# SupportBack 2

**Supporting self-management of low back pain with an internet intervention in primary care: A randomised controlled trial of clinical and cost-effectiveness**

**V2 10-Aug-2018**

**SPONSOR:** University of Southampton
**COORDINATING CENTRE:** Southampton Clinical Trials Unit

| | |
|---|---|
| ISRCTN reference: | [Insert] |
| Ethics reference number: | 18/SC/0388 |
| Sponsor reference number: | 31333 |
| Funder reference number: | 16/111/78 |
| ICD10 | M54.5 |

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**Protocol authorised by:**

| | | | |
|---|---|---|---|
| **Name:** | Dr Adam Geraghty | **Role:** | Chief Investigator |
| **Signature:** | | **Date:** | |
| **Name:** | Prof Gareth Griffiths | **Role:** | Director of SCTU |
| **Signature:** | | **Date:** | |
| **Name:** | Dr Diana Galpin | **Role:** | On behalf of Sponsor |
| **Signature:** | | **Date:** | |

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## MAIN STUDY CONTACT


Chief Investigator: Dr Adam Geraghty

Primary Care and Population Sciences
Faculty of Medicine
University of Southampton

Tel: 023 8059 1770
Email: A.W.Geraghty@soton.ac.uk


## STUDY COORDINATION CENTRE

For general study and clinical queries e.g. participant queries, study supplies, data collection, please contact in the first instance:


SupportBack2 Trial Manager: Abigail Jones Tel: 023 8120 5556

Email: SupportBack2@soton.ac.uk

Address: Southampton Clinical Trials Unit
Southampton General Hospital
Tremona Road
SOUTHAMPTON
SO16 6YD

Tel: 023 8120 5154
Fax: 0844 774 0621
Email: ctu@soton.ac.uk
Web: www.southampton.ac.uk/ctu


## SPONSOR

The University of Southampton is the research sponsor for this study. For further information regarding sponsorship conditions, please contact the Head of Research Governance at:


Address: Research Governance Office
The University of Southampton
Room 4079, Building 37
Highfield Campus
Southampton
SO17 1BJ

Tel: 023 8059 5058
Fax: 023 8059 5781
Email: rgoinfo@soton.ac.uk


## CO-INVESTIGATOR(S)

Co-Investigators can be contacted via Southampton Clinical Trials Unit.


Co-applicant Professor Paul Little University of Southampton
Co-applicant Professor Lucy Yardley University of Southampton
Co-applicant Associate Professor Lisa Roberts University of Southampton
Co-applicant Professor Nadine Foster Keele University
Co-applicant Dr Jonathan Hill Keele University
Co-applicant Professor Elaine Hay Keele University
Co-applicant Dr Beth Stuart University of Southampton
Co-applicant David Turner University of East Anglia
Co-applicant Professor Gareth Griffiths University of Southampton
Co-applicant Mrs Linda Leigh Patient and Public Involvement Representative

**FUNDER**

This study is funded by the National Institute of Health Research (NIHR) Health Technology Assessment programme (HTA).

**Protocol Information**

This protocol describes the SupportBack2 study and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other non- study participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study, but PICs entering participants for the first time are advised to contact Southampton Clinical Trials Unit to confirm they have the most recent version.

**Compliance**

This study will adhere to the principles of Good Clinical Practice (GCP). It will be conducted in compliance with the protocol, in accordance with current Data Protection Regulations and all other regulatory requirements, as appropriate.

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| BCT | Behaviour Change Techniques |
| CAM | Complementary or Alternative Medicine |
| CARE | Congratulate Ask Reassure Encourage |
| CBT | Cognitive Behaviour Therapy |
| CECAC | Cost-Effectiveness Acceptability Curve |
| CI | Chief Investigator |
| CRF | Case Report Form |
| CRN | Clinical Research Network |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTIMP | Clinical Trial of a Medicinal Product |
| DMEC | Data Monitoring and Ethics Committee |
| DMP | Data Management Plan |
| EQ-5D-5L | Quality of Life Questionnaire |
| EU | European Union |
| FAO | For the Attention of |
| GCP | Good Clinical Practice |
| GP | General Practitioner |
| HE | Health Economic |
| HTA | Health Technology Assessment |
| ICER | Incremental Cost-Effectiveness Ratio |
| IDMC | Independent Data Monitoring Committee |
| IRB | Institutional Review Board |
| LBP | Low Back Pain |
| MHRA | Medicines and Healthcare Products Regulatory Agency |
| MLMM | Multi-Level Mixed Model |
| MRC | Medical Research Council |
| MRI | Magnetic Resonance Imaging |
| MSK-HQ | Musculoskeletal Health Questionnaire |
| NCI | National Cancer Institute |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NIHR | National Institute for Health Research |
| NSAID | Non-Steroidal Anti-Inflammatory |
| OTC | Over the Counter |
| PA | Physical Activity |
| PBA | Person Based Approach |
| PCS | Pain Catastrophizing Scale |
| PEI | Patient Enablement Instrument |
| PETS | Problematic Experiences of Therapy |
| PHQ-4 | Patient Health Questionnaire |
| PIC | Participant Identification Centres |
| PID | Personal Identifying Data |
| PIS | Participant Information Sheet |
| PSEQ | Pain Self-Efficacy Questionnaire |
| QALY | Quality Adjusted Life Years |
| RCT | Randomised Controlled Trial |
| R&D | Research and Development |
| REC | Research Ethics Committee |

| | |
|---|---|
| RfPB | Research for Patient Benefit |
| RMDQ | Roland Morris Disability Questionnaire |
| SAE | Serious Adverse Event |
| SCT | Social Cognitive Theory |
| SCTU | Southampton Clinical Trials Unit |
| SDT | Self Determination Theory |
| SE | Self-Efficacy |
| SSRI | Selective Serotonin Reuptake Inhibitors |
| TMG | Trial Management Group |
| TSC | Trial Steering Committee |
| TSK | Tampa Scale for Kinesiophobia |
| UK | United Kingdom |
| UoS | University of Southampton |


## KEYWORDS

Behavioural Self-Management
Low Back Pain
Supported Internet Intervention
Unsupported Internet Intervention
Physical Disability
Physical Activity
Telephone Physiotherapy Support
Primary Care
Graded Goal Setting
Self Monitoring

## STUDY SYNOPSIS

| | |
|---|---|
| **Short title/Acronym:** | SupportBack 2 |
| **Full title:** | Supporting self-management of low back pain with an internet intervention in primary care: A randomised controlled trial of clinical and cost-effectiveness |

| | |
|---|---|
| **Study Phase:** | Phase III |
| **Population:** | Primary care patients with a current episode of low back pain (LBP). |
| **Primary Objective:** | To determine the clinical effectiveness of the SupportBack intervention on LBP-related physical disability delivered with and without telephone Physiotherapist support in addition to usual care, compared to usual care alone. |
| **Secondary Objectives:** | • To determine cost-effectiveness of the SupportBack intervention with and without telephone Physiotherapist support, compared to usual care.<br>• To determine the effect of the interventions on secondary outcomes including pain intensity, risk of persistent disability, fear of movement, catastrophizing, and pain self-efficacy.<br>• To understand the results from the randomised controlled trial (RCT) by conducting a mixed methods process evaluation exploring implementation, mechanisms of action, and context. |
| **Rationale:** | LBP places substantial burden on the UK National Health Service (NHS). The latest National Institute for Health and Care Excellence (NICE) guidelines for LBP, updated in 2016 (3), place a central focus on promoting self-management and providing advice to remain active. Latest recommendations for analgesia are restricted to non-steroidal anti-inflammatory prescriptions at the lowest effective dose for the shortest period of time. Determining how best to support effective behavioural self-management is a priority in light of the prevalence of LBP. Internet interventions are automated digital programmes that offer tailored advice, reassurance and support for behaviour change. Internet interventions have the potential to provide low cost, effective self-management support for primary care patients experiencing LBP. |
| **Study Design:** | Randomised Controlled Trial (RCT) |
| **Sample size :** | 806 |
| **Treatment/Intervention:** | 1. Usual care for primary care patients with LBP (control)<br>2. Usual care + internet intervention for primary care patients with LBP.<br>3. Usual care + internet intervention + telephone Physiotherapist support for primary care patients with LBP |

| | |
|---|---|
| **URL for Database:** | www.imedidata.com/, www.lifeguideonline.org |

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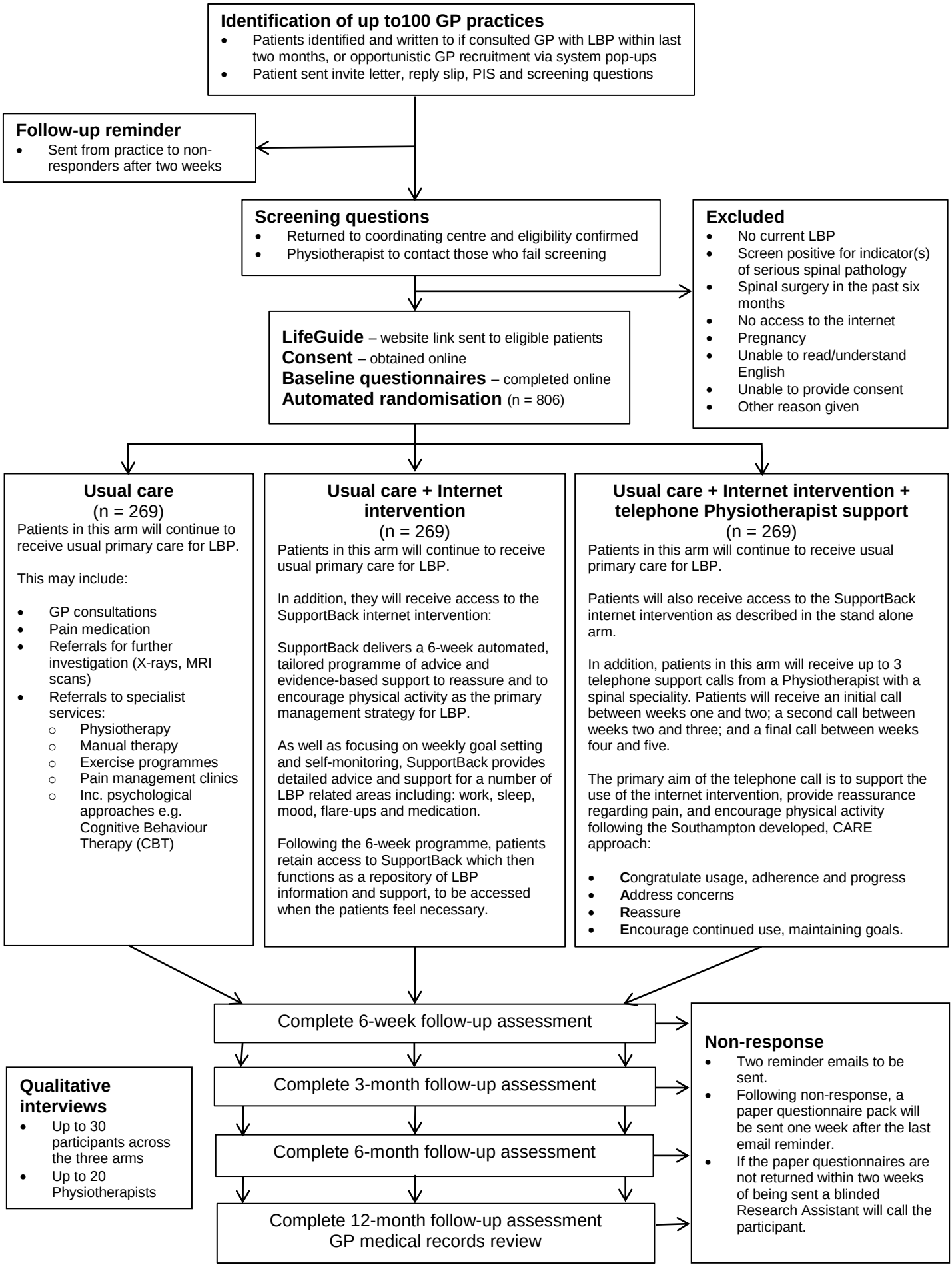
|---|---|
| **Primary Study Endpoints:** | Low back pain related physical function measured over 12 months using the Roland Morris Disability Questionnaire (RMDQ). |
| **Secondary Study Endpoints:** | **Health economics**<br>• EQ-5D-5L – health related quality of life<br>• Self-reported over the counter (OTC) medication use<br>• Participant borne costs – participant reported resource use<br>• Brief occupational items - time off workGP medical records review – health care resource use including GP appointments, Nurse appointments, referrals and hospital stays and medication between specified dates. Data will also be collected on pre-existing conditions. |
| | **Pain**<br>• Pain duration – recent time spent pain free<br>• Days in pain – number of troublesome days in pain over the last month<br>• Pain index – numerical pain rating scale<br>• The Keele STarT Back screening tool – risk of persistent disability |
| | **Psychological processes related to pain**<br>• Tampa scale for kinesiophobia (TSK-11) – fear of movement<br>• Pain catastrophizing scale (PCS) – negative orientation towards pain<br>• Pain self-efficacy questionnaire (PSEQ) – confidence in ability to manage pain<br>• Self-efficacy for managing low back pain – single item from Keele's musculoskeletal health questionnaire tool (MSK-HQ)<br>• Modified expectancy questionnaire – how much the intervention may reduce limitation due to back pain<br>• Patient health questionnaire (PHQ-4) – mental health assessment with two items regarding depression and two items regarding anxiety |
| | **Physical activity/adherence**<br>• Godin leisure-time exercise questionnaire – physical activity assessment tool<br>• SupportBack related physical activity – back specific physical activity assessment tool<br>• Adherence to back specific exercise – self reported adherence to back specific exercises<br>• Problematic experiences of therapy scale (PETS) – how easy/difficult it was to carry out therapy |
| | **Satisfaction/enablement**<br>• Satisfaction – satisfaction with back pain care<br>• Patient enablement instrument (PEI) – ability to cope as a result of healthcare received |
| | **Use of internet resources**<br>• Use of internet resources – participant reported use of internet resources for back pain (1 item) |
| **Total Number of PICs:** | Up to 100 GP practices |

# STUDY SCHEMA



# 1 SCHEDULE OF OBSERVATIONS AND PROCEDURES

| Trial point | Identification | Screening | Baseline | Week 1-2 | Week 2-3 | Week 4-5 | Week 6 (+ 6 weeks) Follow-up 1 | 3 Months (+ 6 weeks) Follow-up 2 | 6 Months (+ 6 weeks) Follow-up 3 | 12 Months (+ 6 weeks) Follow-up 4 | End of study |
|---|---|---|---|---|---|---|---|---|---|---|---|
| LBP patients identified by GP medical records review or during a GP consultation | X | | | | | | | | | | |
| Invite letter, screening questions and PIS sent to patient by post [1] | | X | | | | | | | | | |
| Screening questions returned to coordinating centre | | X | | | | | | | | | |
| Physiotherapist to contact screening failures [2] | | X | | | | | | | | | |
| Eligible patients sent link to LifeGuide [3] | | X | | | | | | | | | |
| Online consent obtained | | | X | | | | | | | | |
| Baseline questionnaires (including demographics) completed online [4] | | | X | | | | | | | | |
| Participant randomised on completion of baseline questionnaires | | | X | | | | | | | | |
| Usual care [5] | X | X | X | X | X | X | X | X | X | X | |
| Use of SupportBack internet intervention [6] | | | | X | X | X | X | | | | |
| Telephone Physiotherapist support [7] | | | | X | X | X | | | | | |
| Follow-up questionnaires [8] | | | | | | | X | X | X | X | |
| GP notes review [9] | | | | | | | | | | X | |
| Serious adverse events [10] | | | X | X | X | X | X | X | X | X | |
| Participant qualitative interviews (optional, up to 30 participants) | | | | | | | | X | X | X | |
| Physiotherapist qualitative interviews (up to 20 Physiotherapists) | | | | | | | | | | X | |
| End of study [11] | | | | | | | | | | | X |

[1] A reminder postcard will be sent two weeks after the initial mailing if the study pack is not returned.
[2] Eligible patients to be entered into trial. Those who fail safety screening questions to be referred back to their GP.
[3] LifeGuide software provides the SupportBack internet intervention, consent and all questionnaires.
[4] Three arms: usual care (control); usual care + internet intervention; usual care + internet intervention + telephone Physiotherapist support.
[4] Refer to Table 3 for more details of questionnaires to be completed.
[5] All participants.
[6] For participants in the intervention arms only. The SupportBack internet intervention is designed to be used over a six week period however participants can access the website at any time during the study period.
[7] For participants in the usual care + internet intervention + telephone Physiotherapist support arm only.
[8] Questionnaires will primarily be completed online in LifeGuide. Two reminder emails will be sent. Following non-response a paper questionnaire pack will be sent one week after the last email reminder. If the paper questionnaires are not returned within two weeks of being sent a blinded Research Assistant will call the participant to collect the primary outcome measure (RMDQ) and quality of life questionnaire (EQ-5D-5L).
[9] This will collect information on health care resource use and concomitant medication.
[10] To be reported by the GP and followed up by SCTU.
[11] Completion of study or withdrawal (e.g. lost to follow-up, pregnancy). See Section 5.6 for more information.

# 2 INTRODUCTION

## 2.1 BACKGROUND

Low back pain (LBP) places substantial burden on the UK National Health Service (NHS). Associated health care costs are reported upward of 1.6 billion per annum (1), and each year between 6-9% of the UK population will visit general practice with LBP (2). The latest National Institute for Health and Care Excellence (NICE) guidelines for LBP, updated in 2016 (3), place a central focus on promoting self-management and providing advice to remain active. Although referrals to specialist services including physiotherapy and pain management are possible, in reality access to these services is variable in different areas and complicated by variable wait times. Latest recommendations for analgesia are restricted to non-steroidal anti-inflammatory (NSAID) prescriptions at the lowest effective dose for the shortest period of time (taking into account gastrointestinal, liver and cardio-renal toxicity) (3). Paracetamol, opioids, and selective serotonin reuptake inhibitors (SSRI) are not recommended for LBP. Determining how best to support effective behavioural self-management is a priority in light of the prevalence of LBP and the urgent need to reserve limited specialist services for those who need them most.

Internet interventions are automated digital programmes that offer tailored advice, reassurance and support for behaviour change. Accessible from anywhere with an internet connection, internet interventions have the potential provide to low cost, effective self-management support for primary care patients experiencing LBP. There have been four recent systematic reviews (including one Cochrane review) (4–7). Due to the proximity in their publication dates, they contain many of the same trials. The conclusions are consistent across the reviews: research on internet intervention for pain is at an early stage, the majority of trials conducted to date have had small sample sizes, comparisons to non-active (waiting list) controls, contained heterogeneous outcome measures and have had short follow-up periods (4–7). With regard to outcomes, internet interventions for LBP appear to show promise, with reductions in catastrophizing (the belief that the pain is terrible and will never improve), and some trials showing small reductions in disability, although methodological issues are a primary concern. Importantly, none of the completed trials in these reviews focused on patients in UK primary care, and the interventions were often developed without patient input (excluding the protocol published by Geraghty et al (2018) (8) included in Nicholl's review (7)). There is a critical need to examine the long-term effectiveness of internet-based interventions versus active comparisons such as usual primary care.

Geraghty et al, (2018) (8, 9) developed and conducted a feasibility randomised controlled trial (RCT) of an internet intervention 'SupportBack', specifically designed for LBP patients in primary care (including acute, recurrent and chronic LBP). The intervention development and feasibility trial were funded by the National Institute for Health Research (NIHR) Research for Patient Benefit programme (RfPB) (Project PB-PG-1111-26080, Chief Investigator: Geraghty). The feasibility RCT was conducted in 12 general practices with patients with current LBP (9). Three arms were compared: usual care versus usual care + internet intervention versus usual care + internet intervention + telephone Physiotherapist support. 87 patients with LBP were recruited (target 60-90). Adherence to the internet intervention was satisfactory in the two arms offering it. Physiotherapists adhered to the telephone support protocol. Clinical outcome data were available at the final three month follow-up from 84% of participants. LBP-related physical disability measured using the Roland Morris Disability Questionnaire (RMDQ) improved between baseline and three months by 0.6 points more in the usual care + internet intervention arm than usual care alone, and by 2.4 points more in the usual care + internet intervention + telephone Physiotherapist support arm, after controlling for baseline RMDQ score and confounders. The trial was completed in early 2016, and met all success criteria.

The proposed full trial of the SupportBack internet intervention for LBP delivered with and without telephone Physiotherapist support, would represent the first trial of its kind with direct applicability to UK primary care practice. If positive, the interventions could be rapidly rolled out and implemented within the NHS.

### 2.2 RATIONALE AND RISK BENEFITS FOR CURRENT STUDY

Digital health technologies, including internet interventions, are well positioned to play a key role in widening access to services within the NHS. However, the move toward integration of digital technologies for promoting self-management must occur in the presence of robust evidence for their clinical and cost-effectiveness, compared to usual care. The proposed SupportBack 2 trial will be the largest of its kind in the UK, led by a team that combines world-leading expertise in applied digital interventions and musculoskeletal health in primary care.

The trial and its nested studies will:

- Determine the effectiveness of a remotely supported internet intervention supporting the self-management of LBP in primary care.
- Contrast the effectiveness of Physiotherapist supported and stand-alone internet interventions in comparison to usual care for LBP.
- Determine the cost-effectiveness of supported and unsupported internet interventions.
- Through triangulation of quantitative and qualitative process data, provide a model for how the intervention affects LBP-related disability and pain. This will enable the extrapolation of principles to related digital interventions.

Each element will substantially contribute to understanding how best to apply internet-based technologies in supporting LBP self-management within primary care, as well as providing a health technology for rollout and use by practitioners and patients. The rapidly increasing relevance of digital, internet-based, support coupled with the critical need for alternative care strategies to encourage and facilitate effective self-management of LBP, underscores the importance of the proposed trial at the current time. Additionally, given the current crisis in general practice (10), internet interventions could provide efficiency gains; improve quality; and deliver support for self-management without adding to demands on GPs' extremely limited consultation times.

## 3 STUDY OBJECTIVES

**Table 1: Primary and secondary study objectives**

| Objectives | |
|---|---|
| **Primary** | • To determine the clinical effectiveness of the SupportBack intervention on LBP-related physical disability delivered with and without telephone Physiotherapist support in addition to usual care, compared to usual care alone. |
| **Secondary** | • To determine cost-effectiveness of the SupportBack intervention with and without telephone Physiotherapist support, compared to usual care.<br>• To determine the effect of the interventions on secondary outcomes including pain intensity, risk of persistent disability, fear of movement, catastrophizing and pain self-efficacy. |

| | |
|---|---|
| | • To understand the results from the RCT by conducting a mixed methods process evaluation exploring implementation, mechanisms of action and context. |

# 3 STUDY DESIGN

Three parallel arm, multicentre randomised controlled trial to determine the clinical and cost effectiveness of the SupportBack internet intervention on LBP-related physical disability.

## 3.1 STUDY ENDPOINTS

### *3.1.1 Primary endpoint*

Low Back Pain related physical function measured over 12 months using the Roland Morris Disability Questionnaire (RMDQ).

### *3.1.2 Secondary endpoints*

**Health Economics**

- EQ-5D-5L – health related quality of life
- Self-reported over the counter (OTC) medication use
- Participant borne costs – participant reported resource use
- Brief occupational items - time off work
- GP medical records review – health care resource use including GP appointments, Nurse appointments, referrals and hospital stays and medication between specified dates. Data will also be collected on pre-existing conditions.

**Pain**

- Pain duration – recent time spent pain free
- Days in pain – number of troublesome days in pain over the last month
- Pain index – numerical pain rating scale
- The Keele STarT Back screening tool – risk of persistent disability

**Psychological processes related to pain**

- Tampa scale for kinesiophobia (TSK-11) – fear of movement
- Pain catastrophizing scale (PCS) – negative orientation towards pain
- Pain self-efficacy questionnaire (PSEQ) – confidence in ability to manage pain
- Self-efficacy for managing low back pain – single item from Keele's musculoskeletal health questionnaire tool (MSK-HQ)
- Modified expectancy questionnaire – how much the intervention may reduce limitation due to back pain
- Patient health questionnaire (PHQ-4) – mental health assessment with two items regarding depression and two items regarding anxiety

**Physical activity/adherence**

- Godin leisure-time exercise questionnaire – physical activity assessment tool
- SupportBack related physical activity – back specific physical activity assessment tool
- Adherence to back specific exercise – self reported adherence to back specific exercises
- Problematic experiences of therapy scale (PETS) – how easy/difficult it was to carry out therapy

**Satisfaction/enablement**

- Satisfaction – satisfaction with back pain care
- Patient enablement instrument (PEI) – ability to cope as a result of healthcare received

**Use of internet resources**

- Use of internet resources – participant reported use of internet resources for back pain (1 item)

### 3.2 DEFINITION OF END OF STUDY

End of trial is defined as 12 months plus six weeks from when the last participant is randomised. A six week window (12 months + 6 weeks) is available for completion of questionnaires at each time point (six weeks, three, six and 12 months).

## 4 SELECTION AND ENROLMENT OF PARTICIPANTS

### 4.1 CONSENT

Consent to enter the study must be sought from each participant only after a Participant Information Sheet (PIS) has been offered and time allowed for consideration and questions. Participant consent will be obtained electronically using LifeGuide software for both the RCT and qualitative interviews (which are optional). Notification of consent will be confirmed by an automated email sent from LifeGuide to the Research Team. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded in the GP medical records which will be reviewed at 12 months. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

### 4.2 INCLUSION CRITERIA

- Aged 18 and above
- Current low back pain (have experienced pain in the last week) with or without sciatica
- Access to the internet and an active email address
- Ability to read/understand English without assistance
- Ability to provide informed consent

### 4.3 EXCLUSION CRITERIA

- 'Red flag' signs and symptoms in a patient with LBP which indicate serious spinal pathology such as infection, malignancy, fracture, inflammatory back pain, progressive neurology and/or cauda equine; or suspected serious pathology
- Have had spinal surgery in the past six months
- Pregnancy
- Taken part in the prior SupportBack feasibility study

## 4.4 IDENTIFICATION AND SCREENING

### *4.4.1 Identification*

This trial will be supported by the NIHR Clinical Research Network (CRN) who will facilitate the recruitment of general practices. General practices will be considered as Participant Identification Centres (PIC) as they will identify subjects only. Potentially eligible participants will be identified in one of two ways, described below.

*Medical records review*

Patients who have consulted with LBP in the last two months will be identified by GP practice staff from computerised records of consultations. Practices will be asked to repeat the searches approximately three times, or until the target number of patients per practice has been reached (e.g. eight). Resulting lists of patients identified by the search will be screened by a practice GP who will rule out patients based on aspects of the eligibility criteria that can be determined from patient notes. Practices will provide the Research Team with the number of patients identified and the number screened out by the GP. No personal data will be recorded from patients who are screened out at this stage.

*GP consultation*

During a patient consultation and on entering a relevant diagnostic or symptom Read code into the patient electronic medical record, GPs will be prompted about the trial and patient eligibility by an automated 'pop-up' screen activated by the Read code. GPs will then screen for eligibility (using the inclusion/exclusion criteria listed) and patients identified as suitable will have their medical record electronically tagged. A download of 'tagged' patients will occur regularly, anticipated to be every two weeks. This method will be used in practices where possible and has previously been used successfully in several LBP trials led by the applicants (STarT Back and SCOPiC trials).

### *4.4.2 Screening*

Patients identified either by a medical records review or GP consultation will be mailed a study pack including an invitation letter from the GP, PIS, reply slip, screening questions and pre-paid envelope. Patients will be sent a reminder post card two weeks after the initial mailing if the study pack has not been returned. The mailout for this invitation will be performed by Docmail, which is a standards-compliant hybrid mail service, providing document management and ISO 27001 secure mailings. Interested patients should return the reply slip and screening questions using the pre-paid envelope to the Research Team. On the PIS, contact details are provided should the patient wish to contact a member of the Research Team for more information. For those who do not wish to take part, the reply slip will have some common reasons for non-participation (lack of time, no longer experiencing back pain), which they can send back to us in the pre-paid envelope, if they so wish.

Screening questions consist of two questions regarding current LBP and access to the internet followed by seven safety questions listing symptoms which may indicate serious spinal pathology. Patients who answer 'Yes' to the first two questions, and 'No' to all safety questions, will be considered eligible. Those who complete the screening questions and fail screening will be called by a Physiotherapist to discuss their symptoms, and will either be referred back to their GP, or entered into the trial. Those who fail the screening will be documented on a screening log maintained by the Research Team. All patients who are considered eligible for the trial are assigned a unique participant identification number and will be sent a link to the study website, LifeGuide, to complete consent and baseline questionnaires.

### 4.5 REGISTRATION/RANDOMISATION PROCEDURES

Once directed to the LifeGuide website, consent will be sought online and participants will be asked to complete online baseline questionnaires including demographics. Following completion of consent and baseline questionnaires, the internet intervention software, LifeGuide, will randomise the participant. The randomisation sequence will be automatically generated, and a computer-generated algorithm will block randomise participants to the trial groups. Participants will be stratified by level of severity, with a score of less than four on the RMDQ being considered as a lower level of severity, and trial centre. As the software randomises participants, the sequencing will be concealed from the Research Team. Participants will be automatically informed of their allocated group via the internet through the intervention website. As the intervention is primarily behavioural, participants will not be blind to allocation. The Trial Managers will not be blind to allocation. The Trial Statistician and Health Economist will remain blind to allocation until full analysis is finalised. See Study Schema for a flow diagram of the study design.

### 4.6 CONTRACEPTION

Whilst contraception is not relevant for this trial, as pregnancy is part of the exclusion criteria, participants will be asked to inform their GP if they fall pregnant during the course of the trial. On notification of pregnancy from the GP, they will be withdrawn. This information will be recorded on the End of Study form on Medidata RAVE EDC.

## 5 STUDY OBSERVATIONS AND PROCEDURES

### 5.1 STUDY PROCEDURES – RCT

Following screening, if patients are deemed eligible they will be emailed a trial link and a unique participant identification number which will be adapted for use in both LifeGuide and Medidata RAVE EDC. Patients will use this link to login to the LifeGuide data collection and intervention delivery website. Here patients will login and complete consent online. Following consent participants will complete baseline measures including demographics and will be automatically randomised to one of three trial arms:

1. Usual care
2. Usual care + internet intervention
3. Usual care + internet intervention + telephone Physiotherapist support.

#### *5.1.1 Trial arms*

*Usual care*

Participants allocated to this arm will continue to receive usual primary care. In the first instance, NICE recommended care for LBP consists of education and self-management advice, including advice to stay active (3). GPs may also prescribe medications for LBP and/or make referrals to other services that can offer other recommended treatments such as exercise programmes, manual therapy or psychological and/or pain management programmes. With regard to pharmacotherapy, recommendations are for NSAIDs or weak opioids only if NSAIDs are contraindicated, not tolerated or ineffective. Paracetamol is not recommended, neither is the routine use of opioids for LBP. Antidepressants (SSRIs or Tricyclics) are not recommended for LBP. In practice, many GPs do not adhere to guidelines for LBP (11), consequently, the latest NICE guidelines for LBP will be highlighted with all participating practices in a telephone call as part of the trial setup. Nonetheless, it is likely that treatment received as part of usual care will vary, and this variation will be ascertained and documented by a medical records review at 12

months and participant borne costs questionnaires at baseline, six months and 12 months. If a participant does not re-consult over the trial period they may receive no additional care beyond that which they received as part of their initial GP consultation, whereas some participants may receive ongoing care from the GP, and/or referrals for diagnostic tests or treatments from other healthcare professionals such Physiotherapists or other specialists.

*Usual care + Internet intervention*

Participants allocated to this arm will continue to receive usual primary care. In addition, they will receive access to SupportBack. SupportBack is an interactive multi-session internet intervention that provides participants with accessible information, tools and support to enable them to effectively manage their LBP. Internet provision allows the material to be accessed, and the suggested activities to be carried out wherever is most convenient for the participants. The intervention was developed using the open source LifeGuide software (www.lifeguideonline.org). The core of the intervention is focused on self-regulatory processes including graded goal setting, self-monitoring, and tailored feedback to encourage physical activity/exercise increases or maintenance (12). The intervention also provides educational advice regarding pain and LBP-related topics. Throughout, the included educational information has a focus on motivating behaviour change through techniques such as reassuring participants about likely consequences of movement and physical activity; helping participants interpret mild pain; modelling managing pain through physical activity using patient stories; reinforcing positive behaviour (using automated feedback); and providing simple instructions/ demonstrations regarding how to perform various back-specific exercises/physical activity behaviours. By combining the above features with in-depth feedback from patients with LBP in development, SupportBack is designed to be a highly accessible intervention supporting changes in self-efficacy and physical activity in order to improve LBP-related physical function.

The SupportBack internet intervention comprises six sessions delivered over a period of up to six weeks. Participants are encouraged to access one session per week, to allow them to engage between sessions with the activity goals they have set themselves. Participants are sent automated emails each week as a reminder to login to their next session. Specifically, in the first session participants are provided with information on how SupportBack will work, including the key rationale underlying the intervention; that keeping active is of primary importance when managing LBP. Likely concerns/potential barriers regarding this primary message are also addressed. The intervention then suggests two forms of physical activity participants can be supported with each week; walking or simple back-specific exercises. Participants select one and set goals for the coming week. The recommendations provided are tailored, based on the extent participants report their LBP is obstructing their ability to engage with activities in their day-to-day lives.

From session two onwards, the intervention follows the same format. Participants review their goals from the previous week and are provided with automated tailored feedback and encouragement. They then have the opportunity to amend their goals, increase difficulty or switch to different physical activities. From session two, after a participant's goal review they can choose to explore one of six modules containing information and advice on a LBP-related topic (see Table 2 for details). Exploration of these information modules becomes part of each broader 'session'. Although participants are advised to work through a session per week, they can view a new session every three days if they wish. If engaged with as recommended, the intervention would take six weeks to complete. After the six weeks of structured sessions, participants will still have access to activity information and LBP-related modules as a static website. The intervention is fully automated and adherence is encouraged through weekly reminder emails containing links back to the intervention.

*Usual care + internet intervention + telephone Physiotherapist support*

Participants allocated to this arm will continue to receive usual primary care. The SupportBack internet intervention will also be offered to participants with the addition of up to one hour of telephone support from an NHS Physiotherapist, over the same period of six weeks. The supporting Physiotherapists will be drawn from those who assess and manage patients with LBP in NHS services linked to participating GP practices. In Southampton, musculoskeletal Physiotherapists will come from Solent NHS Trust whereas in Keele they will be NIHR CRN Research Musculoskeletal Physiotherapists from the West Midlands CRN. Physiotherapists will receive participant contact details via an nhs.net email account or Dropoff, a UoS secure file transfer system.

Although support will vary with participant need, it will not exceed one hour in total (but could be less) and consists of one up to 30-minute phone call followed by two up to 15-minute phone follow-ups over six weeks. The purpose of the Physiotherapist telephone contact is to provide support and encouragement for use of the internet intervention and to address participants' concerns in relation to the internet-based content. The Physiotherapists are asked to closely adhere to a standardised content checklist for each phone call. Whilst they are able to address individual participant concerns, they are asked to avoid additional individualised participant assessment and treatment recommendations beyond the internet intervention content and adherence to this protocol will be assessed. Paper based notes made during the telephone Physiotherapist support will be stored securely at SCTU.

Call one (up to 30 minutes) is planned to take place between weeks one and two after randomisation. In this call, the Physiotherapist explores and addresses the participant's understanding and attitudes (e.g. belief that activity can be helpful for LBP); engagement with the internet intervention (e.g. enquiring how the participant has got on with their goals); and anticipates barriers (by asking what problems they anticipate in participating in the SupportBack programme). Calls two and three (up to 15 minutes) are planned to take place between weeks two and three, and between weeks four and five. In these telephone calls the Physiotherapist discusses general adherence to the internet content and internet sessions; provides positive reinforcement for adherence behaviour to both the internet intervention and physical activity goals; discusses barriers to adherence and how these might be addressed; encourages commitment to goals for the following week; and addresses any remaining concerns.

**Table 2: Summary table of SupportBack module content**

| Session number | Content |
|---|---|
| **Session one** | • How SupportBack works.<br>• How SupportBack differs from other back pain websites.<br>• Why activity is helpful for back pain, including:<br>  ○ Reassurance.<br>  ○ Information about positive health consequences.<br>• Commonly asked questions and responses regarding being more active whilst experiencing back pain.<br>• Setting of activity goals. Walking or back specific exercises tailored to current functioning level.<br>• Access to rationales, videos and benefits of activities.<br>• Free to choose and amend activities.<br>• Set goal level within tailored suggestions. |
| **Session two onwards** | • Goal review.<br>• Feedback based on goal achievement and function level.<br>• Opportunity to select new goals or keep the same. |

| | |
|---|---|
| | • Encouraged to select one additional module.<br>  ○ A new module is available to select at each session.<br>  ○ Participants can access their goals and selected module between sessions. |

| Additional modules | Content |
|---|---|
| **Sleep** | • Stretching before bed<br>• Sleeping positions<br>• Sleep checklist to improve sleep hygiene |
| **Relieving pain** | • Pain medication<br>• Hot and cold therapy<br>• Everyday advice |
| **Flare ups** | • 'First aid' exercises<br>• Taking pain killers<br>• Better posture<br>• Alternative ways of easing pain |
| **Work** | • Getting support from your employer<br>• Taking breaks<br>• Exercises to try at work<br>• Choosing a good chair<br>• Making your desk back friendly<br>• Using a laptop |
| **Mood** | • Overview of mood and its connection to pain<br>• Cognitive Behaviour Therapy (CBT) and Mindfulness techniques for improving mood including:<br>  ○ Self-kindness<br>  ○ Increasing pleasant activities<br>  ○ Mindful walking<br>• Three-minute breathing space |
| **Daily living** | • Sitting, standing and bending<br>• Lifting and carrying<br>• Shopping<br>• Doing housework<br>• In the bedroom<br>• In the bathroom<br>• In the kitchen<br>• Gardening |

### *5.1.2 Design and theoretical/conceptual framework*

**Design:** A three parallel arm, multicentre RCT to determine the clinical and cost effectiveness of the SupportBack internet intervention on LBP-related physical disability. Participants will be followed up at six weeks, three, six and 12 months.

**Theoretical framework:** The SupportBack internet intervention draws on Social Cognitive Theory (SCT) (13, 14), with modules designed to target outcome and self-efficacy expectations, supporting engagement with physical activity. Specifically, within the SCT framework key elements that increase self-efficacy are focused on (15), including performance accomplishment (e.g. through graded goal setting, self-monitoring and outcome-related feedback), verbal persuasion (e.g. text-based encouragement from trusted/expert professionals and patients with lived experience; provision of research evidence for the benefits of activity on LBP), and

modelling (e.g. embedded videos of gentle back exercises; patient stories of effectively reducing LBP-related physical disability through activity).

Self-Determination Theory (SDT) (16) is applied to facilitate engagement with both the intervention content, and the recommended activities. User/participant choice is central in the intervention, both in ways to use the internet intervention, and in the selection of activities to manage LBP. According to SDT, the provision of choice in a non-directive manner promotes autonomy supportive motivation (17), which is particularly important for sustained engagement with internet interventions.

The Physiotherapist telephone support employs the CARE approach (18). The CARE approach was developed at the University of Southampton and refers to **C**ongratulate, **A**sk, **R**eassure and **E**ncourage. It is based on self-determination theory (supporting autonomy, competence and relatedness), evidence from behavioural counselling and previous qualitative work with health professionals led by the Southampton group (18). The CARE approach is specifically designed to provide an easy to deliver, patient-centred protocol for support, specifically focusing on increasing adherence to an internet intervention, which is likely to be novel for Physiotherapists.

The Person-Based Approach (PBA), (19, 20) has been applied to all theory and evidence-based material comprising the interventions to be examined in the proposed trial. The PBA provides a systematic method for the application of qualitative research to intervention development, aiming to ensure resulting material is grounded in an in-depth understanding of participants/users perspective and psychosocial context. As part of the theory-, evidence-, and person-based approach, a logic model for the intervention has been developed. This logic model will continue to be developed and amended through qualitative and quantitative process evaluation carried out as part of the SupportBack 2 trial.

### 5.2 STUDY PROCEDURES – QUALITATIVE INTERVIEWS

In addition to the RCT, up to 30 qualitative interviews will be conducted with participants and up to 20 with Physiotherapists. A nominated Researcher from the University of Southampton (UoS) will conduct interviews either by telephone or at the participant's home using a semi-structured interview schedule. Audio files of the interviews will be transferred via cable onto a secure university computer, where they will be stored as secure, password protected files. Recordings will then be deleted from the recording device. Interviews will be transcribed by a confidential transcription service and then deleted from the university computer. Transcripts will be anonymised and labelled only with a unique participant identification number. Files will be transferred to and from the confidential transcription service using Dropoff, a UoS file transfer system which securely encrypts files.

### 5.3 BASELINE AND FOLLOW UP DATA COLLECTION

Eligibility will be confirmed by returning the postal screening questions with Physiotherapist input for those who fail screening. Data collection will occur primarily online. The LifeGuide system will collect consent, baseline data including demographics and follow-up data across the four time points (six weeks, three, six and 12 months). If patients are sent the link to LifeGuide but do not log on within a week, they will be emailed to check that they received the link and advised to look in their spam mail. If there is no response, one call attempt will be made.

Where there is non-response to the online follow-up questionnaire email, two reminder emails will be sent. Following non-response, a paper questionnaire pack with a pre-paid envelope will be sent one week after the last email reminder. If the paper questionnaires are not returned within two weeks of being sent, a blinded Research Assistant will call the participant to complete the primary outcome measure (RMDQ) and quality of life questionnaire (EQ-5D-5L). This is most likely to be done at the more critical time points of six weeks and 12 months but may be performed at other time points and with other questionnaires as required. In the case of duplicate questionnaires being completed, the first, most complete questionnaire will be used. All participants will receive a £5 voucher when asked to complete questionnaires at the more distant time-points of six and 12 months.

***Primary outcome:*** The primary outcome for this trial will be LBP-related physical disability measured by the RMDQ over 12 months. The RMDQ is recommended as part of the LBP core outcome domain set (21), is sensitive to change and suitable for primary care. Participants will complete measures at baseline, six weeks, three, six and 12 months (repeated measures design).

***Secondary outcome measures:*** See Table 3 for the details of all outcomes and specific measurement tools. Included are the other recommended core outcomes for LBP (pain intensity and health-related quality of life) as well as a range of measures that capture physical, psychological and social outcomes related to LBP, risk of persistent disability, physical activity levels, adherence to physical activity/exercise, exercise self-efficacy, pain self-efficacy, fear of movement, mental health, days lost from work and other valued activities. Measures will also be included to explore potential mediators/moderators that may affect engagement and outcome (see Section 7.6 Process Evaluation). Participant adherence to the internet intervention will be explored by examining objective intervention usage data automatically collected by the LifeGuide internet intervention. This data will provide detailed information on number of logins, number of sessions accessed, physical activity goals set, module(s) accessed as well as time spent on each webpage. Demographic data including gender, age, education and marital status will be collected by LifeGuide at baseline. Brief items related to occupational status will be measured at baseline and at follow-up (including employment status, effect of LBP on work difficulties, time off work).

**Table 3: Measures that will be collected (primarily online by LifeGuide but also on paper questionnaires or by telephone) and the time point they will be collected in the trial**

**Primary study endpoint**

| Questionnaire | Variable | Items | Reliability where available | Administration point, trial arms |
|---|---|---|---|---|
| **Roland Morris Disability Questionnaire (RMDQ)** | Back specific physical disability | 24 | Internal consistency: .77-.93 | Baseline, 6 weeks, 3, 6, 12, month follow-up<br>All arms |

**Secondary study endpoints**

**Health economics**

| Questionnaire | Variable | Items | Reliability where available | Administration point, trial arms |
|---|---|---|---|---|
| **EQ-5D-5L** | Health related quality of life | 6 | Internal consistency: >.80 for both scales | Baseline, 6 weeks, 3, 6, 12, month follow-up<br>All arms |
| **Self-reported over the counter (OTC) medication use** | Single item developed for this study | 1 | | Baseline, 6 months, 12 month follow-up<br>All arms |
| **Participant borne costs** | Participant reported resource use and time off work | 4 | | Baseline, 6 months, 12 month follow-up<br>All arms |
| **Brief occupational items** | Occupational questionnaire | 4 | | Baseline, 6 months, 12 month follow-up<br>All arms |
| **GP medical records review** [a] | Health care resource use including GP appointments, Nurse appointments, referrals and hospital stays and medication between specified dates. Data will also be collected on pre-existing conditions. | 10 | | 12 month follow-up<br>All arms |

**Pain**

| Questionnaire | Variable | Items | Reliability where available | Administration point, trial arms |
|---|---|---|---|---|
| **Pain duration** | Recent time spent pain free | 1 | | Baseline<br>All arms |
| **Days in pain** | Number of troublesome days in pain over the last month | 1 | | Baseline, 6 weeks, 3, 6, 12, month follow-up<br>All arms |
| **Pain index** | Numerical pain rating scale | 3 | Test-retest reliability: .67-.96 | Baseline, 6 weeks, 3, 6, 12, month follow-up<br>All arms |

| Questionnaire | Variable | Items | Reliability where available | Administration point, trial arms |
|---|---|---|---|---|
| **The Keele STarT Back screening tool** | Risk of persistent disability | 9 | Internal consistency: .79 | Baseline, 12 month follow-up<br>All arms |

**Psychological processes related to pain**

| Questionnaire | Variable | Items | Reliability where available | Administration point, trial arms |
|---|---|---|---|---|
| **Tampa scale for kinesiophobia (TSK-11)** | Fear of movement | 11 | Internal consistency: .70-.79 (53) | Baseline, 12 month follow-up<br>All arms |
| **Pain catastrophizing scale (PCS)** | Negative orientation towards pain | 13 | Internal consistency: .81 (55) | Baseline, 12 months follow-up<br>All arms |
| **Pain self-efficacy questionnaire (PSEQ)** | Confidence in ability to manage pain | 10 | | Baseline, 6 weeks, 12 months follow-up<br>All arms |
| **Self-efficacy for managing low back pain** | Single item from Keele's musculoskeletal health questionnaire tool (MSK-HQ) | 1 | | Baseline, 6 weeks, 3, 6, 12, month follow-up<br>All arms |
| **Modified expectancy questionnaire** | How much the intervention may reduce limitation due to back pain | 6 | Internal consistency: .82-.84 (56) | Baseline, following session one of SupportBack Internet intervention arms only |
| **Patient health questionnaire (PHQ-4)** | Mental health assessment with two items regarding depression and two items regarding anxiety | 4 | Internal consistency: >.80 for both scales | Baseline, 12 month follow-up<br>All arms |

**Physical activity/adherence**

| Questionnaire | Variable | Items | Reliability where available | Administration point, trial arms |
|---|---|---|---|---|
| **Godin leisure-time exercise questionnaire** | Physical activity assessment tool | 2 | | Baseline, 12 month follow-up<br>All arms |
| **SupportBack related physical activity** | Back specific physical activity assessment tool | 1 | | Baseline, 6 weeks, 3, 6, 12, month follow-up<br>All arms |

| Questionnaire | Variable | Items | Reliability where available | Administration point, trial arms |
|---|---|---|---|---|
| **Adherence to back specific exercise** | Self-reported adherence to back specific exercises. Items developed specifically for this study. | 4 | | 12 month follow-up<br>All arms |
| **Problematic experiences of therapy scale (PETS)** | How easy/difficult it was to carry out therapy | 12 | | 12 month follow-up<br>Internet intervention arms only |

**Satisfaction/enablement**

| Questionnaire | Variable | Items | Reliability where available | Administration point, trial arms |
|---|---|---|---|---|
| **Satisfaction** | Satisfaction with back pain care. Item developed for this study. | 1 | | 6 weeks |
| **Patient enablement instrument (PEI)** | Ability to cope as a result of healthcare received. | 6 | | 6 weeks, 12 month follow-up<br>All arms |

**Use of internet resources**

| Questionnaire | Variable | Items | Reliability where available | Administration point, trial arms |
|---|---|---|---|---|
| **Use of internet resources** | Participant reported use of internet resources for back pain | 1 | | 12 month follow-up all arms. |

[a] Information collected from the GP medical records review will be entered by the GP practice directly onto Medidata RAVE EDC.

***See Appendix A for a schematic of the data collection points along the trial timeline.***

### 5.4 DEVIATIONS AND SERIOUS BREACHES

Any study protocol deviations/violations and breaches of Good Clinical Practice (GCP) occurring at PICs should be reported to the Southampton Clinical Trials Unit (SCTU) immediately. SCTU will then advise of and/or undertake any corrective and preventative actions as required.

All serious protocol deviations/violations and serious breaches of GCP and /or the study protocol will immediately be reported to the Sponsor and Research Ethics Committee (REC).

### 5.5 STUDY DISCONTINUATION

In consenting to the study, participants have consented to the study intervention, follow-up and data collection. Participants may be discontinued from the study procedures at any time.

#### *5.5.1 Reasons for study discontinuation*

Participants may be discontinued from the study in the event of:

- Clinical decision, as judged by the GP or Chief Investigator (CI)
- Pregnancy

Full details of the reason for study discontinuation should be recorded in the End of Study form on Medidata RAVE EDC and medical records.

### 5.6 WITHDRAWAL

The participant/legal representative is free to withdraw consent from the study at any time without providing a reason.

Investigators should explain to participants the value of remaining in study follow-up and allowing this data to be used for trial purposes. Where possible, participants who have withdrawn from study treatment should remain in follow-up as per the trial schedule. If participants additionally withdraw consent for this, they should revert to standard clinical care as deemed by the responsible clinician. It would remain useful for the study team to continue to collect standard follow-up data and unless the participant explicitly states otherwise, follow-up data will continue to be collected.

Details of study discontinuation (date, reason if known) should be recorded in the End of Study form on Medidata RAVE EDC. The GP will also be notified and asked to record details in the participant's medical record.

### 5.7 PROHIBITED AND RESTRICTED THERAPIES DURING THE STUDY

There are no probhibited or restricted activities.

### 5.8 BLINDING AND PROCEDURES FOR EMERGENCY UNBLINDING

This is not a blinded study.

## 6 SAFETY

### 6.1 DEFINITIONS

**Adverse Event (AE):** any untoward medical occurrence in a participant or clinical study participant which does not necessarily have a causal relationship with study treatment or participation.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the study treatment or participation (regardless of causality assessments).

**Serious Adverse Event (SAE)** is any untoward medical occurrence or effect that:

- **Results in death**
- **Is life-threatening***
- **Requires hospitalisation**, or prolongation of existing hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**
- Other important medical events***.

*'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

***Other important medical events may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

**Note:** It is the responsibility of the GP or delegate to assess an event as 'serious' (SAE).

### 6.2 SERIOUSNESS

All AEs that fulfil the criteria definition of 'serious' in the protocol Section 6.1, must be reported immediately to SCTU using the 'Serious Adverse Event Report Form – Non-CTIMP'. The assessment of the seriousness will be made by the GP or delegate.

#### *6.2.1 6.2.1 Exceptions:*

For the purposes of this study, no SAEs are exempt from immediate reporting.

### 6.3 CAUSALITY

The assessment of causality will be made by the GP or delegate using Table 4 below. If any doubt exists about the causality, the GP/delegate should inform the SCTU who will notify the CI. Other clinicians may be asked for advice in these cases.

**Table 4: Assessment of SAE causality**

| Relationship | Denoted |
|---|---|
| Related | Some or clear evidence of causal relationship |
| Unrelated | No evidence of any causal relationship |

In terms of event status; **Not related to treatment** would highlight that the SAE is not related to the trial intervention. **Related and unexpected SAE** would be classified as an SAE which is related to the trial treatment/intervention and is unexpected.

In the case of discrepant views on causality between the GP and case Clinical Reviewer, SCTU will classify the event as per the worst case classification and where applicable the REC will be informed of both opinions within the required timelines.

### 6.4 EXPECTEDNESS

For the purposes of this trial no SAEs are to be considered expected.

### 6.5 REPORTING PROCEDURES

SAEs should be reported to the SCTU immediately upon GP awareness of an event occurring in a trial participant which fulfils one or more of the seriousness criteria listed above in Section 6.1. A flowchart will be provided to aid in the reporting procedures.

#### *6.5.1 Reporting Details*

A 'Serious Adverse Event Report Form – Non-CTIMP' should be completed for all SAEs and faxed/emailed to SCTU within 24 hours of a GP becoming aware of the event. Complete the SAE form and fax or email a scanned copy of the form with as much detail as possible to the SCTU together with anonymised relevant treatment forms and investigation reports.

**Or**

Contact the SCTU by phone for advice and then fax or email a scanned copy of the completed SAE form.

**SAE REPORTING CONTACT DETAILS**

***Please email or fax a copy of the SAE form to***
***SCTU within 24 hours of becoming aware of the event***

**Fax: 0844 774 0621 or Email: ctu@soton.ac.uk**

FAO: Quality and Regulatory Team

***For further assistance: Tel: 023 8120 4138 (Mon to Fri 09:00 – 17:00)***

Additional information should be provided as soon as possible if the event has not resolved at the time of reporting.

#### *6.5.2 Follow Up and Post- study SAEs*

The reporting requirement for all SAEs affecting participants applies for all events occurring up to 12 months plus six weeks following date of randomisation.

All unresolved SAEs should be followed up until resolved, the participant is lost to follow-up, or another 'end of study' definition is met. The GP should notify the study Sponsor of any death or SAE occurring at any time after a participant has discontinued or terminated study participation that may reasonably be related to this study.

### *6.5.3 Serious Adverse Events*

All SAEs should be reported immediately but at least within 24 hours of the PIC becoming aware of the event. The 'Serious Adverse Event Report Form – Non-CTIMP' asks for nature of event, date of onset, grade, outcome, causality (i.e. unrelated, related). The event term should be a medical term/concept with grades given in accordance with the NCI CTCAE v5. Additional information should be provided as soon as possible if the event has not resolved at the time of reporting.

All SAEs will undergo a second review by a delegated Clinical Reviewer who too will provide a causality assessment on the case. The SCTU will act based on worst case scenario to ensure participant safety; reporting to the REC within 15 days or seven days if life threatening.

### 6.6 SCTU RESPONSIBILITIES FOR SAFETY REPORTING TO REC

The SCTU will notify the REC of all **Related and Unexpected** SAEs occurring during the study within 15 days of the report or within seven days if life threatening. The SCTU submit all safety information to the REC in an Annual Progress Report.

## 7 STATISTICS AND DATA ANALYSES

### 7.1 METHOD OF RANDOMISATION

The randomisation sequence will be automatically generated, and a computer generated algorithm will block randomise participants to the trial groups. Participants will be stratified by level of severity, with a score of less than four on the RMDQ being considered as a lower level of severity and trial centre.

### 7.2 SAMPLE SIZE

Repeated measures primary outcome: A difference of 1.5 points on the RMDQ over the follow-up period of 12 months, assuming a standard deviation of 4.5 in line with the feasibility study, gives an effect size of 0.30. Alpha will be set to 0.025 to allow both interventions to be independently compared with the usual care alone arm. With four repeated measures (six weeks, three, six and 12 months), and assuming a correlation between repeated measures of 0.7 and 90% power, requires 215 participants per arm. Allowing for 20% loss to follow up, this gives a total sample size of **806**.

### 7.3 INTERIM ANALYSIS

See section on internal pilot (Section 7.5).

### 7.4 SUMMARY STATISTICAL ANALYSIS

Quantitative analysis will begin following cleaning and inspection of the data. Descriptive analysis will be conducted to determine outliers and distributions of the data. Where necessary, if data are not normally distributed, transformations will be applied or another appropriate distribution used. The primary analysis for the RMDQ score will be performed using a multilevel mixed model (MLMM) framework with observations at six weeks, three, six and 12 months (level one) nested within participants (level two). Results will be reported adjusting for baseline

severity, stratification factors and any pre-specified confounders. The model will use all the observed data and makes the assumption that missing RMDQ scores are missing at random given the observed data.

As there may not be a constant treatment effect over time, a treatment/time interaction will be modelled and included if significant (at the 5% level), with time treated as a random effect. An unstructured covariance matrix will be used.

Analysis of secondary outcomes will also be conducted using linear regression for continuous outcomes and logistic regression for dichotomous outcomes, again controlling for baseline symptom severity, stratification factors and any potential confounders. The structure and pattern of missing data will be examined, if appropriate, and a sensitivity analysis based on data imputed using a multiple imputation model presented. Data will be analysed on an intention-to-treat basis (they will be analysed as randomised); however, as a secondary analysis a per protocol analysis will also be conducted. Per protocol will be defined as all those who have completed at least Session 1 of the internet intervention (the entry session of the module, which includes setting expectations and containing initial Behaviour Change Techniques (BCT) to support being more active for low back pain).

It is not anticipated that there will be significant practice level effects but this assumption will be tested by comparing a fixed effect model to a random effects model. If there are significant practice level effects then, the model will include a random effect for practice (random intercept) and participant (random intercept and slope on time) to allow for between participant and practice differences at baseline and between participant differences in the rate of change over time (if significant at the 5% level), and fixed effects for baseline covariates.

No interim analyses are planned. Full details of the analyses to be undertaken will be set out in the Statistical Analysis Plan and approved by the Trial Steering Committee (TSC).

#### *7.4.1 Cost-effectiveness analysis:*

A 'within trial' economic analysis will be conducted alongside the RCT to estimate the incremental cost-effectiveness of the support back intervention compared to usual care. The base case perspective will be that of the NHS, but other resources relevant to LBP will be collected to enable additional analysis from a societal perspective. All resources required to provide the internet intervention and the telephone support will be recorded. Details of NHS resource use will be recorded from GP surgery notes review. This will include both primary and secondary care contacts and will cover both general health care usage in addition to LBP specific care in the follow-up period. Additionally, LBP specific drug use will be captured. There may also be differences in LBP related services paid for by study participants: for example, complimentary or alternative medicine (CAM). Participants may also require time off work. Additionally, there may be underreporting of LBP specific resource use from medical records. These resources will be captured by means of a simple questionnaire administered at six and 12 months. The time-off work question and items relating to use of private health care will additionally be asked at baseline. All resources identified will be costed using appropriate local and national data, for example NHS reference costs and Unit Costs of Health and Social Care.

The main outcome measure in the economic evaluation will be the quality adjusted life year (QALY), obtained from the EQ-5D-5L instrument using the published UK value set. In addition, a cost-effectiveness analysis will be carried out using the study primary outcome measure, i.e. the cost per point change in back-related physical function measured using the RMDQ will be estimated. Both costs and effects will be estimated using multiple regression, to allow for potential confounders, such as baseline scores for EQ-5D-5L and RMDQ. Standard practice will

be followed to calculate incremental cost-effectiveness ratios (ICERs), and present ICER(s) where any one option has both higher costs and increased effects compared to another. ICERs will show incremental cost per QALY or incremental cost per point improvement in RMDQ. Bootstrapping will be used to calculate cost-effectiveness acceptability curves (CEACs). These will illustrate the effect of uncertainty on study results. Major assumptions made in the analysis will be tested by means of sensitivity analysis. In particular, assumptions made during the costing of the intervention such as the number of individuals who will be using the website will be explored. Similar methods to the main clinical analysis will be used to handle missing data, i.e., analysis of patterns of missing data with multiple imputation methods employed if deemed appropriate.

### 7.5 INTERNAL PILOT

Progression will occur based on the following criteria:

*Recruitment*
The following progression criteria have been pre-specified and will be assessed by the TSC at nine months:

By nine months into the start of recruitment, the target recruitment is 282 (141 per centre).

- If recruitment exceeds 75% of the target the main trial will continue with additional plans for recruiting further practices.
- If recruitment falls between 50%-75% of the target, recruitment problems will be urgently discussed between the TSC and the Trial Management Group (TMG). Measures to improve recruitment will be implemented, in the form of a rescue plan. Assuming the plan is credible, the trial will proceed with monthly recruitment updates, and the trial will stop should recruitment not pick up (this review will be determined by the TSC).
- If recruitment is ≤ 50%, unless a credible recruitment plan can be rapidly implemented, following a discussion with the TSC and the NIHR Health Technology Assessment (HTA) Board, the trial will stop.

*Response to follow-up*
The SupportBack 2 trial has four follow-up points: six weeks, three, six and 12 months and the aim is to secure 80% follow-up at all time points. To enable timely judgements to be made regarding the trial progression, assessments on follow-up response rate will be based on the six week and three month time point.

Closely aligning with the recruitment criteria, the following will occur:

- If follow-up exceeds 75% of the target (80%) the main trial will continue with additional plans for improving follow-up.
- If follow-up falls between 50%-75% of the target, retention problems will be urgently discussed between the TSC and the TMG. Measures to improve follow-up will be planned. Assuming the plan is credible, the trial proceeds with monthly follow-up updates, and trial stopping is considered should follow-up not increase (this review will be determined by the TSC).
- If follow-up is ≤ 50%, unless a credible follow-up plan can be rapidly implemented, following a discussion with the TSC and the NIHR HTA Board, the trial will be stopped.

## 7.6 PROCESS EVALUATION

A process evaluation will be carried out following Medical Research Council (MRC) guidelines on process evaluations of complex interventions. In order to provide a detailed understanding of the SupportBack intervention three aspects will be examined: Implementation, mechanisms of impact (mediators) and context (moderators). A mixed methods approach will be used to explore these elements.

*Implementation*

Quantitative data describing trial implementation will be presented including number of practices recruited, patient eligibility (including reasons for declined participation where possible, and analysis of screen failures) and recruitment rates. The number of withdrawals from the trial per arm will be presented, along with numbers/percentages of dropouts from the intervention who do not respond to follow-up. Use of the internet intervention will be described by presenting automated data collected on frequency of logins and time spent on the intervention for both the internet intervention and the intervention plus telephone Physiotherapist support arm. With regard to the internet intervention plus telephone Physiotherapist support arm, the number of support calls successfully made (and attempts to get information), along with the mean number per participant in this arm will be described.

Qualitative interviews will be conducted with approximately 30 trial participants (following the three month follow-up point). Interviews will also be conducted with the trial Physiotherapists (approximately 20). Participants across the two intervention arms of the trial will be purposively sampled to ensure diversity in terms of age, gender and symptom severity (physical function, pain intensity and duration). Participants will be also be sampled based on high and low usage of the internet intervention and high and low engagement with the telephone Physiotherapist support. For participants, questions will focus on their experience of using the intervention, including telephone Physiotherapist support and usual care. Interviews with the trial support Physiotherapists will be designed to explore their experience of delivering the intervention, with a particular focus on barriers and facilitators, and determinants of successful exchanges.

*Mechanisms of impact*

A logic model of proposed mechanisms affecting LBP-related physical disability and pain outcomes for the SupportBack intervention has been developed. This model will be used as the basis of both quantitative and qualitative exploration of mechanisms. Quantitative analyses will focus on psychological and behavioural mechanisms influencing outcome following use of the interventions including expectancy, self-efficacy to manage LBP, physical activity, self-reported goal setting across the intervention and objective measures of intervention use (sessions completed, use of additional modules, e.g. mood, sleep etc.). In order to explore whether two core mechanisms' (mediating variables) contribution to outcome is unique to the internet intervention arms, brief single items capturing self-efficacy (SE) and physical activity (PA) will be measured in all three arms (including usual care). SE and PA will be measured at baseline and in the outcome questionnaire sets at six weeks, three, six, and 12 months. Correlations, multiple regression (linear and logistic) and mediation analysis will be used to explore relationships between mediating variables and LBP-related disability and pain intensity across the 12-month follow-up period.

Questions will be included in the qualitative interviews focusing on participants' perceptions of how use of the SupportBack intervention and/or telephone support affected their LBP. This will enable the inductive exploration of participants' views on mechanisms involved. Similar questions will also be explored in the usual care arm, focusing on how elements of their usual care may have led to improvements in their LBP.

*Context*

The relationship between elements of participants' context (moderators) and the effect of the interventions across the 12-month follow-up period will be explored. This will include variables such as LBP severity and duration at baseline, age, educational level and occupation status. Following the analysis of mechanisms, correlations and multiple regression (linear and logistic) will be used to explore relationships between moderating variables and LBP-related disability and pain intensity. Qualitatively, the above aspects of participants' context will feed into analysis when exploring themes regarding participants use of the intervention and their perceptions of benefit.

*Qualitative analysis*

Interview data collected regarding implementation, mechanisms and context will be transcribed verbatim, coded and analysed using an inductive thematic analytic approach. This will ensure participants' qualitative data are not constrained by the direction of a particular theoretical model, and enable novel insights from qualitative work to be added into the theory-driven logic model. Qualitative and quantitative data will be systematically triangulated to ensure a rich and robust account of the processes involved in the SupportBack 2 trial.

# 8 REGULATORY

## 8.1 CLINICAL TRIAL AUTHORISATION

This study is not considered to be a clinical trial of a medicinal product, so clinical trial authorisation from the UK Competent Authority the Medicines and Healthcare products Regulatory Agency (MHRA) is not applicable.

# 9 ETHICAL CONSIDERATIONS

The study will be conducted in accordance with the recommendations for physicians involved in research on human participants adopted by the 18th World Medical Assembly, Helsinki 1964 as revised and recognised by governing laws and EU Directives. Each participant's consent to participate in the study should be obtained after a full explanation has been given of treatment options, including the conventional and generally accepted methods of treatment. The right of the participant to refuse to participate in the study without giving reasons must be respected.

After the participant has entered the study, the clinician may give alternative treatment to that specified in the protocol, at any stage, if they feel it to be in the best interest of the participant. However, reasons for doing so should be recorded and the participant will remain within the study for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the participant remains free to withdraw at any time from protocol treatment and study follow-up without giving reasons and without prejudicing their further treatment.

## 9.1 SPECIFIC ETHICAL CONSIDERATIONS

None.

### 9.2 ETHICAL APPROVAL

The study protocol has received the favourable opinion of a REC or Institutional Review Board (IRB) in the approved national participating countries.

### 9.3 INFORMED CONSENT PROCESS

Informed consent is a process that is initiated prior to an individual agreeing to participate in a study and continues throughout the individual's participation. In obtaining and documenting informed consent, the Investigator should comply with applicable regulatory requirements and should adhere to the principles of GCP.

Potential participants will receive a PIS. This information will emphasise that participation in the trial is voluntary and that the participant may withdraw from the trial at any time and for any reason. The participant will be given the opportunity to ask any questions that may arise by speaking with the trial team and provided the opportunity to discuss the study with family members, friend or an independent healthcare professional outside of the research team and time to consider the information prior to agreeing to participate.

### 9.4 CONFIDENTIALITY

SCTU will preserve the confidentiality of participants taking part in the study. The Investigator must ensure that participant's anonymity will be maintained and that their identities are protected from unauthorised parties. On Case Report Forms (CRFs) participants will not be identified by their names, but by a unique participation identification number.

## 10 SPONSOR

SCTU, CI and other appropriate organisations have been delegated specific duties by the Sponsor and this is documented in the trial Task Allocation Matrix.

The duties assigned to the study PICs (NHS Trusts or others taking part in this study) are detailed in the Non-Commercial Agreement.

### 10.1 INDEMNITY

The UoS's public and professional indemnity insurance policy provides an indemnity to UoS employees for their potential liability for harm to participants during the conduct of the research. This does not in any way affect an NHS' Trust's responsibility for any clinical negligence on the part of its staff.

### 10.2 FUNDING

NIHR HTA are funding this study.

#### *10.2.1 PIC payments*

The payments assigned to the study PICs (NHS Trusts or others taking part in this study) are detailed in the Service Level Agreement.

This study is automatically eligible for the NIHR portfolio. Agreed service support costs will be paid by the local CRN.

#### *10.2.2 Participant payments*

Participants will receive £5 gift vouchers to return postal questionnaires at six and 12 months.

### 10.3 AUDITS AND INSPECTIONS

The study may be participant to inspection and audit by the UoS (under their remit as Sponsor), SCTU (as the Sponsor's delegate) and other regulatory bodies to ensure adherence to the principles of GCP, Research Governance Framework for Health and Social Care, applicable contracts/agreements and national regulations.

## 11 STUDY OVERSIGHT GROUPS

The day-to-day management of the study will be co-ordinated through the SCTU working closely with Keele CTU (SupportBack 2 trial second centre) and oversight will be maintained by the TMG, the TSC and the Data Monitoring and Ethics Committee (DMEC).

### 11.1 TRIAL MANAGEMENT GROUP (TMG)

The TMG is responsible for overseeing progress of the study, including both the clinical and practical aspects. The Chair of the TMG will be the CI of the study.

The SupportBack 2 TMG Charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the TMG, including the timing of meetings, frequency and format of meetings and relationships with other trial committees.

### 11.2 TRIAL STEERING COMMITTEE (TSC)

The TSC act as the oversight body on behalf of the Sponsor and Funder. The TSC will meet in person at least yearly and have at least one further teleconference meeting during the year. The majority of members of the TSC, including the Chair, should be independent of the study.

The SupportBack 2 TSC Charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the TSC, including the timing of meetings, frequency and format of meetings and relationships with other trial committees.

### 11.3 INDEPENDENT DATA MONITORING COMMITTEE (IDMC) /DATA MONITORING AND ETHICS COMMITTEE (DMEC)

*(**NB** for the purposes of this protocol, IDMC and DMEC refer to the same committee, and these terms can be used interchangeably).*

The aim of the DMEC is to safeguard the interests of study participants, monitor the main outcome measures including safety and efficacy, and monitor the overall conduct of the study.

The SupportBack 2 DMEC Charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the DMEC, including the timing of meetings, methods of providing information to and from the DMEC, frequency and format of meetings, statistical issues and relationships with other trial committees.

# 12 DATA MANAGEMENT

Participant data will be entered primarily remotely, by the participants themselves using the LifeGuide digital intervention software. 'LifeGuide' is software that was developed by the UoS Electronic and Computer Sciences department, working with Psychology. If participants do not complete questionnaires in LifeGuide but do so using paper questionnaires, when received at SCTU this information will be recorded in the Medidata RAVE EDC data collection tool. When questionnaires are completed by telephone the Research Assistant will enter data directly into Medidata RAVE EDC. In the case of questionnaires being duplicated in different formats the first, most complete questionnaire will be retained. SAEs and end of study information will be recorded on Medidata RAVE EDC. At the 12 month GP medical records review, GP practices will enter information onto Medidata RAVE EDC. The investigator is responsible for ensuring the accuracy, completeness and timeliness of the data entered by GP practices. Participant data will be retained in accordance with current Data Protection Regulations.

The participant data is pseudo anonymised by assigning each participant a participant identification number which will adapted for use in both LifeGuide and Medidata RAVE EDC. This will be used to identify the participant during the study and for any participant specific clarification between SCTU and the PIC. The PIC retains a participant identification code list which is only available to PIC staff.

The online Informed Consent Form will specify the participant data to be collected and how it will be managed or might be shared; including handling of all Personal Identifiable Data (PID) and sensitive PID adhering to relevant data protection law. Trained personnel with specific roles assigned will be granted access to the electronic data. Only the Investigator and personnel authorised by them should enter or change data in the databases.

A Data Management Plan (DMP) providing full details of the study specific data management strategy for the trial will be available and a Trial Schedule with planned and actual milestones, data tracking and central monitoring for active trial management created. Where there is source data that can be verified i.e. at the 12 month medical records review, data queries will be automatically generated within the Medidata RAVE ECD data collection tool. All alterations made to the database will be visible via an audit trail which provides the identity of the person who made the change, plus the date and time. At the end of the study after all queries have been resolved and the database frozen, the Investigator will confirm the data integrity. Data may be requested from the Data Access Committee at SCTU. Requests will be considered on a monthly basis.

# 13 MONITORING

## 13.1 CENTRAL MONITORING

Data stored at SCTU on the Medidata RAVE EDC database will be checked for missing or unusual values (range checks) automatically by the Medidata RAVE EDC database or by the Data Management Team. Any suspect data will be returned to the Research Team in the form of data queries. The Research Team will respond to the data queries providing an explanation/resolution to the discrepancies using the Medidata RAVE EDC system. These will

be closed when complete by the Data Management Team. There are a number of monitoring features in place at SCTU to ensure reliability and validity of the trial data, which are detailed in the Trial Monitoring Plan. The DMEC also have responsibility for specific central monitoring activities, as described in protocol Section 11.3.

### 13.2 PIC MONITORING

Given the nature of the trial, PIC monitoring is not expected.

### 13.3 SOURCE DATA

Source documents are where quantitative data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to GP practice records (from which medical history and previous and concurrent medication may be summarised), electronic data completed by participants online using LifeGuide and paper questionnaires (completed by participants or a Research Assistant).

## 14 RECORD RETENTION AND ARCHIVING

Study documents will be retained in a secure location during and after the trial has finished.

The Investigator or delegate must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. After study closure the Investigator will maintain all source documents and study related documents. All source documents will be retained for a period of 15 years following the end of the study. PICs are responsible for archiving the Investigator Site File and participants' medical records. The Sponsor is responsible for archiving the Trial Master File and other relevant documentation.

## 15 PUBLICATION POLICY

Data from all PICs will be analysed together and published as soon as possible. Individual investigators may not publish data concerning their patients that are directly relevant to questions posed by the trial until the TMG has published its report. The TMG will advise on the nature of publications. All publications shall include a list of investigators, and named authors, these should include the CI, Co-Investigators, Trial Manager, and Statistician(s) involved in the trial. Named authors will be agreed by the CI and Director of SCTU.

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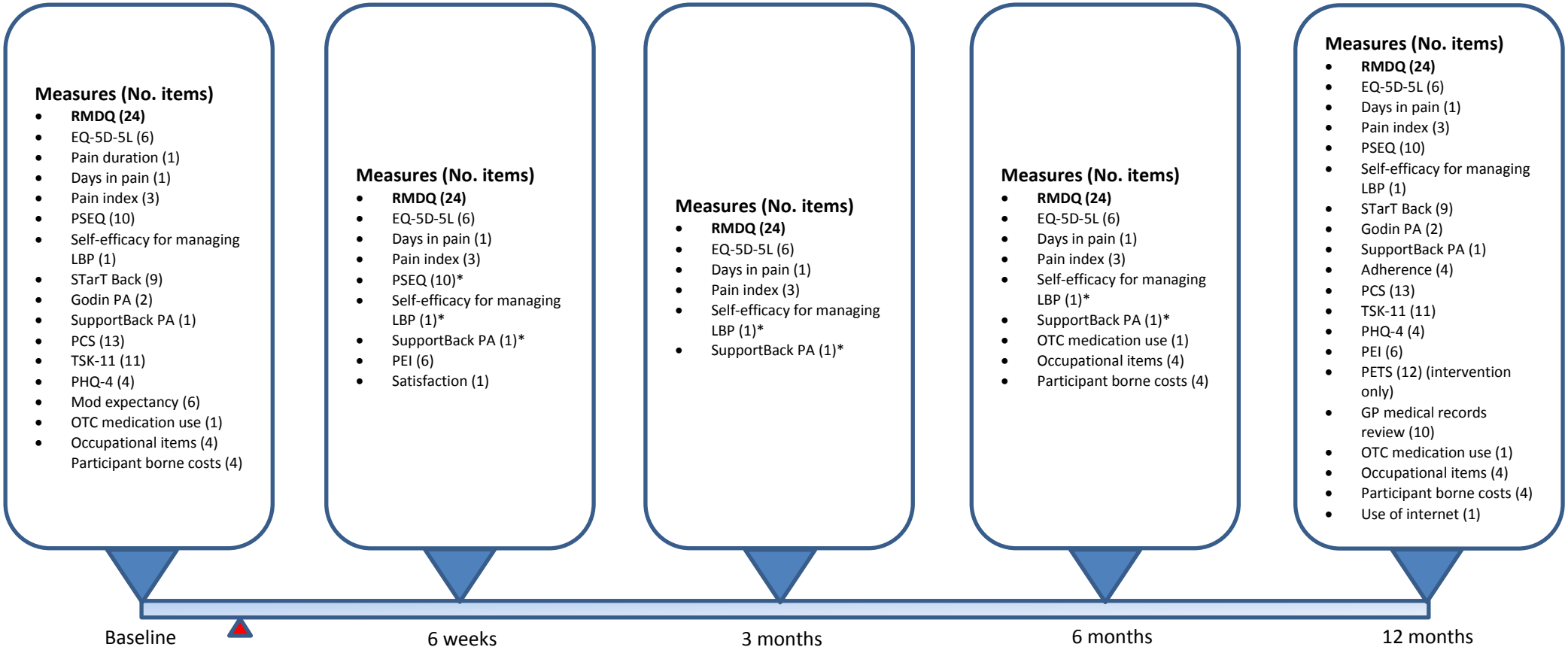
# 17 APPENDICES

**Appendix A: SupportBack 2 overview of measures and time of collection**




Modified expectancy questionnaire will be measured in the intervention groups only following session one with SupportBack.

*These variables, the full pain self-efficacy measure, a single item self-efficacy measure and SupportBack PA, will be used for a mediation analysis.

*Participants who fail to respond at each follow-up point will receive two email reminders, if no response is received a paper questionnaire pack will be posted.* ***At week 6*** *and* ***month 12*** *if the paper packs are not returned,* ***participants will be telephoned*** *by a blinded Research Assistant to collect the primary outcome measure (RMDQ) and the EQ-5D5L quality of life questionnaire (some flexibility with calls may be applied).*

# 18 SUMMARY OF SIGNIFICANT CHANGES TO THE PROTOCOL

| Protocol date and version | Summary of significant changes |
|---|---|
| V1 01-June-2018 | First Protocol |
| V2 10-Aug-2018 | 1. Secondary outcomes grouped into categories following REC review.<br>2. Section 4.4.1 – only GP practice staff will identify potential participants (removal of CRN Research Facilitators who will not identify potential participants). |
| | |