether an individual's capacity for neuroplasticity during an acute episode of LBP can predict LBP outcome.

Finally, evidence supports the capacity for psychosocial factors to predict the development of chronic LBP.<sup>31</sup> When psychosocial factors such as cognitive coping strategy and depression are assessed in prognostic models, they explain ~26% of the total variance in 3-month LBP outcome.<sup>32-34</sup> These figures suggest that although psychosocial factors contribute to the development of CLBP, a

large proportion of variation in outcome is due to factors that are currently unmeasured or unknown.<sup>35 36</sup> The inclusion of both psychosocial and biological variables in prognostic models has the potential to predict a greater proportion of LBP outcome than psychosocial or biological variables in isolation.<sup>37</sup>

The UPWaRD (Understanding persistent Pain Where it ResiDes) study aims to determine whether S1 and M1 activity, an individual's capacity for plasticity and psychosocial features assessed during an acute episode of LBP, predict 6-month LBP outcome. This study is the first adequately powered, longitudinal investigation of candidate predictors related to S1 and M1 activity and neuroplasticity in acute LBP. This protocol paper describes the method and analysis plan for the UPWaRD trial.

## METHODS

### Design

This study uses a multicentre prospective longitudinal cohort design with 6-month follow-up of individuals experiencing an acute episode of LBP. The study is being carried out between December 2014 and June 2019 at two sites (Western Sydney University; Neuroscience Research Australia) in Sydney, Australia. Measures of candidate predictor variables are assessed within 6 weeks of acute LBP onset (T1) and the primary outcome measures (pain and disability) are assessed at 6-month follow-up (T2). Ethical approval has been obtained.

### Setting

Participants are recruited via: local hospitals in South East Sydney and South Western Sydney local health districts, New South Wales, Australia, primary care practitioners (eg, general practitioners and physiotherapists), newspaper/online advertisements, flyers and social media sites such as Facebook.

### Patient and public involvement

Patients and the public were not involved in the design of this protocol. Patient advocacy groups (Chronic Pain Australia, Pain Australia) will provide support for recruitment through dissemination of recruitment flyers in newsletters, websites and social media. Individual test results will be provided to participants on request and a summary of the overall outcomes of the study will be available to all participants on completion of the trial.

### Participants

Potential participants are screened to determine whether they meet the following inclusion and exclusion criteria.

### Inclusion criteria

Eligible participants must be 18 years or older and currently experiencing acute non-specific LBP—defined as pain in the region of the lower back, superiorly bound by the thoracolumbar junction and inferiorly by the gluteal fold.<sup>38</sup> Participants remain eligible if they have pain referred beyond this region that is not suspected

radicular pain from neural tissue involvement. Pain must have been present for more than 24 hours and less than 6 weeks duration following a period of at least 1-month pain-free.<sup>38–40</sup> As we aim to determine which variables predict LBP outcome, regardless of whether this is the first episode of pain, participants need not be experiencing their first LBP episode. Previous history of LBP will be included as a candidate predictor in the statistical model. Participants must provide written informed consent to participate and be able to speak and read English.

#### Exclusion criteria

Known or suspected serious spinal pathology (fracture; malignancy, inflammatory or infective diseases of the spine; cauda equina syndrome or widespread neurological disorder); suspected or confirmed pregnancy or less than 6 months post partum; suspected radicular pain (dominant leg pain, positive neural tissue provocation tests and/or any two of altered strength, reflexes, or sensation for the same nerve root, assessed clinically); previous lumbar spinal surgery (eg, spinal fusion, intervertebral disc replacement); presence of another painful condition (eg, fibromyalgia, neuropathy, rheumatoid arthritis); comorbidities affecting sensorimotor function or causing neurological deficit (eg, multiple sclerosis, spinal cord injury); history of psychological disorders requiring medication for symptom control (eg, major depressive disorder, bipolar disorder, schizophrenia) and/or contraindications to transcranial magnetic stimulation.<sup>41</sup>

#### Outcome measures

##### Primary outcome

##### *Pain intensity*

Participants complete the Brief Pain Inventory (BPI) at T1 and T2<sup>42</sup> where they are asked to score their pain intensity on average over the previous week using an 11-point numerical rating scale (NRS: 0='no pain', 10='worst pain imaginable'). At T2, NRS score  $\leq 1$  will be classified as recovered LBP and NRS score  $\geq 2$  will be classified as chronic LBP. Similar classification has been reported previously.<sup>43 44</sup>

##### Secondary outcome

##### *Disability*

Participants complete the 24-point Roland Morris Disability Questionnaire (RMDQ) at T1 and T2.<sup>45</sup> This questionnaire detects the level of disability experienced as a result of LBP. At T2, RMDQ score  $\leq 6$  will be classified as recovered LBP and RMDQ score  $\geq 7$  will be classified as chronic LBP. This definition of chronic LBP replicates the cut-off used in other prognostic tools.<sup>13 46</sup>

#### Candidate predictors

Fifteen candidate predictors are selected a priori based on a theoretical association with the development of chronic LBP (table 1).

**Table 1** A priori candidate predictors

Assessment domain	Predictor variable
Sensory and anterior cingulate cortex activity	SEP N80 component area SEP N150 component area SEP P260 component area
Motor cortex activity	L3 map volume L5 map volume L3/L5 centre of gravity overlap
Capacity for neuroplasticity	BDNF genotype BDNF serum concentration
Psychological status	PCS DASS-21 PSEQ
Demographics	Age Sex
Baseline pain intensity	NRS score at T1 Previous history of low back pain

BDNF, brain-derived neurotrophic factor; DASS-21, Depression, Anxiety and Stress Scale; L3, electrode recording site 3 cm lateral to the L3 spinous process; L5, electrode recording site 1 cm lateral to the L3 spinous process; PCS, Pain Catastrophising Scale; PSEQ, Pain Self-Efficacy questionnaire; SEP, sensory evoked potential; T1, within 6 weeks of acute low back pain onset; NRS, 11-point numerical rating scale.

#### Sensory and anterior cingulate cortex activity

Sensory evoked potentials (SEPs) will be recorded in response to electrical stimulation of the paraspinal muscles<sup>22</sup> through surface electrodes positioned 3 cm lateral to the L3 spinous process, ipsilateral to the side of worst LBP. The side of worst LBP is determined on the day of baseline testing by asking the participant 'on average over the past 24 hours which side of your back is most painful'? If the participant is unable to determine the most painful side, and reports central LBP at all times over the past 24 hours, stimulation is applied ipsilateral to their dominant hand. Participants are seated comfortably in a chair, with feet on the floor and arms relaxed. A constant current stimulator (Digitimer, DS7AH) delivers the non-noxious electrical stimuli through bipolar electrodes (silver-silver chloride disposable electrodes; Noraxon USA, Arizona, USA) at 3 x an individual's perceptual threshold. If this stimulus evokes pain, the intensity is reduced as required. Electrical stimuli are applied with a pulse duration of 1 ms and a frequency of 2 Hz. A variable interval schedule of 20% is applied to reduce accommodation. Two blocks of 500 stimuli are recorded for each participant.<sup>47</sup>

S1 activity is recorded using electroencephalography (EEG) via gold-plated cup electrodes (Digitimer, Reusable Au and Ag EEG Cup Electrodes) positioned over S1 (3 cm lateral and 2 cm posterior to Cz) on the side contralateral to worst LBP and referenced to Fz according to the International 10/20 EEG placement system.<sup>48</sup> EEG signals are amplified 50000x, bandpass filtered between 5 and 500 Hz and sampled at 1000 Hz using a Micro1401



data acquisition system and Signal software (Cambridge Electronic Design [CED], Cambridge, UK). To exclude the potential interference of repeated sensory stimuli on motor cortical activity,<sup>47</sup> SEPs are recorded after transcranial magnetic stimulation (see below).

The area of the  $N_{80}$  component (between the first major downward deflection of the curve after stimulation and the first major negative peak,  $N_{80}$ ),  $N_{150}$  component (between the first negative peak,  $N_{80}$  and second negative peak,  $N_{150}$ ) and  $P_{260}$  component (between the second negative peak,  $N_{150}$  and the positive deflection of the curve starting around 150 ms after stimulus onset,  $P_{260}$ ) of the SEP are used in the analysis. The  $N_{80}$  component is thought to represent activity in S1, the  $N_{150}$  activity in the secondary sensory cortex (S2) and  $P_{260}$  activity in the anterior cingulate cortex.<sup>18 22 49</sup>

### Motor cortex activity

Participants are seated comfortably in a chair, with their feet on the floor and arms relaxed. A tight fitting bathing cap is applied to each participants head, with the vertex determined using the 10/20 International EEG Electrode Placement system.<sup>50</sup> Single-pulse, monophasic transcranial magnetic stimulation (TMS) is delivered to the M1 contralateral to the side of worst LBP (Magstim 200 stimulator/7 cm figure-of-eight coil; Magstim Co., Dyfed, UK). During testing, the coil is positioned tangential to the skull and moved lateral to the midline. This orientation has been shown to minimise concurrent excitation of the opposite hemisphere and elicit consistent motor evoked potential (MEP) responses in paraspinal muscles.<sup>40</sup> Using a stimulator intensity of 100%, with an interstimulus interval of ~5 s, five stimuli are delivered over premarked scalp sites on a 6×7 cm grid, commencing at the vertex.<sup>21</sup>

Surface electromyography (EMG) is recorded from the paraspinal muscles with electrodes (silver-silver chloride disposable electrodes; Noraxon USA, Arizona, USA) placed longitudinally at 1 cm lateral to the L5 spinous process, and 3 cm lateral to the L3 spinous process ipsilateral to the side of worst LBP. These sites have been used previously<sup>36</sup> and are appropriate for recording EMG from the back muscles.<sup>37</sup> Ground electrodes are placed bilaterally over the anterior superior iliac spines. EMG data are preamplified 2000 times, bandpass filtered (20 to 1000 Hz) and sampled at 2000 Hz using a Power 1401 Data Acquisition System with Signal two software (CED, UK).

As paraspinal MEPs are difficult to elicit at rest,<sup>20 36–38</sup> M1 stimulation is conducted during submaximal paraspinal muscle contractions. Participants are asked to perform three maximum voluntary contractions (MVCs) of the paraspinal muscles against resistance for ~3 s. The target EMG amplitude is determined as 20% of the highest root mean square (RMS) EMG for 1 s from the average of the three MVCs. Target muscle activation is achieved by leaning backward into resistance provided from a pillow, while keeping the back straight. Visual and verbal feedback are provided to

the participant throughout the procedure to ensure paraspinal muscle contraction remains at 20% of MVC during stimulation.

TMS map data are exported and analysed using MATLAB 7 (The MathWorks, USA). EMG traces of the five MEPs recorded at each scalp site are averaged. MEP onset and offset are visually identified from the averaged traces and the RMS EMG amplitude between the onset and offset times calculated.<sup>20 21 51–53</sup> Background RMS EMG between 55 and 5 ms prior to stimulation is subtracted.<sup>21</sup>

MEP responses are superimposed over the respective scalp sites to construct a topographical representation of the target paraspinal muscle and normalised to the peak response for each participant.<sup>25</sup> Normalised values below 25% of the peak response are removed and the remaining values rescaled between 0% and 100%.<sup>21</sup>

Two parameters are calculated from the normalised motor cortical maps. First, map volume, a measure of total excitability of the motor cortical representation, is calculated as the sum of the mean normalised RMS MEP at all active scalp sites. A scalp site is considered active if the normalised MEP response is equal to or greater than 25% of the peak response. Second, the centre of gravity, defined as the amplitude weighted centre of the map, is calculated for the motor cortical representation of L3 and L5 paraspinal muscles using the formula:  $CoG = CoG = \frac{\sum V_i \cdot X_i}{\sum V_i}, \frac{\sum V_i \cdot Y_i}{\sum V_i}$  where:  $V_i$  = mean MEP response at each site with the coordinates  $X_i, Y_i$ .<sup>54 55</sup>

### Capacity for neuroplasticity

#### BDNF genotyping

Cheek swabs taken on the day of baseline testing are used to prepare genomic DNA (Isohelix DNA Isolation Kit). Samples taken at T1 are immediately frozen at -80°C and stored until analyses. PCR is performed to amplify a 197 bp product with the  $VAL_{66}MET$  polymorphism located at 73 bp, with reaction conditions of denaturation at 95°C for 2 min, 35 cycles of 95°C for 15 s, 60°C for 15 s and 72°C for 30 s, with final extension at 72°C for 5 min.<sup>56</sup> Restriction digests are resolved on a 2% agarose gel. As the  $VAL_{66}MET$  polymorphism destroys the Eco721 site, the samples can be classified as VAL/VAL, VAL/MET or MET/MET based on the observed banding pattern. All samples are genotyped using two independent PCRs.<sup>56</sup>

#### BDNF serum concentration

Peripheral venous blood is drawn into serum tubes (BD Vacutainer, SST II Advance) and clotted (30 min, room temperature) at T1. Serum is then separated by centrifugation (2500 rpm, 15 min) and stored separately at -80°C until measurement. BDNF serum concentration is measured using ELISA (Simple Plex Cartridge Kit, Biotrend). All samples are measured in duplicate and averaged for analysis. The detection limit is 62.5 pg/mL with intra-assay and interassay coefficients of variation <10%.<sup>57</sup>

## Psychological status

### Pain Catastrophising Scale

The Pain Catastrophising Scale (PCS) is included to assess catastrophising thoughts about pain. PCS includes 13 items, scored on a five-point scale. A total score between 0 and 52 is calculated, with higher scores indicating more severe catastrophic thoughts about pain.<sup>58</sup>

### Depression, Anxiety and Stress Scale

A 21-item version of the Depression, Anxiety and Stress Scales Questionnaire (DASS-21) will be administered. The questionnaire includes three seven-item subscales: DASS-depression, DASS-anxiety, DASS-stress. A total score is obtained for the DASS-21 with higher scores indicating greater depression, anxiety and/or stress.<sup>59 60</sup>

### Pain Self-Efficacy Questionnaire

The pain self-efficacy questionnaire consists of 10 items, each scored on a seven-point scale. The questionnaire evaluates the confidence of an individual in their ability to perform a range of functional activities while in pain. A total score between 0 and 60 is calculated, with higher scores representing greater self-efficacy beliefs.<sup>61</sup>

## Demographics and baseline pain intensity

Age and sex data will be collected from all participants at baseline. Baseline pain intensity will be drawn from the BPI administered at T1 (as described under primary outcome measures) where participants score their pain intensity on average over the previous week using the NRS.

## Statistical analysis

Data analysis will be carried out using SPSS for Windows (V.25; SPSS, Chicago, Illinois, USA). Continuous variables will be presented through centrality measures (mean, median), dispersion (SD and IQR) according to the distribution and categorical variables through frequencies and percentages. A primary and secondary analysis will occur to interpret the collected data.

### Primary analysis

The primary analysis will use multivariate linear regression models to determine the candidate predictors associated with (1) pain intensity (NRS: 0='no pain', 10='worst pain imaginable') and (2) disability at T2. Recovery from LBP is complex and highly individual<sup>45</sup>; there remains no clear consensus on what constitutes recovery from an episode of LBP. For this reason, we will first explore the data using a linear regression model that does not attempt to dichotomise outcomes into recovered/non-recovered. Maintaining continuous outcome variables also minimises information loss, increasing statistical power.

The cumulative probability of being recovered from an episode of LBP is reported to be 39.9% at 6 weeks, 58.2% at 12 weeks and 72.5% at 12 months.<sup>62</sup> These figures suggest data will be normally distributed. Therefore, we expect to analyse pain intensity and disability scores at T2 using linear regression, generalised linear models with normal

distribution and identity link function. All predictors with a  $p$  value  $<0.20$  in a univariate analysis will be considered for inclusion in the final linear regression multivariate model. Model assumptions will be tested, including a test of multicollinearity. Goodness of fit of the final linear regression model will be reported with adjusted  $R^2$  values. In the event that the data are overdispersed, we will opt for a Poisson or negative binomial model and log likelihood and Akaike's information criterion (AIC) will be reported.

### Secondary analysis

The secondary analysis will use logistic regression to investigate the relationship between baseline candidate predictors and measures of chronic LBP (pain intensity and disability). Logistic regression analysis will allow for development of a prognostic model in line with recommendations of the Prognosis Research Strategy group and Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement.<sup>63 64</sup> Further, the generated predicted probabilities of recovery at T2 will allow for direct comparison with other published LBP prognostic tools.<sup>12-14 65-67</sup>

### Variable selection

Multivariable logistic regression with backward stepwise selection will be employed. Backward stepwise selection is the preferred automated predictor selection technique, as correlations between predictors are considered in the modelling procedure.<sup>68</sup> AIC will be used as a stopping rule for variable selection. Using AIC as a stop rule corresponds to a significance level of  $\alpha=0.157$ , is favourable in smaller data sets and accounts for model fit.<sup>68 69</sup>

Continuous predictor variables will be treated as linear in the primary analyses. As per the TRIPOD statement, categorisation of continuous variables is not necessary for statistical analysis and contributes to significant information loss.<sup>68</sup> The linearity of continuous predictor variables will be examined with the predicted probability of chronic LBP as the dependent variable using scatter plots and the Box-Tidwell transformation.<sup>70</sup> A check for linearity will be performed and possible improvement of fit investigated by allowing some form of non-linearity.<sup>68</sup> For continuous predictor variables that demonstrate a significant non-linear relationship with the dependent variable, transformation will occur.

### Model performance

We will examine the predictive performance of the prognostic models by analysing measures of calibration and discrimination. Calibration reflects the agreement between predictions from the model and observed outcomes, assessed graphically. The observed risk is plotted on the y-axis, against predicted risks on the x-axis. We will test for agreement between predicted and observed probabilities using the Hosmer-Lemeshow test.<sup>71</sup> Discrimination refers to the ability of the prediction model to differentiate between those who will

recover from LBP and those who will not. This will be reported using the concordance index, which equals the area under the receiver operating characteristic curve.<sup>72</sup>

### Sample size estimation

#### Primary analysis

Ten subjects will be ensured per variable (SPV) in the linear regression model to assess whether baseline variables are associated with pain intensity at T2. More than one-third of variables (>5 candidate predictors) are not anticipated to demonstrate a significant association during univariate analysis with the outcome of interest, or display multicollinearity, and will subsequently be excluded from the model. Thus, allowing for 20% loss to follow-up, with 10 remaining candidate predictors, we require 120 participants with acute LBP to ensure at least 10 SPV.<sup>73</sup>

#### Secondary analysis

We will seek a minimum of five events per variable for logistic regression analysis.<sup>74</sup> In line with the above sample size estimation for linear regression, we will recruit 120 participants with acute LBP. Considering a maximum of 10 candidate predictors remaining in the multivariable logistic regression model following backward stepwise selection, we require a minimum of 50 events (ie, presence of chronic LBP at T2). There is substantial variability in the clinical course of acute LBP with estimates for the risk of developing chronic LBP reportedly as high as 56%.<sup>75</sup> Further, recurrence of LBP is common, with 12-month recurrence rates reported in the literature ranging from 24% to 80%.<sup>40 76 77</sup> This variability suggests a sample size of 120 participants with acute LBP should be adequate to power the logistic regression analysis.

#### Missing data

Cases with missing values will be removed from the data set if follow-up rates are higher than 95%. If missing data exceed 5%, multiple imputation will be used in line with recommendations from the TRIPOD statement.<sup>68</sup> Multiple imputation involves creating multiple copies of the data set, with the missing values replaced by imputed values drawn from their predicted distribution in observed data.<sup>78 79</sup> The number of imputations should be related to the fraction of missing data.<sup>80</sup> We will report the methods used for combining all reported estimates following multiple imputation (ie, Rubin's rules).<sup>68 81</sup> Where data are missing at random (ie, missing randomly, conditional on covariates), estimates based on multiple imputation are unbiased.<sup>82</sup>

### ETHICS AND DISSEMINATION

Ethical approval has been obtained. Dissemination will occur through presentations at National and international conferences and publications in international peer-reviewed journals.

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