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CLINICAL TRIAL PROTOCOL

A randomised controlled trial of implementation of a guideline-based clinical pathway of care to improve health outcomes following whiplash injury (*Whiplash ImPaCT*): Statistical analysis plan

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Abstract
Background: Statistical analysis plans describe the processes of data handling and analysis in clinical trials; by doing so they increase the transparency of the analysis and reporting of studies. This paper reports the planned statistical analysis plan for the *Whiplash ImPaCT* study. For individuals with whiplash injury, *Whiplash ImPaCT* aims to assess the effectiveness of a guidelines-based clinical pathway of care compared with usual care.
Methods: We report the planned procedures, methods, and reporting for the primary and secondary analyses of the *Whiplash ImPaCT* study. The primary outcomes are Global Recovery and Neck Disability Index at 3 months post-randomisation. Outcomes will be analysed according to the intention to treat principle using linear mixed models. A cost-utility analysis will be conducted to compute the incremental cost-effectiveness of the intervention to usual care. We

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describe data handling, our analytical approach, assumptions about missing data, and our planned methods of reporting.
Discussion: This paper will provide a detailed description of the planned analyses for the *Whiplash ImPaCT* trial.

Introduction

Background and rationale

Whiplash-associated disorders (WAD), resulting from road traffic crashes (RTC), are a substantial worldwide health and economic burden.[1,2] The propensity to progress to chronic disabling conditions[3,4] influences the rise in health and economic costs associated with treatment, productivity loss, and compulsory third party insurance claims.[1] Established treatments fail to address the heterogeneity of the condition and this may partly account for their lack of effectiveness.[5]

The stratification of patients based on their risk of developing chronic pain, or other poor health outcomes, has been gaining momentum in both the research and clinical management of musculoskeletal pain; for acute WAD, a clinical risk-screening tool (*WhipPredict*) has been developed and validated.[6,7] In a risk-stratified approach for patients with WAD, those identified at low risk of poor recovery would receive minimalistic care, comprising advice and exercise, while those identified at medium-to-high risk would require more comprehensive assessment of physical and psychological risk factors, with treatment then targeted toward these risk factors.[8] While a risk-stratified approach in patients with acute low back pain has shown promise in improving health outcomes,[9] such a model of care has not been evaluated for patients with acute WAD.

Whiplash ImPaCT is the first randomised controlled trial to evaluate the implementation of a risk-stratified, guideline based, clinical care pathway for acute WAD. The trial was prospectively registered (ACTRN 12615001367538) and the study protocol has been published elsewhere.[8] This statistical analysis plan describes the planned statistical analyses and reporting for the primary and secondary outcomes of the trial. The plan follows the recommendations of the Guidelines for the Content of Statistical Analysis Plans in Clinical Trials.[10]

Objectives

The primary objective of *Whiplash ImPaCT* is to implement and evaluate the effect of a guideline-based clinical pathway of care (CPC) on health outcomes (Global Rating of Change, GRC[11]; Neck Disability Index, NDI[12,13]). Secondary objectives are: (i) to investigate the effect of CPC on a range of secondary health outcomes (described in detail in the methods section); (ii) to investigate any differential effect of risk of recovery ('low risk' or 'medium/high risk') on health outcomes for the CPC; (iii) To conduct an economic evaluation of the CPC, and (iv) via an embedded observational study, to conduct a comparison of professional practice between the CPC and usual care.

Methods

Trial design

The trial was approved by the Human research ethics approval committees: Griffith University (AHS/10/14/HREC), University of Sydney (2014/778); NSW Sydney Local Health District (HREC/15/RPAH/73), The University of Queensland (2015001908) and Queensland Health (HREC/15/RPAH/73)

Whiplash ImPaCT is a multi-centre two-arm parallel randomised controlled trial with 1:1 allocation, and conducted in two Australian states (Queensland, New South Wales). Outcome assessors are blinded to group allocation.

Full details of the interventions are described in the trial protocol.[8] In brief, participants were randomised to either (i) a usual care pathway, defined as care provided by the primary health care professional that is based on their clinical judgement, or (ii) a CPC, with care matched to the predicted risk of recovery identified using *WhipPredict*. For patients randomised to the CPC, those at low risk of ongoing pain and disability (hence, predicted to fully recover) received up to three sessions of guideline-based advice and exercise with their primary healthcare professional. Participants at medium/high risk of developing ongoing pain and disability were referred to a specialist (defined as a practitioner with expertise in the management of WAD) who conducted a more in-depth physical and psychological assessment. As a result, the specialist would liaise with the original primary healthcare provider and determine one of three further pathways of care (shared care with the original primary health care provider; the specialist took over the patient's care, or the specialist referred to another practitioner, for example a clinical psychologist).

Whiplash ImPaCT was funded by the National Health and Medical Research Council of Australia (NHMRC APP 075736), the Motor Accident Insurance Commission (MAIC) Queensland, and the State Insurance Regulatory Authority (SIRA) New South Wales.

Randomisation

An independent researcher, not otherwise involved in recruitment or analysis, drew up the randomisation schedule. For sequence generation, they used a computer-based system (Stata version 12) to create permuted blocks of size 4 to 8, stratified for the *WhipPredict* risk subgroup and treatment site. Subsequently, they used consecutively numbered, sealed, opaque envelopes to ensure allocation concealment.

Sample size

The study has two primary health outcome measures, GRC and NDI; we used the NDI for calculation of study sample size. With the outcome being change in NDI pre-post, based on detecting a medium effect size (10% change on the NDI is considered clinically worthwhile, SD: 18) in a 2 × 2 interaction with a power of 0.80 and alpha of 0.05, the required minimum is $n = 196$ participants. Given that we anticipated recruiting 50% medium/high vs low risk participants, this equates to 50 participants in each cell (high-low risk, *usual care-CPC*). Allowing for a 15% dropout rate, the study aimed to recruit $n = 236$ participants. This sample size would be sufficient for the second primary outcome (GRC), where we anticipated the effect size to be larger at 0.75 (clinically worthwhile change is 1.5 points, SD: 2.0).

Statistical interim analysis and stopping guidance

No interim analyses or stopping guidelines were specified.[8]

Timing of final analysis

All outcomes will be analysed collectively, the analysis will occur following the collection of all follow-up data for all participants.

Timing of outcome assessments

Outcomes were measured at baseline, 3, 6, and 12 months post-randomisation.

Statistical principles

Confidence intervals and *p* values

We will calculate and interpret between group differences and 95% confidence intervals for all outcomes. Statistical tests will be two-tailed with α=0.05.

Adherence and protocol deviations

For adherence, alignment of treatment decisions with the aims of the CPC will be evaluated. For patients as assessed as *low-risk*, the aim of the CPC was to provide minimal treatment (up to 3 sessions). For patients assessed as *medium/high-risk* the aims of the CPC were: timely referral to specialists (within 6 weeks), and for primary health care providers to provide guideline-based treatment. Adherence to these aims will be assessed by reviewing treatment questionnaires completed by the primary health care provider and the patient participants at 3 months post-randomisation. These data will be descriptively analysed and reported.

Analysis populations

Analyses will be conducted according to intention-to-treat principle (i.e. participants will be analysed in the group to which they were randomised to, regardless of whether the participant received the allocated intervention).

Trial population

Eligibility

The eligibility criteria are outlined in detail in the published protocol.[8] In brief, participants with acute WAD Grades I-III (i.e. without fracture or dislocation), and within 6 weeks of injury were eligible for inclusion.

Recruitment

We will report the flow of participants through the trial using a CONSORT flow diagram. A dummy flowchart (**Fig. 1**) shows the presentation of information that we will report. Participants may withdraw from the trial intervention, decline to provide follow up data, or both. Additionally, participants may withdraw their consent from the trial completely.

Withdrawal/Follow-up

Where known, reasons for patient withdrawal will be summarised. Frequencies of patients lost to follow-up at each time will be reported in text, with the frequency of those remaining in the trial at each time point reported in the header of **Table 2**.

Baseline patient characteristics

We will examine the distribution of all baseline variables stratified by treatment group. Continuous variables will be summarised using the following statistics: number (non-missing sample size), mean and standard deviation for approximately normally distributed variables; median, range, and interquartile range for non-normally distributed variables. Normality will be assessed visually using normal quantile-quantile (Q-Q) plots, and statistically using skewness/kurtosis tests. We will report the number and proportions of missing observations. For categorical data, variables will be summarised by percentages along with their frequencies (numerator) and the number of patients for whom data are available (denominator). In accordance with the recommendations of the CONSORT statement, between-arm characteristics will not be tested statistically,[14] but based on the judgement of the research team, any important observed imbalances will be described. **Table 1** shows the data items used to describe the characteristics of the sample and groups at baseline.

Outcome definitions

Outcomes were collected online using REDCap (Vanderbilt University). Hard copies of the questionnaires were sent to participants without Internet access, or those who preferred to complete hard-copy questionnaires.

We will assesses two primary health outcomes: (i) GRC, an 11-point scale ranging from −5 (very much worse) to +5 (completely recovered) where the midpoint 0=unchanged,[11] and (ii) neck related disability, measured using the NDI.[12,13] The timing of the primary end point was not initially specified in the trial protocol; here we define it as 3 months post-randomisation.

We will assess six secondary health outcomes: (i) pain self-efficacy, measured using the Pain Self Efficacy Questionnaire[15]; (ii) pain intensity over the last week and the

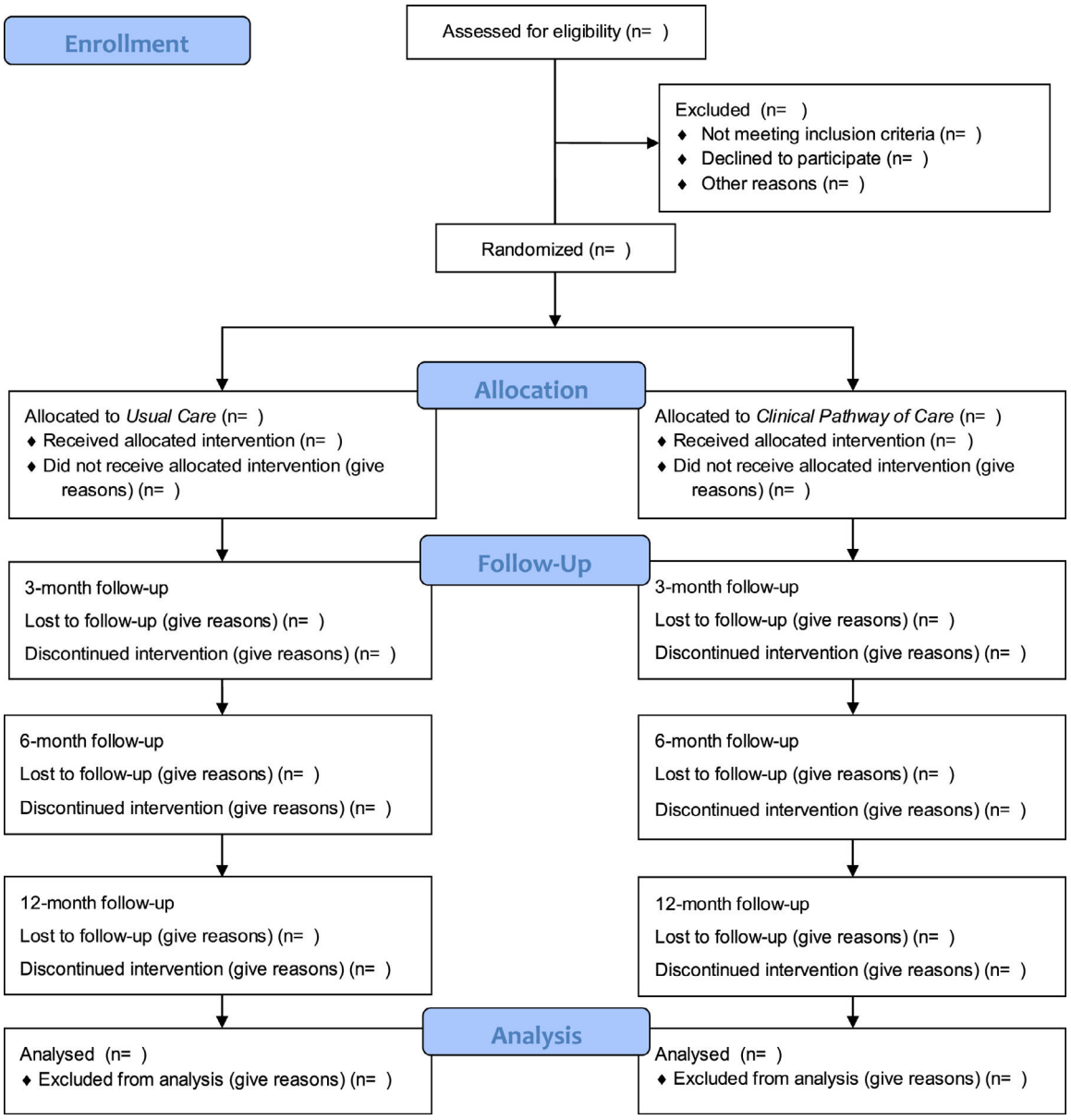

Fig. 1 Flow of participants through the trial.

last 24 h, measured using a numerical rating scale assessing average pain[16]; (iii) general disability using the World Health Organization disability assessment schedule II short form (WHODASII)[17]; (iv) health related quality of life status, measured using the SF-12[18-20]; (v) post-traumatic stress symptoms, using the Posttraumatic Stress Diagnostic Scale (PDS)[21]; and (vi) pain-catastrophising, measured using the Pain Catastrophising Scale.[22]

The cost-effectiveness outcome will be the incremental cost-effectiveness ratio (ICER) for the CPC, compared with usual care.

Analysis methods

A statistician blinded to treatment allocation will perform the primary and secondary analyses. The cost-utility analysis will be conducted by a health economist, also blinded to treatment allocation.

Data integrity

For data collected online, cross-checking will not be conducted because the data required no manual handling by the research team. Data from participants who completed hard copy questionnaires were single-entered manually into Redcap and will be cross-checked by a second researcher. Variables will be inspected for out-of-range values and corrected where possible by reference to the source questionnaires. Any remaining out-of-range values will be dropped.

Health outcomes

For each primary outcome (GRC, NDI) we will use a separate linear mixed-effects model to analyse the effect of study group allocation at 3 months post-randomisation. Such models can yield unbiased estimates and are robust to missing data, where those data are missing at random (MAR).[23]

Table 1 Baseline characteristics *of participants.* values are n (%), except for those marked (*) which are Mean ± SD.

Variable		CPC Pathway	Usual Care
Risk status	*low*	XX (XX.X)	XX (XX.X)
	medium/high	XX (XX.X)	XX (XX.X)
Age in years*		XX.XX (XX.X)	XX.XX (XX.X)
Female		XX.XX (XX.X)	XX.XX (XX.X)
Level of education	*Secondary*	XX (XX.X)	XX (XX.X)
	Tertiary- technical	XX (XX.X)	XX (XX.X)
	Tertiary - academic UG	XX (XX.X)	XX (XX.X)
	Tertiary - academic PG	XX (XX.X)	XX (XX.X)
	Others	XX (XX.X)	XX (XX.X)
	Not specified	XX (XX.X)	XX (XX.X)
Employment Status	*Employed*	XX (XX.X)	XX (XX.X)
	Self-employed	XX (XX.X)	XX (XX.X)
	Home duties	XX (XX.X)	XX (XX.X)
	Unemployed	XX (XX.X)	XX (XX.X)
	Retired	XX (XX.X)	XX (XX.X)
	Entitled leave	XX (XX.X)	XX (XX.X)
	Student	XX (XX.X)	XX (XX.X)
Job type	*Managers*	XX (XX.X)	XX (XX.X)
	Professional	XX (XX.X)	XX (XX.X)
	Technicians and associate professionals	XX (XX.X)	XX (XX.X)
	Clerical support	XX (XX.X)	XX (XX.X)
	Service and sales	XX (XX.X)	XX (XX.X)
	Skilled agricultural, forestry and fishery	XX (XX.X)	XX (XX.X)
	Craft and related trades	XX (XX.X)	XX (XX.X)
	Plant and machine operators, and assemblers	XX (XX.X)	XX (XX.X)
	Elementary occupations	XX (XX.X)	XX (XX.X)
	Other (including home duties)	XX (XX.X)	XX (XX.X)
Working hours	*Working usual hours*	XX (XX.X)	XX (XX.X)
	Working reduced hours	XX (XX.X)	XX (XX.X)
	Not working	XX (XX.X)	XX (XX.X)
If reduced hours, reduced FTE*		XX.XX (XX.X)	XX.XX (XX.X)
Gross annual income	*0 to $18,200*	XX (XX.X)	XX (XX.X)
	$18,201 to $37,000	XX (XX.X)	XX (XX.X)
	$37,001 to $87,000	XX (XX.X)	XX (XX.X)
	$87,001 to $180,000	XX (XX.X)	XX (XX.X)
	More than $180,000	XX (XX.X)	XX (XX.X)
	Not provided	XX (XX.X)	XX (XX.X)
Time since crash in weeks*		XX.XX (XX.X)	XX.XX (XX.X)
Role in crash	*Driver*	XX (XX.X)	XX (XX.X)
	Front seat passenger	XX (XX.X)	XX (XX.X)
	Back seat passenger	XX (XX.X)	XX (XX.X)
	Motor bike	XX (XX.X)	XX (XX.X)
Type of collision	*Rear end*	XX (XX.X)	XX (XX.X)
	Front end	XX (XX.X)	XX (XX.X)
	Rear and front end	XX (XX.X)	XX (XX.X)
	Side impact	XX (XX.X)	XX (XX.X)
Admitted to hospital admission following crash (yes)		XX (XX.X)	XX (XX.X)
Previous major surgery/ injuries (yes)		XX (XX.X)	XX (XX.X)
Type of major surgery/ injuries	*None*	XX (XX.X)	XX (XX.X)
	Abdominal	XX (XX.X)	XX (XX.X)
	Spinal	XX (XX.X)	XX (XX.X)
	Upper limb	XX (XX.X)	XX (XX.X)
	Lower limb	XX (XX.X)	XX (XX.X)
	Brain	XX (XX.X)	XX (XX.X)
	Other	XX (XX.X)	XX (XX.X)
	More than one surgery	XX (XX.X)	XX (XX.X)

Table 1 (*Continued*)

Variable		CPC Pathway	Usual Care
Other medical conditions (yes)		XX (XX.X)	XX (XX.X)
Type of medical conditions	*None*	XX (XX.X)	XX (XX.X)
	Cardiorespiratory	XX (XX.X)	XX (XX.X)
	Diabetes/ metabolic	XX (XX.X)	XX (XX.X)
	*Abdominal related (*e.g., *liver, kidney, stomach)*	XX (XX.X)	XX (XX.X)
	Cancer	XX (XX.X)	XX (XX.X)
	*Psychological (*e.g., *PTSD, depression)*	XX (XX.X)	XX (XX.X)
	Arthritis/musculoskeletal	XX (XX.X)	XX (XX.X)
	Other	XX (XX.X)	XX (XX.X)
	>1 medical condition	XX (XX.X)	XX (XX.X)
GPE (−5 to +5)*		XX.XX (XX.X)	XX.XX (XX.X)
Neck pain intensity over the past week (0−10)*		XX.XX (XX.X)	XX.XX (XX.X)
Neck pain intensity over the past 24 h (0−10)*		XX.XX (XX.X)	XX.XX (XX.X)
Claim lodged (yes)		XX (XX.X)	XX (XX.X)
Type of claim	*CTP*	XX (XX.X)	XX (XX.X)
	Workers compensation	XX (XX.X)	XX (XX.X)
	Other	XX (XX.X)	XX (XX.X)
Engaged a lawyer (yes)		XX (XX.X)	XX (XX.X)
Investigations received	*Radiographs*	XX (XX.X)	XX (XX.X)
	Magnetic Resonance Imaging	XX (XX.X)	XX (XX.X)
	Computerised Axial Topography Scan	XX (XX.X)	XX (XX.X)
	None performed	XX (XX.X)	XX (XX.X)
Treatment received to date	*Physical therapy*	XX (XX.X)	XX (XX.X)
	Chiropractic	XX (XX.X)	XX (XX.X)
	Massage	XX (XX.X)	XX (XX.X)
	Acupuncture	XX (XX.X)	XX (XX.X)
	Surgery	XX (XX.X)	XX (XX.X)
	Other	XX (XX.X)	XX (XX.X)
	No treatment received	XX (XX.X)	XX (XX.X)
Number of treatment sessions*	*Physical therapy*	XX.XX (XX.X)	XX.XX (XX.X)
	Chiropractic	XX.XX (XX.X)	XX.XX (XX.X)
	Massage	XX.XX (XX.X)	XX.XX (XX.X)
	Acupuncture	XX.XX (XX.X)	XX.XX (XX.X)
	Others	XX.XX (XX.X)	XX.XX (XX.X)

CPC, Clinical Pathway of Care; FTE, Full Time Equivalent; GPE, Global Perceived Effect; CTP, Compulsory Third Party.

Each model will include time (modelled as a categorical variable with 4 levels corresponding to the repeated measures), treatment group (modelled as a binary variable), and time *X* study-arm interaction as fixed effects, with a random intercept for subject specific effects and an unstructured correlation matrix. For each continuous outcome (NDI and GRC), the difference in estimated marginal means (95% CI) between the groups will be predicted for each time point, after adjustment for baseline measurement.

We will base our conclusions concerning the effectiveness of the clinical pathway on the coefficient of the time *X* study-arm interaction term.[24]

We will specify the models as follows:

$$Y_{ij} = \beta_1 t1 + \beta_1 t2 + \beta_3 t3 + \beta_4 t4 + \beta_5 arm_i\ X\ t1 + \beta_6 arm_i\ X\ t2 + \beta_7 arm_i\ X\ t3 + \beta_8 arm_i\ X\ t4 + \beta_i + e_{ij}$$

Where Y_{ij} is the outcome for participant i at time j, t1, t2, t3 and t4 are indicator variables representing time at baseline, 3 months, 6 months, and 12 months post-randomisation respectively; arm represents the study arm; study arm, and the treatment *X* time interaction are modelled as fixed effects. β_i are the between person effects, modelled as a random effects $\beta_i = \sim N(0, {\sigma_b}^2)$ with ${\sigma_b}^2$ between-person variance; e_{ij} are the within-person effects $e_{ij} = \sim N(0, {\sigma_e}^2)$, with ${\sigma_e}^2$ within-person variance.

We will also use linear mixed models to estimate the effect of the intervention on secondary outcomes of pain self-efficacy; pain intensity over the last week and the last 24 h; general disability (*WHODASII*); a generic measure of health status, the *SF-12*; posttraumatic stress symptoms and pain catastrophising. These models will be similar to those used in the analysis of the primary outcome. We will use appropriate coefficients and their 95% CIs to estimate the effects of intervention at each time point post-randomization.

We will report all adverse effects and serious adverse effects during the trial period by study arm. If appropriate, we will compare the number of adverse events and serious adverse events between groups using a Chi^2 Test, or Fisher's Exact test.

Table 2 will depict the unadjusted means (SD) for each outcome by study arm and follow-up time point.

Table 2 Unadjusted means ± standard deviations for each outcome by study arm and follow-up time point.

	Baseline		3 months		6 months		12 months	
	CPC Pathway (n=XX)	*Usual Care (n=XX)*	*CPC Pathway (n=XX)*	*Usual Care (n=XX)*	*CPC Pathway (n=XX)*	*Usual Care (n=XX)*	*CPC Pathway (n=XX)*	*Usual Care (n=XX)*
Primary outcomes								
NDI (0–100)	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X
Global recovery (−5 to +5)	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X
Secondary outcomes								
PSEQ (0–60)	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X
Neck pain intensity, past week (0–10)	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X
Neck pain intensity, past 24 h (0–10)	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X
WHODASII	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X
PDS Total Score	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X
PCS Total (0–52)	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X
SF-12	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X
PCS	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X
MCS	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X	XX.*X* ± XX.X

*n represents the number of participants with primary outcome data at each time point; CPC, Clinical Pathway of Care; NDI, Neck Disability Index; PSEQ, Pain Self-Efficacy Questionnaire; WHODASII, The World Health Organization Disability Assessment Schedule II; PDS, Posttraumatic Stress Diagnostic Scale; PCS, Pain Catastrophizing Scale; SF-12 PCS, Generic measure of health status – physical component; SF-12 MCS, Generic measure of health status – mental component.

Table 3 Treatment effects expressed as predicted mean differences (95% CI) between the study arms at each follow-up time point (3, 6 and 12 months).

	3 months	6 months	12 months
Primary outcomes			
NDI (0—100)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)
Global recovery (—5 to +5)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)
Secondary outcomes			
PSEQ (0—60)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)
Neck pain intensity, past week (0—10)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)
Neck pain intensity, past 24 h (0—10)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)
WHODASII	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)
PDS Total Score	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)
PCS Total (0—52)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)
SF-12			
PCS	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)
MCS	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)

NDI, Neck Disability Index; PSEQ, Pain Self-Efficacy Questionnaire; WHODASII, The World Health Organization Disability Assessment Schedule II; PDS, Posttraumatic Stress Diagnostic Scale; PCS, Pain Catastrophizing Scale; SF-12 PCS, Generic measure of health status — physical component; SF-12 MCS, Generic measure of health status — mental component.

Table 3 will depict the treatment effects expressed as predicted mean differences (95% CI) between the study arms at each follow-up time point (3, 6, and 12 months).

Potential differential effect of risk of recovery on health outcomes for the CPC

We will explore whether the risk of recovery as measured at baseline by *WhipPredict* ('low risk' or 'medium/high risk') is associated with differential effects of the health outcome measures. We will test this by adding a *risk X arm X time* interaction term as a fixed-effect to each mixed-effects model.

Supplementary Table 1 will depict the unadjusted means ± SD for each outcome by study arm and risk category at each time-point.

Economic evaluation of the CPC

We will proceed with the economic evaluation regardless of the effect of the intervention on the primary outcomes; the cost-effectiveness outcome will use the ICER for the CPC compared to usual care.

The cost-effectiveness analyses will be conducted from the societal perspective and reported in Australian Dollars. The time horizon of the economic evaluation is 12 months, the period of time participants completed cost diaries. The ICER denominator will be calculated using utility weights generated using participants' SF-12 responses, translated to SF-6D utilities using the Brazier et al. algorithm.[25] An ICER will be calculated by dividing the between-group difference in costs by the between-group difference in treatment effectiveness measured by the primary outcomes. Cost-effectiveness ratios will be estimated using bootstrapping techniques (5000 replications), and graphically presented on cost-effectiveness planes. Acceptability curves and net monetary benefit will also be estimated. Sensitivity analyses on the most important cost drivers will be performed to assess the robustness of the results. In the event of no statistically-significant differences between the intervention and control groups, the economic evaluation will compare the costs of the CPC and usual care.

The cost outcomes will include direct and indirect costs with suitable attention paid to avoiding double-counting with respect to utilities and costs avoided. These will be measured by cost diaries completed by participants. Participants were asked to record their costs over a period of 2 weeks prior to the respective follow-up, including: (i) use of healthcare services (e.g. general practitioner, physical therapist, psychologist, including number of consultations); (ii) hours taken off normal paid work; (iii) use of prescription medicine (name, pharmacological class, daily dosage, and number of days); (iv) use of over-the-counter medication; (v) other out-of-pocket costs (e.g. purchase of cervical collars, ergonomic devices); (vi) any assistance required (e.g. home help, domestic help, help from family and friends). The use of imaging (e.g. radiographs, magnetic resonance imaging) will be recorded for the 3 months prior to the follow-up.

Costs of the study treatment will be derived from the cost of providing the CPC plus the cost of services, medications, and equipment purchased outside of the study intervention. Health service costs will be valued at standard rates published by the Australian Government (eg, Medical Benefits Scheme standard fees, the Pharmaceutical Benefits Scheme cost for medications). Costs of the study treatments and private non-medical healthcare services (eg, physical therapy) will be valued at standard rates published by the relevant professional body or third-party payer. Costs of community services (eg, gym attendance; home help) and other out-of-pocket costs (eg, purchase of a cervical collar) will be based on the self-reported costs of participants. Indirect costs include the participants lost economic productivity due to poor health. A shadow wage rate will be used to identify the opportunity cost of time spent away from work due to their injury. These costs will be calculated using income and employment data collected via a baseline questionnaire. The reference year for the derivation of cost measures will

be 2018, the year when most participants were recruited. Careful attention will be paid to the possibility that cost differences for some of these categories may also be reflected in utility differences between the two groups.

Comparing professional practice of the CPC to usual care

Clinical decisions made by specialists in the CPC arm, and their reasons will be assessed. Professional practice outcomes will be captured by questionnaires completed by the primary health care providers, specialists, and patients at 3 months post-randomisation, and have been adapted from professional practice questionnaires used in previous research.[26-29] In addition, further treatment pathways chosen by the specialists in the CPC arm and the reasons for these will be captured online (www.mywhiplash.com.au).

Professional practice outcomes will be analysed using both descriptive statistics and qualitative content analysis. Median scores will be calculated for ordinal data and frequency distribution will be reported. Codes or keywords will be identified from literature prior to analysis of the responses from the open-ended questions. Occurrences of the identified codes or keywords will be documented through frequency counts. Given this was an embedded observational study, professional practice outcomes may be reported in detail in a separate publication to the main trial outcomes.

Missing data

We monitored patterns of missing data during study data collection and will conduct our analyses based on the assumption that any missing data are missing at random (MAR).

Statistical software

We will conduct all analyses using STATA version 15.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjpt.2021.05.004.

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