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Pragmatic cluster randomised double-blind pilot and feasibility trial of an active behavioural physiotherapy intervention for acute non-specific neck pain: a mixed methods protocol

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ABSTRACT

Introduction: Non-specific neck pain causes pain and disability and contributes substantial socio-economic burden internationally. Up to 50% of adults experience neck pain annually, leading to reduced quality of life. An active behavioural physiotherapy intervention (ABPI) may be feasible to manage patients with acute non-specific neck pain to prevent transition to chronicity. A recent pilot and feasibility trial investigating patients with acute whiplash-associated disorder found that 95% of participants fully recovered with ABPI and required less treatment sessions compared to the standard physiotherapy arm; supporting a definitive trial. Qualitative findings from the physiotherapists supported the potential of the ABPI in a non-specific neck pain population.

Methods and analysis: Two phases. (1) Pragmatic cluster randomised double-blind, parallel 2-arm (ABPI vs usual care) pilot and feasibility trial to evaluate procedures and feasibility of the ABPI for the management of acute non-specific neck pain. Six physiotherapy departments from 6 public hospitals in Thailand will be recruited and cluster randomised by a computer-generated randomisation sequence with block sampling. Sixty participants (30 each arm, 10 per hospital) will be assessed at baseline and 3 months following baseline for neck disability index, numerical rating scale for pain intensity, cervical range of motion, fear-avoidance beliefs questionnaire and EQ-5D-5L outcomes. (2) Embedded qualitative study using semi-structured interviews to explore acceptability of the ABPI to participants (n=12) and physiotherapists (n=3). Descriptive analysis of quantitative data and interpretative phenomenological analysis to code and analyse qualitative data (deductive and inductive) will inform evaluation of success.

Ethics and dissemination: This trial is approved by the Naresuan University Institutional Review Board (NUIRB_0380/61).

Trial registration: TCTR20180607001

Keywords (3-5 words): Non-specific neck pain, active behavioural physiotherapy intervention, complex intervention, pilot and feasibility trial, cluster randomisation

Strengths and limitations

- This trial is the first investigation of the active behavioural physiotherapy intervention (ABPI) in patients with acute non-specific neck pain after finding potential benefits in patients with acute Whiplash-Associated Disorder (WAD) in the previous Acute Whiplash Injury Study (AWIS) trial.
- A mixed method (quantitative and qualitative) trial will be performed to evaluate procedures, feasibility and acceptability of the ABPI in managing acute non-specific neck pain within the Thai public hospitals.
- The quantitative phase will be conducted using a cluster randomised double-blind design to avoid treatment contaminations and for administrative conveniences.
- The qualitative phase is designed to explore the treatment perceptions from all stakeholders, specifically patients and physiotherapists.
- Although the ABPI was originally developed for managing patients with acute WAD, it may be helpful in patients with acute non-specific neck pain owing to the similar characteristics of both conditions.
- This trial is the first cluster randomised controlled trial in a Thai public physiotherapy setting.

INTRODUCTION

Background and rationale

Neck pain is the 4th cause of disability [1] and the second biggest contributor to disability-adjusted life years (DALYs) among musculoskeletal disorders in the world.[2] In each year, approximately 50% of adults experience neck pain,[3] leading to a reduced quality of life.[4] Furthermore, the pain and disability associated with neck pain has a substantial impact contributing social and economic burden (e.g. health-care utilisation, work absenteeism and lost productivity).[1 5] In the USA, the health-care spending on neck and back pain is approximately $86.7 billion, following diabetes and ischemic heart disease.[6] For sickness absence in the UK, approximately 31 million days were lost due to musculoskeletal problems (mostly neck and back pain) among workers in 2016.[7] In Thailand, the 4th greatest health problem is musculoskeletal diseases (n=22 million people in 2015),[8] and up to 50% of these individuals' problems can be caused by neck pain,[8 9] leading to a socioeconomic burden of approximately ฿11 billion.[10] Therefore, an effective intervention for managing neck pain is required to improve quality of life and reduce socioeconomic burden.

Physical (e.g. pain and disability)[1 2] and psychological (e.g. anxiety, depression and fear avoidance)[11-13] problems are observed in patients with non-specific neck pain. The current clinical guidelines [14 15] and low-moderate quality evidence [16 17] suggest that manual and exercise therapy may be useful in managing patients with non-specific neck pain. However, high recurrence and chronicity amongst patients with non-specific neck pain are reported, suggesting limited success of existing interventions.[1 2 18 19] For drug therapy, the recent systematic review and meta-analysis of randomised placebo controlled trials found that there were no effects of paracetamol for pain reduction, reducing disability and improving quality of life,[20] and no clinical importance of Nonsteroidal Anti-inflammatory

Drugs (NSAIDs) for spinal pain.[21] Additionally, use of paracetamol and NSAIDs are documented to contribute a 4 times increase in abnormal liver function [20] and 2.5 times increased risk of gastrointestinal reactions.[21] Owing to these unwanted side effects from pharmacological management, non-specific neck pain is commonly managed by physiotherapists,[14 15 22] and effective conservative management in the acute stage (≤4 weeks) [11 23] is required to prevent the transition to chronicity and recurrence.

According to the current evidence, non-specific neck pain is a complex biopsychosocial disorder.[1 2 11-13] Subsequently, the management of patients with non-specific neck pain can be complex, encompassing both physical and psychological perspectives. All individuals with acute non-specific neck pain can be variously impacted by psychological problems and can lead to poor recovery.[11] Unfortunately, using multimodal therapy or multifaceted implementation strategies to date have not been useful.[24] Although whiplash-associated disorders (WAD) and non-specific neck pain can be different in mechanism of injury and severity, both conditions and their clinical characteristic are similar.[24-27] An active behavioural physiotherapy intervention (ABPI) may therefore be useful in managing patients with non-specific neck pain based on the findings of the previous Acute Whiplash Injury Study (AWIS) pilot and feasibility trial.[28-31] The potential value of the ABPI was supported by physiotherapists who used it during the trial to manage their patients and they have continued to apply the ABPI in managing their patients with other pathologies (e.g. neck and low back pain) after trial completion.[31]

Originally, the ABPI was developed through a sequential multiphase project using rigorous, precise and transparent methodologies in order to manage patients with acute WAD.[31] The intervention development process consisted of a systematic review and meta-analysis of randomised controlled trials,[28] a modified Delphi study using international researchers and UK clinical whiplash experts,[29] underpinned by social cognitive theory focusing on self-efficacy enhancement in line with the Medical Research Council (MRC) Framework of Complex Interventions,[31 32] and a cluster randomised double-

blind pilot and feasibility and an embedded qualitative study.[30] The findings of the pilot and feasibility trial [31] demonstrated that 95% of patients who received the ABPI fully recovered at 3 months follow-up whereas ~17% of patients who received standard physiotherapy fully recovered using a cut-off on the Neck Disability Index ≤ 4.[30 31] This suggests that the ABPI could prevent chronicity among patients with WADII (≥3 months is classified as chronic stage).[33] Moreover, the ABPI appeared better than standard physiotherapy in terms of pain reduction (visual analogue scale for pain intensity), cervical range of motion (cervical range of motion device), pressure pain threshold (digital pressure algometer) and general health status (EQ-5D). Furthermore, the number of physiotherapy sessions and the costs of management in the ABPI arm were lower than standard physiotherapy. The ABPI was acceptable to physiotherapists and patients, leading to the possibility for it enhancing physiotherapy practice in the future.[31] According to no report of WAD as a health problem in Thailand but non-specific neck pain being a substantial problem,[34] a pilot and feasibility clinical trial is first required to investigate the potential of the ABPI in patients with acute non-specific neck pain in a public Thai physiotherapy setting.

AIM

To evaluate procedures, feasibility and acceptability of an active behavioural physiotherapy intervention for the management of patients experiencing acute non-specific neck pain in a Thai public physiotherapy setting in order to inform the design and sample size requirements for a future definitive randomised controlled trial.

Objectives

- To evaluate the feasibility of procedures for a cluster randomised controlled trial in the public physiotherapy sector in Thailand (i.e. randomisation, recruitment, data collection, adherence, trial management and follow-up) [35-38]
- To explore the acceptability of the ABPI among Thai physiotherapists and patients with acute non-specific neck pain [36]
- To estimate sample size in order to conduct an adequately powered definitive trial [36-40]

METHODS

The protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) to ensure adequate transparency.[41] This protocol contains 2 phases: 1) a quantitative study to evaluate the procedures and feasibility of the ABPI will follow research methods and reporting in line with the CONSORT 2010 statement: extension to cluster randomised trials [42] and the CONSORT 2010 statement: extension to randomised pilot and feasibility trials [43]; and 2) an embedded exploratory qualitative study to investigate the acceptability of the ABPI of patients and physiotherapists in the ABPI arm will follow research methods and reporting of the Consolidated criteria for Reporting Qualitative research (COREQ): a 32-item checklist for interviews and focus groups.[44] Subsequent deviations of the protocol will be submitted to the Naresuan University Institutional Review Board for an amendment and reported in the full trial.

Trial design and setting

Phase I: pilot and feasibility trial

A pilot and feasibility trial of a pragmatic cluster randomised double-blind (assessors and participants), parallel two-arm design, comparing ABPI with usual care, will be conducted to evaluate procedures and feasibility of the ABPI for acute non-specific neck pain management. Six physiotherapy departments from 6 public hospitals in Thailand will be recruited. The cluster randomisation design has several benefits in terms of reducing treatment contamination, enhancing participant adherence,[42 45-47] participant blinding,[42] administrative convenience [45] and logistical conveniences.[45]

The heads of 6 physiotherapy departments or their hospital directors will be invited to participate by signing consent forms (cluster-level consent) prior to cluster randomisation.[42] One physiotherapist and one blinded assessor (another physiotherapist who will be familiar with and trained for outcome measurements) will be provided in each hospital. Following randomisation, consecutive potential participants will be screened and recruited by physiotherapists. The participant information sheet and consent form will be given to potential participants. The recruiting physiotherapists will then discuss any issues relating to the trial, provide an opportunity to ask questions, confirm eligibility and obtain written consent (individual-level consent). After giving informed written consent, participants will be assessed on all outcome measures by blinded assessors at each site using standardised instruments with established measurement properties. Assessments will be performed at this baseline and at 3-months follow-up post baseline. All outcome assessments will be independent from treatment sessions to ensure the blinding of the assessors from treatment allocation. Both assessors and participants will not know to which intervention arm the participants are allocated. To evaluate blinding, at the end of the 3-month follow-up, participants and assessors will be asked which intervention they/their department have been allocated to in order to

consider the blinded procedures of definitive phase III trial. The participants will receive a reminder 2 days prior to the 3-month follow-up appointment using e-mail, message or telephone calling depending on their preference.

Phase II: qualitative semi-structured interviews

An embedded qualitative using interpretative phenomenological analysis (IPA) [48] will explore the acceptability of the ABPI for participants (n=12) and physiotherapists (all physiotherapists, n=3) in the ABPI arm.[30] For convenience to interviewer and interviewees, semi-structured interviews will be conducted by TW. Topic guides adapted from the AWIS trial [30] will be pilot tested 2-3 times prior to conducting the first interview. Potential participants will be recruited via telephone. The information sheet and consent form will be sent to them via e-mail or post depending on their preference in order to provide an opportunity to decide whether they wish to complete the consent form in advance. Demographic characteristics of the participants (e.g. age, gender, occupation and ethnicity) will be recorded and reported.[44] The participants will be interviewed for 30-90 minutes in a private room of their local hospital, and the interview will be recorded using a digital recorder.

Participants

Participants will be recruited from the physiotherapy departments of 6 public hospitals. Demographic characteristics, including age, gender, present drugs, and information regarding non-specific neck-pain symptoms will be collected by the blinded assessors at the baseline assessment.

Eligibility criteria for clusters: Physiotherapy departments in public hospitals in Thailand.

Inclusion criteria: Participants aged 20-60 years presenting with non-specific neck pain within the previous 4 weeks.[11 23]

Exclusion criteria: Signs and symptoms WAD or traumatic neck pain,[49] upper cervical instability,[50] cervical artery dysfunction,[51] suspected serious spinal pathology, active inflammatory arthritis, tumours, infection of the skin and soft tissue, bleeding disorders or using anti-coagulant medication,[50] any current or previous treatment from any other third party, or presenting with any serious injuries, history of cervical surgery,[52] previously symptomatic degenerative diseases of the cervical spine or neck pain within 6 months prior to the recruitment,[53] neurological conditions, alcohol abuse,[53 54] dementia,[53 54] serious mental diseases,[53 54] psychiatric diseases,[55 56] osteoporosis, serious medical conditions (e.g. severe diabetes and hypertension), pregnant and/or non-Thai speaking and reading.

Interventions

Intervention details are provided in line with the Template for Intervention Description and Replication (TIDieR).[57] All participants will attend face-to-face physiotherapy for up to 10 sessions in a physiotherapy department based on their physiotherapist's clinical judgement. The frequency of appointment will depend on their physiotherapists' strategies but each session will be limited to 30 minutes. A minimum of a Bachelor Degree in Physiotherapy with 5 years of post-registration experience will be required for the qualifications of all physiotherapists. TW will randomly select treatment sessions to observe in the experimental arm to evaluate fidelity of the ABPI. Also, this will enable provide an opportunity to monitor and feedback regarding the intervention to the treating physiotherapists.[30]

Usual care

Patients will be managed according to current practice reflecting the recommendations provided in the non-specific neck pain clinical guidelines.[14 19 23 58] Usual care will consist of cervical or thoracic mobilisation/manipulation, exercises (e.g. stretching, coordination, strengthening and endurance), upper

quarter and nerve mobilisation, appropriate advice (e.g. remain active as possible, restore their neck movement as pain allows using neck range of motion exercises, correct poor posture, sleep with one pillow which provides lateral support and also gives support to hollow of the neck), simple analgesia and other physiotherapy interventions (e.g. manual therapy and modalities). All physiotherapists in the usual care arm will be trained and updated for the existing clinical guidelines to reach the standard physiotherapy management. Appropriate interventions will be selected depending on the physiotherapist's decision-making for the individual patient based on examination findings and clinical reasoning.[51]

Active Behavioural Physiotherapy Intervention (ABPI)

The ABPI has been developed through a systematic review,[28] a modified Delphi study internationally,[29] use of social cognitive theory focusing on self-efficacy enhancement [59] and has been tested for WAD patients in a AWIS pilot and feasibility trial.[30] Full details of the ABPI (e.g. concept, phases and strategies) are provided by the previous published articles.[29 30] The ABPI is delivered within a flexible framework, and will be modified to manage individuals with acute non-specific neck pain based on clinical examination findings. The intervention will focus on reducing psychological stress and increasing confidence in exercises and/or home programmes using self-efficacy enhancement at the beginning prior to improving physical functions based on the concept, phases and strategies of the ABPI.

Physiotherapists in the experimental arm will be trained to deliver the ABPI in advance of data collection. Training will consist of a group tutorial (1 day) and workshop followed by individual training sessions (4 weeks) to enable them to tailor the intervention to an individual patients with acute non-specific neck pain based on the findings from the patient history and physical examination data, and their evidence-informed clinical reasoning.[51] Physiotherapists and their treatment notes will be randomly observed by

TW during data collection to ensure fidelity of the intervention and to provide feedback throughout the trial.

Outcomes

Planned definitive trial primary outcome measure

The Neck Disability Index (NDI) is a patient-reported questionnaire with 10 sections to evaluate pain intensity and functional activities (e.g. personal care, lifting, reading, headache, concentration, work, driving, sleeping and recreation.[60] Each section is scored from 0 to 5 (the highest score representing the greatest disability). The NDI is a valid, reliable and responsive tool in assessing pain and disability in both acute and chronic neck problems.[60-63] The level of participant's disability will be indicated by the overall score.[60] The NDI version Thai has been reported as a reliable tool (Cronbach α=0.85, Intra-class Correlation Coefficient (ICC)=0.85) in assessing patients with neck pain, and will be used in this trial.[64] The minimum clinically importance difference (MCID) of the NDI in patients with neck pain is 8.[64-66]

Secondary outcome measures

Numerical Rating Scale for pain intensity

Pain will be measured using a 0 (no pain) to 10 (worst possible pain) by the Numerical Rating Scale (NRS).[67 68] It is a simple and the preferred tool for assessing pain intensity, with high validity and reliability (ICC=0.76).[69-72] The MCID of NRS for patients with mechanical neck pain without upper limb symptoms is 1.5.[73]

Cervical Range of Motion (CROM)

A common problem among patients with neck pain is a decrease cervical mobility.[74] In this trial, cervical range of motion (CROM) will be measured using the CROM device.[75] The CROM device is reported as a highly valid and reliable ($ICC_{3,3}$ ranging 0.89-0.98 for all neck movement directions) device in assessing CROM.[76] In assessment process, participant will sit on a comfortable chair with both hips and knees flexed to 90º and be attached by the CROM device to the head.[77-79] The average of 3 measurements will be performed for data analysis. The MCID of CROM for non-specific neck pain is 10°.[80]

Fear-Avoidance Beliefs Questionnaire

Fear-Avoidance Beliefs Questionnaire (FABQ) is a valid and reliable tool to predict prolong disability in patients with neck pain.[81 82] It consists of 16 items (each scored 0 to 6) covering both work and physical activity.[83] The FABQ has translated to several languages (e.g. Chinese, Persian and Greek) for patients with neck pain.[84-86] In Thailand, the translation and cross-cultural adaptation of the FABQ was conducted and tested the psychometric properties for Thai patients with non-specific neck pain (n=129) by TW and his colleagues. The findings reveal that the FABQ version Thai is a valid (Cronbach α=0.80-0.87 for all items) and reliable ($ICC_{2,1}$=0.98) tool (preparing for publication) to quantify fear and avoidance beliefs in patients with non-specific neck pain. The minimum detectable change of the Thai version is 5.85. Unfortunately, the published MCID of the FABQ is not available for patients with non-specific neck pain.

EuroQol-5 Dimensions (EQ-5D-5L)

The EQ-5D-5L is a valid and reliable self-report quality of life (QoL) questionnaire.[87-89] It is recommended as a useful tool for measuring generic QoL in order to provide information for cost-effectiveness analysis.[90] The EQ-5D-5L has been translated into many languages including Thai with valid and reliable tool ($ICC_{2,1}$=0.70).[91-93] The MCID of the EQ-5D-5L can be 0.32.[89] Unfortunately, the information for non-specific neck pain is not available.

Assessment of outcome

All participants will be assessed at baseline and at 3-months post baseline. Participants who continue with symptoms and problems after 3 months will be defined as chronic.[23] The number of fully recovered patients with non-specific neck pain at 3 months will be evaluated using a cut-off of NDI ≤ 4.[60] Telephone contact will be used in case of participants do not attend the 3-month follow-up assessment and they will be asked if they would like to make a new appointment. When participants cannot make a new appointment, the assessors will ask them to complete the NDI, NRS, FABQ and EQ-5D via telephone interview; these outcomes have established reliability and validity via telephone.[94-96]

Feasibility of cost-effectiveness analysis

In order to assess the feasibility of data collection for the planned cost-effectiveness analysis in the definitive trial, direct and indirect medical costs will be collected and recorded. The diary pocket book of the previous AWIS trial [30] will be modified to Thai in order to record any activities related to non-specific neck pain management such as using medication, consulting other health professionals; along with any costs they incurred, and days of sick leave. The information will be collected by the blinded assessors each week replacing self-record which was unsuccessful in the previous trial.[31] Furthermore, general information of participants (e.g. work status, income and distance between home and hospital) will be collected at the baseline assessment. Costs related to physiotherapy management will be collected from the physiotherapy departments throughout the trial. Training costs of physiotherapists in the ABPI arm will be also included.

Sample size

According to a pilot and feasibility trial, a power calculation is not required and targeted sample sizes for pilot/feasibility trials is still controversial.[36] This trial will be planned to recruit 60 participants (30 per arm, 10 from each department) in order to provide sufficient power of parameters for designing a high quality of a definitive RCT.[97]

Randomisation

A computer-generated randomisation programme with block sampling will be used by TW to random 6 physiotherapy departments to either usual care (n=3 departments) or ABPI (n=3 departments) in order to minimise selection bias. The allocation will be concealed before assignment. Cluster randomisation will be performed prior to participant recruitment (**Figure 1: CONSORT flow diagram**).

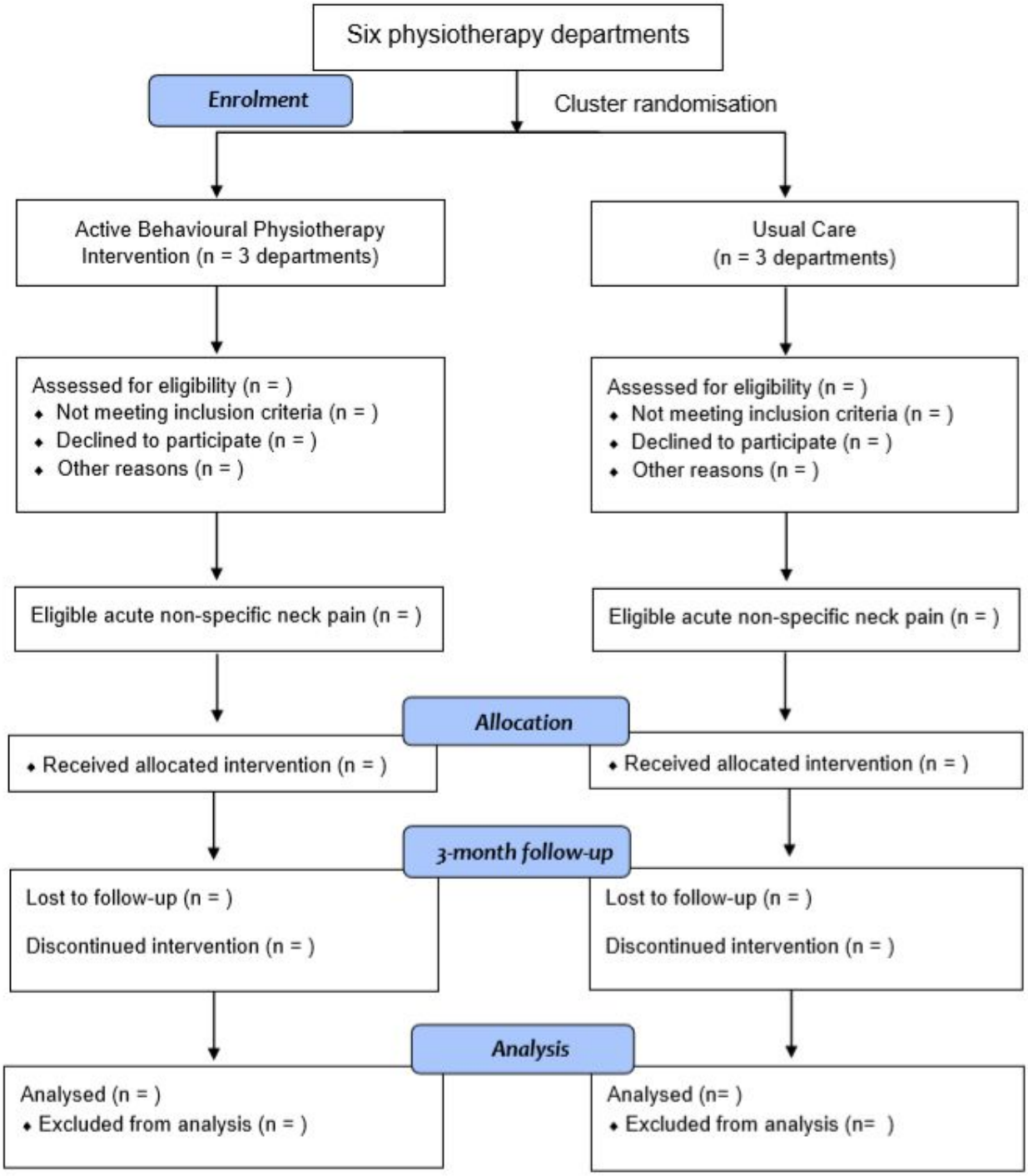

Figure 1: CONSORT flow diagram (adapted from CONSORT 2010).

Data analysis

Phase I: Quantitative data will be analysed and summarised to evaluate eligibility, recruitment and follow-up rates, using IBM SPSS version 22. The feasibility of the ABPI for non-specific neck pain management will be assessed using descriptive statistics (e.g. frequencies, percentages, means, standard deviations, medians and interquartile ranges depending on data).[37] Intention-to-treat analyses will be used in this trial. Multiple imputation will be performed if missing data are found. The evaluation of the number of fully recovered participants will be performed by consideration of NDI ≤4 at 3-month follow-up.[60] The intra-cluster correlation coefficient (ICC) will be provided to calculate the sample size within a clustered definitive trial. The analyses and findings of the trial will be discussed with the research team at each stage, and by the trial steering and data monitoring committee.

After trial completion, the following are the possible decisions for progressing to definitive trial: (i) stop if the main trial is not possible or valuable, (ii) continue but modify the protocol if the main trial is possible and valuable, (iii) continue without modifications but monitor closely if the main trial is possible and valuable with close monitoring, (iv) continue without modifications if the main trial is possible and valuable.[37] **Table 1** shows the criteria to consider a future definitive trial.

Table 1: Considerations for a future definitive trial

Objectives	Criteria for success
To evaluate the feasibility of procedures for a cluster randomised controlled trial in the public physiotherapy sector in Thailand (i.e. randomisation, recruitment, data collection, adherence, trial management and follow-up)	Feasible to conduct a phase III trial • No major obstruction issue and/or serious adverse event • Feasible for the type of study (randomised design) • Feasible for procedures of data collection, trial management and follow-up • At least 3 participants a month per hospital
To explore the acceptability of the ABPI among	• The ABPI can be acceptable to Thai

Thai physiotherapists and patients with acute non-specific neck pain	physiotherapists and patients with acute non-specific neck pain (explored by qualitative study). • Acceptable rate ≥60% of participants in each group
To estimate sample size in order to conduct an adequately powered definitive trial	• All parameters can be provided to calculate sample size for an adequately powered definitive trial

Phase II: All interviews will be verbatim transcribed and analysed in line with IPA.[48] All participants will be anonymous using a pseudonym. Transcripts will be read a number of times to enable familiarisation. Qualitative data will be coded and grouped by TW and a coder to minimise potential bias. Related themes of the acceptability of the ABPI for non-specific neck pain management will be identified by QRS Nvivo 10. The analyses will be performed case by case in both deductively (to identify themes) and inductively (to identify additional themes).[98 99] After the completion of the initial coding, similarities of the themes between coders will be examined. Then, a table of emergent theme will be established. The process will be used throughout the study. The analysis and findings from the qualitative data will be reviewed and discussed with the research team and the trial management group to ensure the accuracy of data analysis and provide other interpretations and suggestions.

Trial management and monitoring

The Trial Management Group (combing The Trial Steering Committee and the Data Monitoring Committee consistent with the pilot and feasibility nature of the trial) consisting of TW (the lead researcher), AR (the experienced trialist), SU (the neck expert), a non-specific neck pain patient, an external member, and an independent chair will meet at the start of recruitment, after 3 months of recruitment, and at the completion of data collection.

Adverse events

This trial can be considered as a low risk trial for adverse event owing to no reporting of any adverse/ serious adverse event in using the ABPI in physiotherapy setting of the previous AWIS trial.[30 31] Moreover, patients with non-specific neck pain have reported less severity than patients with WAD. Both interventions are conservative treatments without existing reporting of serious adverse events in managing neck pain.[31 100-102] From the literature, the most common adverse event after physiotherapy intervention is muscle soreness and it can recover within 1-2 days.[103]

Serious adverse events

Serious adverse event can be evaluated as a very low risk owing to the nature of patient pathology and treatment management. This trial is designed to exclude patients with high severity using experienced physiotherapists who will be trained further in screening participants. Furthermore, the International Federation of Orthopaedic Manipulative Physical Therapists (IFOMPT) cervical framework [51], which has provided clinical reasoning to identify the risk of adverse events regarding vascularity and instability of the neck, will be used to inform examination for eligibility. However, a serious adverse event will be defined if participants have worsening symptoms within 3 days and been admitted to the hospital due to non-specific neck pain problems.[30]

Procedures for reporting adverse and serious adverse events

An adverse event reporting form will be provided to all physiotherapy departments. Participants will be required to report any unpleasant symptoms to their physiotherapists by completing the form. Then, physiotherapists will report any event to TW within 24 hours, and TW will report to the trial steering

committee within 24 hours to enable analysis of the event and any required action. Any unexpected serious adverse events (e.g. a life-threatening situation, inpatient hospitalisation and/or significant disability) will be immediately reported with a written form and verbal contact by physiotherapists to TW. Subsequently, TW will report any event to the trial steering committee; immediately to discuss for an action.

Data management

All information of participants will be preserved safely from any third party to maintain the participants' privacy at the Faculty of Allied Health Sciences, Naresuan University. All collected documents will be stored in a secure place and electronic data will be confidentially stored in a password-protected computer. Only members of the research team can access the data. All data will be securely destroyed after being kept for 10 years.

Ethics and dissemination

The trial will be conducted in accordance with the Declaration of Helsinki and the ethical guidelines for medical human research and is approved by the Naresuan University Institutional Review Board (NUIRB_0380/61). The findings of the trial (completely unattributable format or at an aggregate level) will be submitted to medical journals and presented at international and/or local conferences/lectures.

DISCUSSION

The findings of the previous AWIS trial reported that the ABPI was feasible for acute WADII management to prevent the transition to chronicity (e.g. 95% of the participants fully recovered by the ABPI within 3 months whereas ~17% by the standard physiotherapy) and was acceptable to physiotherapists and

patients.[30 31] Furthermore, physiotherapists have applied the ABPI to manage other neck pathologies and regions owing to the possible success of this management approach.[31] According to the similarity of the situations and symptom characteristics between the WAD and non-specific neck pain populations,[25 27] it is interesting to investigate if the ABPI is feasible for managing non-specific neck pain in the acute stage to prevent chronicity. Therefore, this phase II trial will be conducted to evaluate feasibility and acceptability of the ABPI for acute non-specific neck pain in a Thai physiotherapy setting and/or to prepare information in designing an adequate powered, high quality definitive trial.

Owing to some limitations of the previous AWIS trial, this trial is designed to enhance quality. [30 31] First, this trial will provide one blinded assessor at each site to accelerate the recruitment rate and logical convenience. Second, the trial will use individual semi-structured in-depth interviews to explore the acceptability of the participants replacing a focus group. In the previous trial, only one participant can attend the focus group (3 participants verbally agreed previously) although the research team tried to use several strategies (e.g. contacting all participants, arranging based on their preference and convenience, reminding (2 days) for the date and location of the meeting prior to the date of the focus group and providing convenient facilities (e.g. the nearest parking area and meals). Subsequently, the focus group was modified to an individual interview. Third, the qualitative data will be analysed using two independent coders to establish higher trustworthiness.

In Thailand, neck pain is a substantial health problem among musculoskeletal disorders leading to socioeconomic burden. According to the findings of the AWIS trial,[31] the ABPI may be potentially effective intervention to manage acute non-specific neck pain. Thus, this trial will be conducted to evaluate feasibility of the ABPI in patients with acute non-specific neck pain and its procedures. This trial is the first investigation of the ABPI in Thai clinical setting and the first time in conducting a cluster randomised design in Thai physiotherapy setting.

Trial status

Recruiting commenced 01/02/2019.

Competing interests

No competing interests.

Authors' contributions

TW is the chief investigator and guarantor leading to drafting the initial manuscript, protocol development, analyses and dissemination. TW, SU and AR have contributed to clinical and methodological decisions to ensure the trial quality and will contribute to data interpretation, conclusions and dissemination. All authors have read and agreed the final manuscript.

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Pages
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	-
Protocol version	3	Date and version identifier	-
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 22
	5b	Name and contact information for the trial sponsor	1, 22
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	18-20
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7-9

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8-9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9-10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	18-20
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11-12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10-12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	16
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8, 21
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	15

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	15
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	15
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8, 18-20
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12-15, 18
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	20
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17-18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	-
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18-20

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	18-20
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	18-20
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	18-20
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	20
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	7, 20
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8-9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	20
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	20
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	19-20
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
	31b	Authorship eligibility guidelines and any intended use of professional writers	22
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	-
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Pragmatic cluster randomised double-blind pilot and feasibility trial of an active behavioural physiotherapy intervention for acute non-specific neck pain: a mixed methods protocol

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Pragmatic cluster randomised double-blind pilot and feasibility trial of an active behavioural physiotherapy intervention for acute non-specific neck pain: a mixed methods protocol

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ABSTRACT

Introduction: Non-specific neck pain causes pain and disability and contributes substantial socio-economic burden internationally. Up to 50% of adults experience neck pain annually, leading to reduced quality of life. An active behavioural physiotherapy intervention (ABPI) may be feasible to manage patients with acute non-specific neck pain to prevent transition to chronicity. A recent pilot and feasibility trial investigating an acute whiplash-associated disorder population found potential value of the ABPI with 95% of participants fully recovered (neck disability index: NDI≤4, compared to 17% in the standard physiotherapy arm); supporting a definitive trial. Qualitative findings from the physiotherapists supported the potential of the ABPI in a non-specific neck pain population.

Methods and analysis: Two phases. (1) Pragmatic cluster randomised double-blind, parallel 2-arm (ABPI vs usual care) pilot and feasibility trial to evaluate procedures and feasibility of the ABPI for the management of acute non-specific neck pain. Six physiotherapy departments from 6 public hospitals in Thailand will be recruited and cluster randomised by a computer-generated randomisation sequence with block sampling. Sixty participants (30 each arm, 10 per hospital) will be assessed at baseline and 3-month following baseline for neck disability index, numerical rating scale for pain intensity, cervical range of motion, fear-avoidance beliefs questionnaire and EQ-5D-5L outcomes. (2) Embedded qualitative study using semi-structured interviews to explore acceptability of the ABPI to participants (n=12) and physiotherapists (n=3). Descriptive analysis of quantitative data and interpretative phenomenological analysis to code and analyse qualitative data (deductive and inductive) will inform feasibility for a future definitive trial.

Ethics and dissemination: This trial is approved by the Naresuan University Institutional Review Board (NUIRB_0380/61).

Trial registration: TCTR20180607001

Keywords (3-5 words): Non-specific neck pain, active behavioural physiotherapy intervention, complex intervention, pilot and feasibility trial, cluster randomisation

Strengths and limitations

- This trial is the first investigation of the active behavioural physiotherapy intervention (ABPI) in patients with acute non-specific neck pain after finding potential benefits in patients with acute Whiplash-Associated Disorder (WAD) in the previous Acute Whiplash Injury Study (AWIS) trial.
- A mixed method (quantitative and qualitative) trial will be performed to evaluate procedures, feasibility and acceptability of the ABPI in managing acute non-specific neck pain within the Thai public hospitals.
- The quantitative phase will be conducted using a cluster randomised double-blind (participants and assessors) design to avoid treatment contaminations and for administrative convenience.
- The qualitative phase is designed to explore the treatment perceptions from all stakeholders, specifically patients and physiotherapists.
- Although the ABPI was originally developed for managing patients with acute WAD, it may be helpful in patients with acute non-specific neck pain owing to the similar characteristics of both conditions.

INTRODUCTION

Background and rationale

Neck pain is the 4th cause of disability [1] and the second biggest contributor to disability-adjusted life years (DALYs) among musculoskeletal disorders in the world.[2] Each year, approximately 50% of adults experience neck pain,[3] leading to a reduced quality of life.[4] Furthermore, the pain and disability associated with neck pain has a substantial impact contributing to social and economic burden (e.g. health-care utilisation, work absenteeism and lost productivity).[1 5] In the USA, the health-care spending on neck and back pain is approximately $86.7 billion, following diabetes and ischemic heart disease.[6] For sickness absence in the UK, approximately 31 million days were lost due to musculoskeletal problems (mostly neck and back pain) among workers in 2016.[7] In Thailand, the 4th greatest health problem is musculoskeletal diseases (n=22 million people in 2015),[8] and up to 50% of these individuals' problems can be caused by neck pain,[8 9] leading to a socioeconomic burden of approximately 11 billion Thai baht.[10] Therefore, an effective intervention for managing neck pain is required to improve quality of life and reduce socioeconomic burden.

Physical (e.g. pain and disability)[1 2] and psychological (e.g. anxiety, depression and fear avoidance)[11-13] problems are observed in patients with non-specific neck pain. The current clinical guidelines [14 15] and low-moderate quality evidence [16 17] suggest that manual and exercise therapy may be useful in managing patients with non-specific neck pain. However, high recurrence and chronicity amongst patients with non-specific neck pain are reported, suggesting limited success of existing interventions.[1 2 18 19] For drug therapy, the recent systematic review and meta-analysis of randomised placebo controlled trials found that there were no effects of paracetamol for pain reduction, reducing disability and improving quality of life,[20] and no clinical importance of Nonsteroidal Anti-inflammatory

Drugs (NSAIDs) for spinal pain.[21] Additionally, use of paracetamol (3000-4000 mg total) and NSAIDs (the median duration of included trial=7 days) are documented to contribute a 4 times increase in abnormal liver function [20] and 2.5 times increased risk of gastrointestinal reactions, respectively.[21] Owing to these unwanted side effects from pharmacological management, non-specific neck pain is commonly managed by physiotherapists,[14 15 22] and effective conservative management in the acute stage (≤4 weeks) [11 23] is required to prevent the transition to chronicity and recurrence.

According to the current evidence, non-specific neck pain is a complex biopsychosocial disorder.[1 2 11-13] Subsequently, the management of patients with non-specific neck pain can be complex, encompassing both physical and psychological perspectives. All individuals with acute non-specific neck pain can be variously impacted by psychological problems which can lead to poor recovery.[11] Unfortunately, using multimodal therapy or multifaceted implementation strategies to date have not been useful.[24] Although whiplash-associated disorders (WAD) and non-specific neck pain can be different in mechanism of injury and severity, their conditions and clinical characteristics are similar.[24-27] An active behavioural physiotherapy intervention (ABPI) may therefore be useful in managing patients with non-specific neck pain based on the findings of the previous Acute Whiplash Injury Study (AWIS) pilot and feasibility trial.[28-32] The findings demonstrated that 95% of patients who received the ABPI fully recovered at 3 months follow-up whereas ~17% of patients who received standard physiotherapy fully recovered using a cut-off on the neck disability index ≤ 4.[30-32] This suggests that the ABPI could prevent chronicity among patients with WADII (≥3 months is classified as chronic stage).[33] Moreover, the ABPI appeared better than standard physiotherapy in terms of pain reduction (visual analogue scale for pain intensity), cervical range of motion (cervical range of motion device), pressure pain threshold (digital pressure algometer) and general health status (EQ-5D-5L). Furthermore, the number of physiotherapy sessions and the costs of management in the ABPI arm were lower than standard physiotherapy.[32] The

ABPI was acceptable to physiotherapists and patients, leading to the possibility for it enhancing physiotherapy practice in the future.[31]

Originally, the ABPI was developed through a sequential multiphase project using rigorous, precise and transparent methodologies in order to manage patients with acute WAD.[28-32] The ABPI is a flexible complex intervention combining active physiotherapy and behavioural intervention (underpinned by social cognitive theory focusing self-efficacy enhancement).[28-31] It contains logical concept and phases (i.e. understanding, maturity, stamina and coping) covering both physical and psychological management [29-31] which seems to be suitable to address the problems in the patients with non-specific neck pain. Owing to no report of WAD as a health problem in Thailand but non-specific neck pain being a substantial problem [34] and possible value of the ABPI, the ABPI is therefore first investigate as a pilot and feasibility clinical trial in order to manage patients with acute non-specific neck pain in a public Thai physiotherapy setting, leading to the possibility for its enhancing physiotherapy practice in managing neck pain more broadly in the future.

AIM

To evaluate procedures, feasibility and acceptability of an active behavioural physiotherapy intervention for the management of patients experiencing acute non-specific neck pain in a Thai public physiotherapy setting in order to inform the design and sample size requirements for a future definitive randomised controlled trial.

Objectives

- To evaluate the feasibility of procedures for a cluster randomised controlled trial in the public physiotherapy sector in Thailand (i.e. randomisation, recruitment, data collection, adherence, trial management and follow-up) [35-38]
- To explore the acceptability of the ABPI among Thai physiotherapists (e.g. ABPI contents, barriers to use, distinctiveness and acceptance) and patients (e.g. received treatment and acceptance) with acute non-specific neck pain [36]
- To synthesise parameters to inform the sample size of an adequately powered definitive trial [36-40]

METHODS

Trial design and setting

The protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) to ensure adequate transparency.[41] This protocol contains 2 phases: 1) a quantitative study to evaluate the procedures and feasibility of the ABPI will follow research methods and reporting in line with the CONSORT 2010 statement: extension to cluster randomised trials [42] and the CONSORT 2010 statement: extension to randomised pilot and feasibility trials [43]; and 2) an embedded exploratory qualitative study to investigate the acceptability of the ABPI of patients and physiotherapists in the ABPI arm will follow research methods and reporting of the Consolidated criteria for Reporting Qualitative research (COREQ): a 32-item checklist for interviews and focus groups.[44] Subsequent deviations of the protocol will be submitted to the Naresuan University Institutional Review Board for an amendment and reported in the full trial.

Phase I: pilot and feasibility trial

A pilot and feasibility trial of a pragmatic cluster randomised double-blind (assessors and participants), parallel two-arm design, comparing ABPI with usual care, will be conducted to evaluate procedures and feasibility of the ABPI for acute non-specific neck pain management. Six physiotherapy departments from 6 public hospitals in Thailand will be recruited. The cluster randomisation design has several benefits in terms of reducing treatment contamination, enhancing participant adherence,[42 45-47] participant blinding,[42] administrative convenience [45] and logistical conveniences.[45]

The heads of 6 physiotherapy departments or their hospital directors will be invited to participate by signing consent forms (cluster-level consent) prior to cluster randomisation.[42] One physiotherapist and one blinded assessor (another physiotherapist who will be familiar with and trained for outcome measurements) will be provided by our research team in each hospital. Only physiotherapists, who will treat participants, will be informed their intervention arm. However, they will not be allowed to talk or discuss any concepts/treatments with the assessors, colleagues or other physiotherapists/people during the trial to ensure blinding assessors and participants. The physiotherapists can discuss with other physiotherapists within their intervention arm to provide an opportunity to exchange their experiences. Following randomisation, consecutive potential participants will be screened and recruited by physiotherapists. The participant information sheet and consent form will be given to potential participants. The recruiting physiotherapists will then discuss any issues relating to the trial, provide an opportunity to ask questions, confirm eligibility and obtain written consent (individual-level consent). After giving informed written consent, participants will be assessed on all outcome measures by blinded assessors at each site using standardised instruments with established measurement properties. Assessments will be performed at this baseline and at 3-months follow-up post baseline. All outcome assessments will be independent from treatment sessions to ensure the blinding of the assessors from treatment allocation.

Additionally, the assessors will not be permitted to ask any question related to participants' received treatment from participants and treating physiotherapists throughout the trial. Both assessors and participants will not know to which intervention arm the participants are allocated. To evaluate blinding, at the end of the 3-month follow-up, participants and assessors will be asked which intervention they/their department have been allocated to in order to consider the blinded procedures of definitive phase III trial. The participants will receive a reminder 2 days prior to the 3-month follow-up appointment using e-mail, message or telephone calling depending on their preference.

Phase II: qualitative semi-structured interviews

An embedded qualitative study using interpretative phenomenological analysis (IPA) [48] will explore the acceptability of the ABPI for participants (n=12) and physiotherapists (all physiotherapists, n=3) in the ABPI arm.[30] There are several advantages of the IPA in terms of exploring personal experience, concerning personal perception, producing an objective statement and emphasising an active role for a research in dynamic process.[49] For convenience to interviewer and interviewees, semi-structured interviews will be conducted by TW (a key person with physiotherapy background in developing the ABPI) who is the key to data quality from the interviews. His previous experiences and involvements are seen as positive rather than negative (e.g. understanding of the context or the experiences of the interviewees).[50] Topic guides adapted from the AWIS trial [30] will be pilot tested 2-3 times prior to conducting the first interview. Potential participants will be recruited via telephone. The information sheet and consent form will be sent to them via e-mail or post depending on their preference in order to provide an opportunity to decide whether they wish to complete the consent form in advance. Demographic characteristics of the participants (e.g. age, gender, occupation and ethnicity) will be recorded and reported.[44] The participants will be interviewed for 30-90 minutes in a private room of their local hospital. In the Thai context, we are not sure that the interviewees can provide a private room for the

interviews in their homes. However, the interviewees will be paid for their journey to ensure that they are reimbursed for any expenses that they incur. The interviews will be recorded using a digital recorder.

Participants

Participants will be recruited from the physiotherapy departments of 6 public hospitals. Demographic characteristics, including age, gender, present medications, and information regarding non-specific neck-pain symptoms will be collected by the blinded assessors at the baseline assessment.

Eligibility criteria for clusters: Physiotherapy departments in public hospitals in Thailand.

Inclusion criteria: Participants aged 20-60 years presenting with non-specific neck pain within the previous 4 weeks.[11 23]

Exclusion criteria: Signs and symptoms WAD or traumatic neck pain,[51] upper cervical instability,[52] cervical artery dysfunction,[53] suspected serious spinal pathology, active inflammatory arthritis, tumours, infection of the skin and soft tissue, bleeding disorders or using anti-coagulant medication,[52] any current or previous treatment from any other third party, or presenting with any serious injuries, history of cervical surgery,[54] previously symptomatic degenerative diseases of the cervical spine or neck pain within 6 months prior to the recruitment,[55] neurological conditions, alcohol abuse,[55 56] dementia,[55 56] serious mental diseases,[55 56] psychiatric diseases,[57 58] osteoporosis, serious medical conditions (e.g. severe diabetes and hypertension), pregnant and/or non-Thai speaking and reading.

Interventions

Intervention details are provided in line with the Template for Intervention Description and Replication (TIDieR).[59] All participants will attend face-to-face physiotherapy for up to 10 sessions in a physiotherapy department based on their physiotherapist's clinical judgement. The frequency of

appointment will depend on their physiotherapists' strategies but each session will be limited to 30 minutes. A minimum of a Bachelor Degree in Physiotherapy with 5 years of post-registration experience will be required for the qualifications of all physiotherapists. TW will randomly select treatment sessions to observe in the experimental arm to evaluate fidelity of the ABPI. Also, this will enable provide an opportunity to monitor and provide feedback regarding the intervention to the treating physiotherapists.[30]

Usual care

Patients will be managed according to current practice reflecting the recommendations provided in the non-specific neck pain clinical guidelines.[14 19 23 60] Usual care will consist of cervical or thoracic mobilisation/manipulation, exercises (e.g. stretching, coordination, strengthening and endurance), upper quarter and nerve mobilisation, appropriate advice (e.g. remain active as possible, restore their neck movement as pain allows using neck range of motion exercises, correct poor posture, sleep with one pillow which provides lateral support and also gives support to hollow of the neck), simple analgesia and other physiotherapy interventions (e.g. manual therapy and modalities). All physiotherapists in the usual care arm will be trained and updated for the existing clinical guidelines to reach the standard physiotherapy management. Appropriate interventions will be selected depending on the physiotherapist's decision-making for the individual patient based on examination findings and clinical reasoning.[53]

Active Behavioural Physiotherapy Intervention (ABPI)

The ABPI has been developed through a systematic review,[28] a modified Delphi study internationally,[29] use of social cognitive theory focusing on self-efficacy enhancement [61] and has been tested for WAD patients in a AWIS pilot and feasibility trial.[30] Full details of the ABPI (e.g. concept, phases and strategies) are provided by the previous published articles.[29 30] The ABPI is delivered within

a flexible framework, and will be modified to manage individuals with acute non-specific neck pain based on clinical examination findings. The intervention will focus on reducing psychological stress and increasing confidence in exercises and/or home programmes using self-efficacy enhancement at the beginning prior to improving physical functions based on the concept, phases and strategies of the ABPI.

Physiotherapists in the experimental arm will be trained to deliver the ABPI in advance of data collection. Training will consist of a group tutorial (1 day) and workshop followed by individual training sessions (4 weeks) to enable them to tailor the intervention to an individual patients with acute non-specific neck pain based on the findings from the patient history and physical examination data, and their evidence-informed clinical reasoning.[53] Physiotherapists and their treatment notes will be randomly observed by TW during data collection to ensure fidelity of the intervention and to provide feedback throughout the trial.

Outcomes

Planned definitive trial primary outcome measure

The Neck Disability Index (NDI) is a patient-reported questionnaire with 10 sections to evaluate pain intensity and functional activities (e.g. personal care, lifting, reading, headache, concentration, work, driving, sleeping and recreation.[62] Each section is scored from 0 to 5 (the highest score representing the greatest disability). The NDI is a valid, reliable and responsive tool in assessing pain and disability in both acute and chronic neck problems.[62-65] The level of participant's disability will be indicated by the overall score.[62] The NDI version Thai has been reported as a reliable tool (Cronbach α=0.85, Intra-class Correlation Coefficient (ICC)=0.85) in assessing patients with neck pain, and will be used in this trial.[66] The minimum clinically importance difference (MCID) of the NDI in patients with neck pain is 8.[66-68]

Secondary outcome measures

Numerical Rating Scale for pain intensity

Pain will be measured using a 0 (no pain) to 10 (worst possible pain) by the Numerical Rating Scale (NRS).[69 70] It is a simple and the preferred tool for assessing pain intensity, with high validity and reliability (ICC=0.76).[71-74] The MCID of NRS for patients with mechanical neck pain without upper limb symptoms is 1.5.[75]

Cervical Range of Motion (CROM)

A common problem among patients with neck pain is decreased cervical mobility.[76] In this trial, cervical range of motion (CROM) will be measured using the CROM device.[77] The CROM device is reported as a highly valid and reliable ($ICC_{3,3}$ ranging 0.89-0.98 for all neck movement directions) device in assessing CROM.[78] In the assessment process, participants will sit on a comfortable chair with both hips and knees flexed to 90º and be attached by the CROM device to the head.[79-81] The average of 3 measurements will be performed for data analysis. The MCID of CROM for non-specific neck pain is 10°.[82]

Fear-Avoidance Beliefs Questionnaire

Fear-Avoidance Beliefs Questionnaire (FABQ) is a valid and reliable tool to predict prolonged disability in patients with neck pain.[83 84] It consists of 16 items (each scored 0 to 6) covering both work and physical activity.[85] The FABQ has been translated into several languages (e.g. Chinese, Persian and Greek) for patients with neck pain.[86-88] In Thailand, the translation and cross-cultural adaptation of the FABQ was conducted and tested the psychometric properties for Thai patients with non-specific neck pain (n=129) by TW and his colleagues. The findings reveal that the FABQ version Thai is a valid (Cronbach α=0.80-0.87 for all items) and reliable ($ICC_{2,1}$=0.98) tool (preparing for publication) to quantify fear and avoidance

beliefs in patients with non-specific neck pain. The minimum detectable change of the Thai version is 5.85. Unfortunately, the MCID of the FABQ is not available for patients with non-specific neck pain.

EuroQol-5 Dimensions (EQ-5D-5L)

The EQ-5D-5L is a valid and reliable self-report quality of life (QoL) questionnaire.[89-91] It is recommended as a useful tool for measuring generic QoL in order to provide information for cost-effectiveness analysis.[92] The EQ-5D-5L has been translated into many languages including Thai and is valid and reliable tool ($ICC_{2,1}$=0.70).[93-95] Unfortunately, the MCID of the EQ-5D-5L for non-specific neck pain is not available.

Assessment of outcome

All participants will be assessed at baseline and at 3-months post baseline. Participants who continue with symptoms and problems after 3 months will be defined as chronic.[23] The number of fully recovered patients with non-specific neck pain at 3 months will be evaluated using a cut-off of NDI ≤ 4.[62] Telephone contact will be used by assessors in case of participants do not attend the 3-month follow-up assessment and they will be asked if they would like to make a new appointment. When participants cannot make a new appointment, the assessors will ask them to complete the NDI, NRS, FABQ and EQ-5D via telephone interview; these outcomes have established reliability and validity via telephone.[96-98]

Feasibility of cost-effectiveness analysis

In order to assess the feasibility of data collection for the planned cost-effectiveness analysis in the definitive trial, direct and indirect medical costs will be collected and recorded. The diary pocket book of the previous AWIS trial [30] will be modified to Thai in order to record any activities related to non-

specific neck pain management such as using medication, consulting other health professionals; along with any health care costs they incurred, and days of sick leave. The information will be collected by the blinded assessors each week replacing self-record which was unsuccessful in the previous trial.[31] Furthermore, general information of participants (e.g. work status, income and distance between home and hospital) will be collected at the baseline assessment. Costs related to physiotherapy management will be collected from the physiotherapy departments throughout the trial. Training costs of physiotherapists in the ABPI arm will be also included.

Sample size

According to a pilot and feasibility trial, a power calculation is not required and targeted sample sizes for pilot/feasibility trials is still controversial.[36] However, 30 participants can be safely assumed to be normal distribution. Therefore, 60 participants (30 per arm, 10 from each department) will be recruited in order to provide parameters for designing a high quality of a definitive RCT.[99]

Randomisation

Stata software version 12 with block sampling will be used by TW to randomise 6 physiotherapy departments to either usual care (n=3 departments) or ABPI (n=3 departments) in order to minimise selection bias at cluster level. The allocation will be concealed before assignment and only TW will involve in the process. Cluster randomisation will be performed prior to participant recruitment (**Figure 1: CONSORT flow diagram**).

Data analysis

Phase I: Quantitative data will be analysed and summarised to evaluate eligibility, recruitment and follow-up rates, using IBM SPSS version 22. The feasibility of the ABPI for non-specific neck pain management will be assessed using descriptive statistics (e.g. frequencies, percentages, means, standard deviations, medians and interquartile ranges depending on data).[37] Intention-to-treat analyses will be used in this trial and missing data will be reported descriptively. The evaluation of the number of fully recovered participants will be performed by consideration of NDI ≤4 at 3-month follow-up.[62] The intra-cluster correlation coefficient (ICC) will be provided to calculate the sample size within a clustered definitive trial. The analyses and findings of the trial will be discussed with the research team at each stage, and by the trial steering and data monitoring committee.

After trial completion, the following are the possible decisions for progressing to a definitive trial: (i) stop if the main trial is not possible or valuable, (ii) continue but modify the protocol if the main trial is possible and valuable, (iii) continue without modifications but monitor closely if the main trial is possible and valuable with close monitoring, (iv) continue without modifications if the main trial is possible and valuable.[37] **Table 1** shows the criteria to consider a future definitive trial.

Table 1: Considerations for a future definitive trial

Objectives	Criteria for success
To evaluate the feasibility of procedures for a cluster randomised controlled trial in the public physiotherapy sector in Thailand (i.e. randomisation, recruitment, data collection, adherence, trial management and follow-up)	Feasible to conduct a phase III trial • No major obstruction issue and/or serious adverse event (assessed by trial monitoring) • Feasible for the type of study (randomised design) (assessed by trial monitoring) • Feasible for procedures of data collection, trial management and follow-up (assessed by trial monitoring)

	• At least 3 participants a month per hospital
To explore the acceptability of the ABPI among Thai physiotherapists and patients with acute non-specific neck pain	• The ABPI can be acceptable to Thai physiotherapists and patients with acute non-specific neck pain (explored by qualitative study). • Acceptable rate ≥60% of participants in each group
To estimate sample size in order to conduct an adequately powered definitive trial	• All parameters can be provided to calculate sample size for an adequately powered definitive trial

Phase II: All interviews will be transcribed verbatim and analysed in line with IPA.[48] All participants will be anonymous using a pseudonym. Transcripts will be read a number of times to enable familiarisation. Qualitative data will be coded and grouped by TW and a coder to minimise potential bias. Related themes of the acceptability of the ABPI for non-specific neck pain management will be identified by QRS Nvivo 10. The analyses will be performed case by case in both deductively (to identify themes) and inductively (to identify additional themes).[100 101] After the completion of the initial coding, similarities of the themes between coders will be examined. Then, a table of emergent themes will be established. The process will be used throughout the study. The analysis and findings from the qualitative data will be reviewed and discussed with the research team and the trial management group to ensure the accuracy of data analysis and provide other interpretations and suggestions.

Trial management and monitoring

The Trial Management Group (combing The Trial Steering Committee and the Data Monitoring Committee consistent with the pilot and feasibility nature of the trial) consisting of TW (the lead researcher), AR (the experienced trialist), SU (the neck expert), a non-specific neck pain patient, an

external member, and an independent chair will meet at the start of recruitment, after 3 months of recruitment, and at the completion of data collection.

Adverse events

This trial can be considered as a low risk trial for adverse event owing to no reporting of any adverse/ serious adverse event in using the ABPI in physiotherapy setting of the previous AWIS trial.[30 31] Moreover, patients with non-specific neck pain have reported less severity than patients with WAD. Both interventions are conservative treatments without existing reporting of serious adverse events in managing neck pain.[31 102-104] From the literature, the most common adverse event after physiotherapy intervention is muscle soreness and it can recover within 1-2 days.[105]

Serious adverse events

Serious adverse event can be evaluated as a very low risk owing to the nature of patient pathology and treatment management. This trial is designed to exclude patients with high severity using experienced physiotherapists who will be trained further in screening participants. Furthermore, the International Federation of Orthopaedic Manipulative Physical Therapists (IFOMPT) cervical framework [53], which has provided guidance for clinical reasoning to identify the risk of adverse events regarding vascularity and instability of the neck, will be used to inform examination for eligibility. However, a serious adverse event will be defined if participants have worsening symptoms within 3 days and been admitted to the hospital due to non-specific neck pain problems.[30]

Procedures for reporting adverse and serious adverse events

An adverse event reporting form will be provided to all physiotherapy departments. Participants will be required to report any unpleasant symptoms to their physiotherapists by completing the form. Then, physiotherapists will report any event to TW within 24 hours, and TW will report to the trial steering committee within 24 hours to enable analysis of the event and any required action. Any unexpected serious adverse events (e.g. a life-threatening situation, inpatient hospitalisation and/or significant disability) will be immediately reported with a written form and verbal contact by physiotherapists to TW. Subsequently, TW will report any event to the trial steering committee; immediately to discuss for an action.

Data management

A participant's data will be assigned an ID code, and the key relating participant to ID code will be stored securely and separately to the project files. All information of participants will be preserved safely from any third party to maintain the participants' privacy at the Faculty of Allied Health Sciences, Naresuan University. All collected documents will be stored in a secure place and electronic data will be confidentially stored in a password-protected computer. Only members of the research team can access the data. All data will be securely destroyed after being kept for 10 years.

Patient and public involvement

The trial is designed by a team of researchers using a part of the results from the previous pilot and feasibility trial which a patient was a member of the trial steering committee.[30 32] A patient will be planned to involve in this trial as a member of the trial management group. He/she will be thanked in the contributorship statement/acknowledgements in a full article.

Ethics and dissemination

The trial will be conducted in accordance with the Declaration of Helsinki and the ethical guidelines for medical human research and is approved by the Naresuan University Institutional Review Board (NUIRB_0380/61). The findings of the trial (completely unattributable format or at an aggregate level) will be submitted to medical journals and presented at international and/or local conferences/lectures.

DISCUSSION

The findings of the previous AWIS trial reported that the ABPI was feasible for acute WADII management to prevent the transition to chronicity (e.g. 95% of the participants fully recovered by the ABPI within 3 months whereas ~17% by the standard physiotherapy) and was acceptable to physiotherapists and patients.[30 31] Furthermore, physiotherapists have applied the ABPI to manage other neck pathologies and regions owing to the possible success of this management approach.[31] According to the similarity of the situations and symptom characteristics between the WAD and non-specific neck pain populations,[25 27] it is interesting to investigate if the ABPI is feasible for managing non-specific neck pain in the acute stage to prevent chronicity. Therefore, this phase II trial will be conducted to evaluate feasibility and acceptability of the ABPI for acute non-specific neck pain in a Thai physiotherapy setting and/or to prepare information in designing an adequately powered, high quality definitive trial.

This trial is designed to prevent potential problems resulting from some limitations of the previous AWIS trial.[30-32] First, this trial will provide one blinded assessor at each site to accelerate the recruitment rate and logistical convenience. Second, the trial will use individual semi-structured in-depth interviews to explore the acceptability of the participants replacing a focus group. In the previous trial, only one participant could attend the focus group (3 participants verbally agreed previously) although the research team tried to use several strategies (e.g. contacting all participants, arranging based on their preference and convenience, reminding (2 days) for the date and location of the meeting prior to the date of

the focus group and providing convenient facilities (e.g. the nearest parking area and meals). Subsequently, the focus group was modified to an individual interview. Third, the qualitative data will be analysed using two independent coders to establish higher trustworthiness.

In Thailand, neck pain is a substantial health problem among musculoskeletal disorders leading to socioeconomic burden. Owing to the similar conditions and clinical characteristics between WAD and non-specific neck pain [25 27] and the findings of the AWIS trial,[31 32] the ABPI may be potentially effective intervention to manage acute non-specific neck pain. Thus, this trial will be conducted to evaluate feasibility of the ABPI in patients with acute non-specific neck pain and its procedures. This trial is the first investigation of the ABPI in Thai clinical setting and the first time in conducting a cluster randomised design in Thai physiotherapy setting.

Trial status

Recruiting commenced 01/02/2019.

Competing interests

No competing interests.

Authors' contributions

TW is the chief investigator and guarantor leading to drafting the initial manuscript, protocol development, analyses and dissemination. TW, SU and AR have contributed to clinical and methodological decisions to ensure the trial quality and will contribute to data interpretation, conclusions and dissemination. All authors have read and agreed the final manuscript.

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Supporting information

Figure 1: CONSORT flow diagram (adapted from CONSORT 2010)

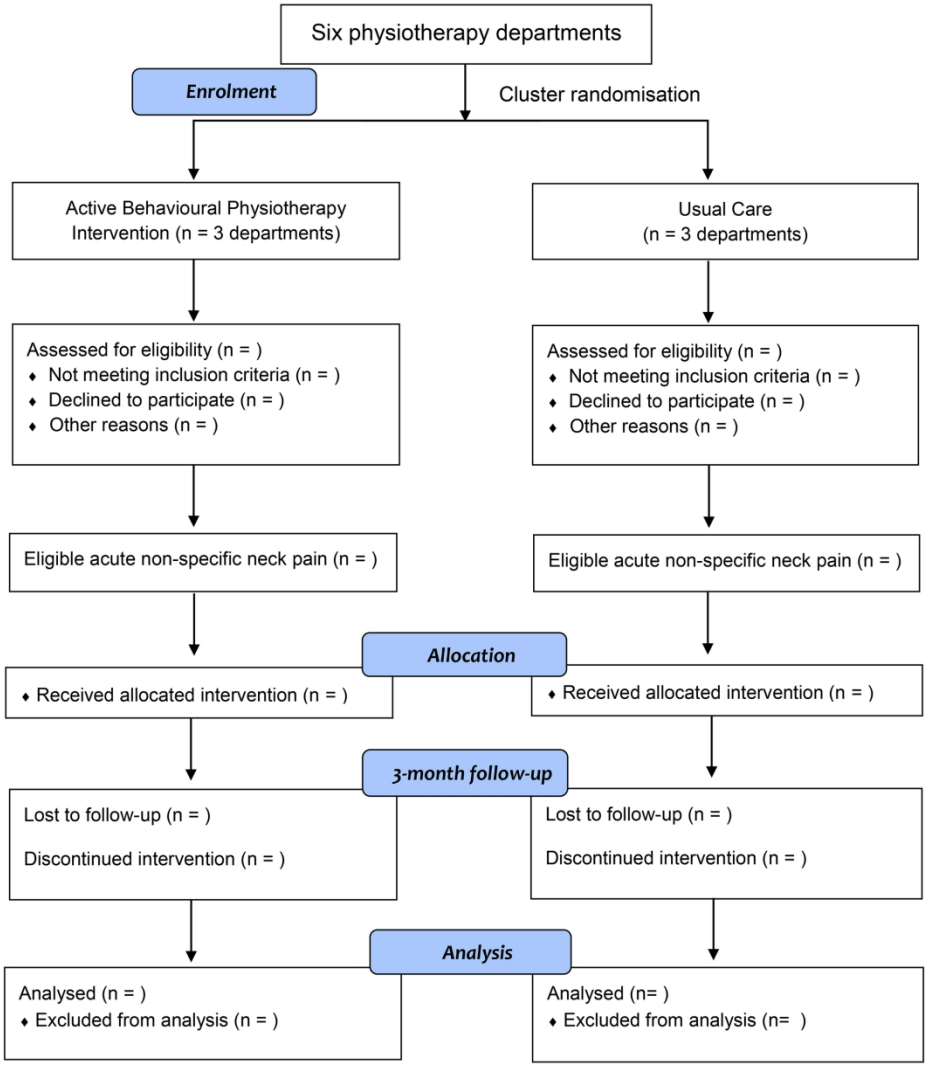

Figure 1: CONSORT flow diagram (adapted from CONSORT 2010).

Figure 1: CONSORT flow diagram (adapted from CONSORT 2010).

175x224mm (300 x 300 DPI)

TIDieR Template for Intervention Description and Replication

The TIDieR (Template for Intervention Description and Replication) Checklist*:

Information to include when describing an intervention and the location of the information

Item number	Item	Where located **	
		Primary paper (page or appendix number)	Other † (details)
	BRIEF NAME		
1.	Provide the name or a phrase that describes the intervention.	1, 5-6, 10-11	
	WHY		
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.	5-6, 10-11	
	WHAT		
3.	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).	10-11	
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	10-11	
	WHO PROVIDED		
5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.	10-11	
	HOW		
6.	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	10-11	
	WHERE		
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	10-11	

	WHEN and HOW MUCH		
8.	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.	___10-11___	_____
	TAILORING		
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.	___10-11___	_____
	MODIFICATIONS		
10.‡	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).	____-____	__protocol__
	HOW WELL		
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.	___10-11___	_____
12.‡	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	____-____	__ protocol __

** **Authors** - use N/A if an item is not applicable for the intervention being described. **Reviewers** – use '?' if information about the element is not reported/not sufficiently reported.

† If the information is not provided in the primary paper, give details of where this information is available. This may include locations such as a published protocol or other published papers (provide citation details) or a website (provide the URL).

‡ If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.

* We strongly recommend using this checklist in conjunction with the TIDieR guide (see *BMJ* 2014;348:g1687) which contains an explanation and elaboration for each item.

* The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study. Other elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist. When a **randomised trial** is being reported, the TIDieR checklist should be used in conjunction with the CONSORT statement (see www.consort-statement.org) as an extension of **Item 5 of the CONSORT 2010 Statement.** When a **clinical trial protocol** is being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement as an extension of **Item 11 of the SPIRIT 2013 Statement** (see www.spirit-statement.org). For alternate study designs, TIDieR can be used in conjunction with the appropriate checklist for that study design (see www.equator-network.org).

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Pages
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	-
Protocol version	3	Date and version identifier	-
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 22
	5b	Name and contact information for the trial sponsor	1, 22
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	18-20
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7-9

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8-9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9-10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	18-20
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11-12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10-12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	16
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8, 21
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	15

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	15
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	15
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8, 18-20
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12-15, 18
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	20
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17-18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	-
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18-20

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	18-20
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	18-20
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	18-20
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	20
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	7, 20
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8-9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	20
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	20
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	19-20
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
	31b	Authorship eligibility guidelines and any intended use of professional writers	22
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	-
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Pragmatic cluster randomised double-blind pilot and feasibility trial of an active behavioural physiotherapy intervention for acute non-specific neck pain: a mixed methods protocol

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Pragmatic cluster randomised double-blind pilot and feasibility trial of an active behavioural physiotherapy intervention for acute non-specific neck pain: a mixed methods protocol

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ABSTRACT

Introduction: Non-specific neck pain causes pain and disability and contributes substantial socio-economic burden internationally. Up to 50% of adults experience neck pain annually, leading to reduced quality of life. An active behavioural physiotherapy intervention (ABPI) may be feasible to manage patients with acute non-specific neck pain to prevent transition to chronicity. A recent pilot and feasibility trial investigating an acute whiplash-associated disorder population found potential value of the ABPI with 95% of participants fully recovered (neck disability index: NDI≤4, compared to 17% in the standard physiotherapy arm); supporting a definitive trial. Qualitative findings from the physiotherapists supported the potential of the ABPI in a non-specific neck pain population.

Methods and analysis: Two phases. (1) Pragmatic cluster randomised double-blind, parallel 2-arm (ABPI versus standard physiotherapy intervention) pilot and feasibility trial to evaluate procedures and feasibility of the ABPI for the management of acute non-specific neck pain. Six physiotherapy departments from 6 public hospitals in Thailand will be recruited and cluster randomised by a computer-generated randomisation sequence with block sampling. Sixty participants (30 each arm, 10 per hospital) will be assessed at baseline and 3-month following baseline for neck disability index, numerical rating scale for pain intensity, cervical range of motion, fear-avoidance beliefs questionnaire and EQ-5D-5L outcomes. (2) Embedded qualitative study using semi-structured interviews to explore acceptability of the ABPI to participants (n=12) and physiotherapists (n=3). Descriptive analysis of quantitative data and interpretative phenomenological analysis to code and analyse qualitative data (deductive and inductive) will inform feasibility for a future definitive trial.

Ethics and dissemination: This trial is approved by the Naresuan University Institutional Review Board (NUIRB_0380/61).

Trial registration: TCTR20180607001

Keywords (3-5 words): Non-specific neck pain, active behavioural physiotherapy intervention, complex intervention, pilot and feasibility trial, cluster randomisation

Strengths and limitations

- This trial is the first investigation of the active behavioural physiotherapy intervention (ABPI) in patients with acute non-specific neck pain after finding potential benefits in patients with acute Whiplash-Associated Disorder (WAD) in the previous Acute Whiplash Injury Study (AWIS) trial.
- A mixed method (quantitative and qualitative) trial will be performed to evaluate procedures, feasibility and acceptability of the ABPI in managing acute non-specific neck pain within the Thai public hospitals.
- The quantitative phase will be conducted using a cluster randomised double-blind (participants and assessors) design to avoid treatment contaminations and for administrative convenience.
- The qualitative phase is designed to explore the treatment perceptions from all stakeholders, specifically patients and physiotherapists.
- Although the ABPI was originally developed for managing patients with acute WAD, it may be helpful in patients with acute non-specific neck pain owing to the similar characteristics of both conditions.

INTRODUCTION

Background and rationale

Neck pain is the 4th cause of disability [1] and the second biggest contributor to disability-adjusted life years (DALYs) among musculoskeletal disorders in the world.[2] Each year, approximately 50% of adults experience neck pain,[3] leading to a reduced quality of life.[4] Furthermore, the pain and disability associated with neck pain has a substantial impact contributing to social and economic burden (e.g. health-care utilisation, work absenteeism and lost productivity).[1 5] In the USA, the health-care spending on neck and back pain is approximately $86.7 billion, following diabetes and ischemic heart disease.[6] For sickness absence in the UK, approximately 31 million days were lost due to musculoskeletal problems (mostly neck and back pain) among workers in 2016.[7] In Thailand, the 4th greatest health problem is musculoskeletal diseases (n=22 million people in 2015),[8] and up to 50% of these individuals' problems can be caused by neck pain,[8 9] leading to a socioeconomic burden of approximately 11 billion Thai baht.[10] Therefore, an effective intervention for managing neck pain is required to improve quality of life and reduce socioeconomic burden.

Physical (e.g. pain and disability)[1 2] and psychological (e.g. anxiety, depression and fear avoidance)[11-13] problems are observed in patients with non-specific neck pain. The current clinical guidelines [14 15] and low-moderate quality evidence [16 17] suggest that manual and exercise therapy may be useful in managing patients with non-specific neck pain. However, high recurrence and chronicity amongst patients with non-specific neck pain are reported, suggesting limited success of existing interventions.[1 2 18 19] For drug therapy, the recent systematic review and meta-analysis of randomised placebo controlled trials found that there were no effects of paracetamol for pain reduction, reducing disability and improving quality of life,[20] and no clinical importance of Nonsteroidal Anti-inflammatory

Drugs (NSAIDs) for spinal pain.[21] Additionally, use of paracetamol (3000-4000 mg total) and NSAIDs (the median duration of included trial=7 days) are documented to contribute a 4 times increase in abnormal liver function [20] and 2.5 times increased risk of gastrointestinal reactions, respectively.[21] Owing to these unwanted side effects from pharmacological management, non-specific neck pain is commonly managed by physiotherapists,[14 15 22] and effective conservative management in the acute stage (≤4 weeks) [11 23] is required to prevent the transition to chronicity and recurrence.

According to the current evidence, non-specific neck pain is a complex biopsychosocial disorder.[1 2 11-13] Subsequently, the management of patients with non-specific neck pain can be complex, encompassing both physical and psychological perspectives. All individuals with acute non-specific neck pain can be variously impacted by psychological problems which can lead to poor recovery.[11] Unfortunately, using multimodal therapy or multifaceted implementation strategies to date have not been useful.[24] Although whiplash-associated disorders (WAD) and non-specific neck pain can be different in mechanism of injury and severity, their conditions and clinical characteristics are similar.[24-27] An active behavioural physiotherapy intervention (ABPI) may therefore be useful in managing patients with non-specific neck pain based on the findings of the previous Acute Whiplash Injury Study (AWIS) pilot and feasibility trial.[28-32] The findings demonstrated that 95% of patients who received the ABPI fully recovered at 3 months follow-up whereas ~17% of patients who received standard physiotherapy fully recovered using a cut-off on the neck disability index ≤ 4.[30-32] This suggests that the ABPI could prevent chronicity among patients with WADII (≥3 months is classified as chronic stage).[33] Moreover, the ABPI appeared better than standard physiotherapy in terms of pain reduction (visual analogue scale for pain intensity), cervical range of motion (cervical range of motion device), pressure pain threshold (digital pressure algometer) and general health status (EQ-5D-5L). Furthermore, the number of physiotherapy sessions and the costs of management in the ABPI arm were lower than standard physiotherapy.[32] The

ABPI was acceptable to physiotherapists and patients, leading to the possibility for it enhancing physiotherapy practice in the future.[31]

Originally, the ABPI was developed through a sequential multiphase project using rigorous, precise and transparent methodologies in order to manage patients with acute WAD.[28-32] The ABPI is a flexible complex intervention combining active physiotherapy and behavioural intervention (underpinned by social cognitive theory focusing self-efficacy enhancement).[28-31] It contains logical concept and phases (i.e. understanding, maturity, stamina and coping) covering both physical and psychological management [29-31] which seems to be suitable to address the problems in the patients with non-specific neck pain. Owing to no report of WAD as a health problem in Thailand but non-specific neck pain being a substantial problem [34] and possible value of the ABPI, the ABPI is therefore first investigate as a pilot and feasibility clinical trial in order to manage patients with acute non-specific neck pain in a public Thai physiotherapy setting.

AIM

To evaluate procedures, feasibility and acceptability of an active behavioural physiotherapy intervention for the management of patients experiencing acute non-specific neck pain in a Thai public physiotherapy setting in order to inform the design and sample size requirements for a future definitive randomised controlled trial.

Objectives

- To evaluate the feasibility of procedures for a cluster randomised controlled trial in the public physiotherapy sector in Thailand (i.e. randomisation, recruitment, data collection, adherence, trial management and follow-up) [35-38]

- To explore the acceptability of the ABPI among Thai physiotherapists (e.g. ABPI contents, barriers to use, distinctiveness and acceptance) and patients (e.g. received treatment and acceptance) with acute non-specific neck pain [36]
- To synthesise parameters to inform the sample size of an adequately powered definitive trial [36-40]

METHODS

Trial design and setting

The protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) to ensure adequate transparency.[41] This protocol contains 2 phases: 1) a quantitative study to evaluate the procedures and feasibility of the ABPI will follow research methods and reporting in line with the CONSORT 2010 statement: extension to cluster randomised trials [42] and the CONSORT 2010 statement: extension to randomised pilot and feasibility trials [43]; and 2) an embedded exploratory qualitative study to investigate the acceptability of the ABPI of patients and physiotherapists in the ABPI arm will follow research methods and reporting of the Consolidated criteria for Reporting Qualitative research (COREQ): a 32-item checklist for interviews and focus groups.[44] Subsequent deviations of the protocol will be submitted to the Naresuan University Institutional Review Board for an amendment and reported in the full trial.

Phase I: pilot and feasibility trial

A pilot and feasibility trial of a pragmatic cluster randomised double-blind (assessors and participants), parallel two-arm design, comparing ABPI with standard physiotherapy intervention (SPI), will be

conducted to evaluate procedures and feasibility of the ABPI for acute non-specific neck pain management. Six physiotherapy departments from 6 public hospitals in Thailand will be recruited. The cluster randomisation design has several benefits in terms of reducing treatment contamination, enhancing participant adherence,[42 45-47] participant blinding,[42] administrative convenience [45] and logistical conveniences.[45]

The heads of 6 physiotherapy departments or their hospital directors will be invited to participate by signing consent forms (cluster-level consent) prior to cluster randomisation.[42] One physiotherapist and one blinded assessor (another physiotherapist who will be familiar with and trained for outcome measurements) will be provided by our research team in each hospital. Only physiotherapists, who will treat participants, will be informed their intervention arm. However, they will not be allowed to talk or discuss any concepts/treatments with the assessors, colleagues or other physiotherapists/people during the trial to ensure blinding assessors and participants. The physiotherapists can discuss with other physiotherapists within their intervention arm to provide an opportunity to exchange their experiences. Following randomisation, consecutive potential participants will be screened and recruited by physiotherapists. The participant information sheet and consent form will be given to potential participants. The recruiting physiotherapists will then discuss any issues relating to the trial, provide an opportunity to ask questions, confirm eligibility and obtain written consent (individual-level consent). After giving informed written consent, participants will be assessed on all outcome measures by blinded assessors at each site using standardised instruments with established measurement properties. Assessments will be performed at this baseline and at 3-months follow-up post baseline. All outcome assessments will be independent from treatment sessions to ensure the blinding of the assessors from treatment allocation. Additionally, the assessors will not be permitted to ask any question related to participants' received treatment from participants and treating physiotherapists throughout the trial. Both assessors and participants will not know to which intervention arm the participants are allocated. To evaluate blinding, at

the end of the 3-month follow-up, participants and assessors will be asked which intervention they/their department have been allocated to in order to consider the blinded procedures of definitive phase III trial. The participants will receive a reminder 2 days prior to the 3-month follow-up appointment using e-mail, message or telephone calling depending on their preference.

Phase II: qualitative semi-structured interviews

An embedded qualitative study using interpretative phenomenological analysis (IPA) [48] will explore the acceptability of the ABPI for participants (n=12) and physiotherapists (all physiotherapists, n=3) in the ABPI arm.[30] There are several advantages of the IPA in terms of exploring personal experience, concerning personal perception, producing an objective statement and emphasising an active role for a research in dynamic process.[49] For convenience to interviewer and interviewees, semi-structured interviews will be conducted by TW (a key person with physiotherapy background in developing the ABPI) who is the key to data quality from the interviews. His previous experiences and involvements are seen as positive rather than negative (e.g. understanding of the context or the experiences of the interviewees).[50] Topic guides adapted from the AWIS trial [30] will be pilot tested 2-3 times prior to conducting the first interview. Potential participants will be recruited via telephone. The information sheet and consent form will be sent to them via e-mail or post depending on their preference in order to provide an opportunity to decide whether they wish to complete the consent form in advance. Demographic characteristics of the participants (e.g. age, gender, occupation and ethnicity) will be recorded and reported.[44] The participants will be interviewed for 30-90 minutes in a private room of their local hospital. In the Thai context, we are not sure that the interviewees can provide a private room for the interviews in their homes. However, the interviewees will be paid for their journey to ensure that they are reimbursed for any expenses that they incur. The interviews will be recorded using a digital recorder.

Participants

Participants will be recruited from the physiotherapy departments of 6 public hospitals. Demographic characteristics, including age, gender, present medications, and information regarding non-specific neck-pain symptoms will be collected by the blinded assessors at the baseline assessment.

Eligibility criteria for clusters: Physiotherapy departments in public hospitals in Thailand.

Inclusion criteria: Participants aged 20-60 years presenting with non-specific neck pain within the previous 4 weeks.[11 23]

Exclusion criteria: Signs and symptoms WAD or traumatic neck pain,[51] upper cervical instability,[52] cervical artery dysfunction,[53] suspected serious spinal pathology, active inflammatory arthritis, tumours, infection of the skin and soft tissue, bleeding disorders or using anti-coagulant medication,[52] any current or previous treatment from any other third party, or presenting with any serious injuries, history of cervical surgery,[54] previously symptomatic degenerative diseases of the cervical spine or neck pain within 6 months prior to the recruitment,[55] neurological conditions, alcohol abuse,[55 56] dementia,[55 56] serious mental diseases,[55 56] psychiatric diseases,[57 58] osteoporosis, serious medical conditions (e.g. severe diabetes and hypertension), pregnant and/or non-Thai speaking and reading.

Interventions

Intervention details are provided in line with the Template for Intervention Description and Replication (TIDieR).[59] All participants will attend face-to-face physiotherapy for up to 10 sessions in a physiotherapy department based on their physiotherapist's clinical judgement. The frequency of appointment will depend on their physiotherapists' strategies but each session will be limited to 30 minutes. A minimum of a Bachelor Degree in Physiotherapy with 5 years of post-registration experience will be required for the qualifications of all physiotherapists. TW will randomly select treatment sessions to observe in the experimental arm to

evaluate fidelity of the ABPI. Also, this will enable provide an opportunity to monitor and provide feedback regarding the intervention to the treating physiotherapists.[30]

Standard Physiotherapy Intervention (SPI)

Patients will be managed according to current practice reflecting the recommendations provided in the non-specific neck pain clinical guidelines.[14 19 23 60] The SPI will consist of cervical or thoracic mobilisation/manipulation, exercises (e.g. stretching, coordination, strengthening and endurance), upper quarter and nerve mobilisation, appropriate advice (e.g. remain active as possible, restore their neck movement as pain allows using neck range of motion exercises, correct poor posture, sleep with one pillow which provides lateral support and also gives support to hollow of the neck), simple analgesia and other physiotherapy interventions (e.g. manual therapy and modalities). All physiotherapists in the control arm will be trained and updated for the existing clinical guidelines to reach the standard physiotherapy management. Appropriate interventions will be selected depending on the physiotherapist's decision-making for the individual patient based on examination findings and clinical reasoning.[53] Treatment sessions and notes will be randomly observed by TW to ensure adhering to the guidelines. Feedback and discussion will be provided throughout the trial.

Active Behavioural Physiotherapy Intervention (ABPI)

The ABPI has been developed through a systematic review,[28] a modified Delphi study internationally,[29] use of social cognitive theory focusing on self-efficacy enhancement [61] and has been tested for WAD patients in a AWIS pilot and feasibility trial.[30] Full details of the ABPI (e.g. concept, phases and strategies) are provided by the previous published articles.[29 30] The ABPI is delivered within a flexible framework, and will be modified to manage individuals with acute non-specific neck pain based

on clinical examination findings. The intervention will focus on reducing psychological stress and increasing confidence in exercises and/or home programmes using self-efficacy enhancement at the beginning prior to improving physical functions based on the concept, phases and strategies of the ABPI.

Physiotherapists in the experimental arm will be trained to deliver the ABPI in advance of data collection. Training will consist of a group tutorial (1 day) and workshop followed by individual training sessions (4 weeks) to enable them to tailor the intervention to an individual patients with acute non-specific neck pain based on the findings from the patient history and physical examination data, and their evidence-informed clinical reasoning.[53] Physiotherapists and their treatment notes will be randomly observed by TW during data collection to ensure fidelity of the intervention and to provide feedback throughout the trial. Treatment fidelity will also be assessed by interviews from all physiotherapists (n=3) and participants (n=12) in the experiment group in an embedded qualitative study (phase II of this study).

Outcomes

Planned definitive trial primary outcome measure

The Neck Disability Index (NDI) is a patient-reported questionnaire with 10 sections to evaluate pain intensity and functional activities (e.g. personal care, lifting, reading, headache, concentration, work, driving, sleeping and recreation.[62] Each section is scored from 0 to 5 (the highest score representing the greatest disability). The NDI is a valid, reliable and responsive tool in assessing pain and disability in both acute and chronic neck problems.[62-65] The level of participant's disability will be indicated by the overall score.[62] The NDI version Thai has been reported as a reliable tool (Cronbach α=0.85, Intra-class Correlation Coefficient (ICC)=0.85) in assessing patients with neck pain, and will be used in this trial.[66] The minimum clinically importance difference (MCID) of the NDI in patients with neck pain is 8.[66-68]

Secondary outcome measures

Numerical Rating Scale for pain intensity

Pain will be measured using a 0 (no pain) to 10 (worst possible pain) by the Numerical Rating Scale (NRS).[69 70] It is a simple and the preferred tool for assessing pain intensity, with high validity and reliability (ICC=0.76).[71-74] The MCID of NRS for patients with mechanical neck pain without upper limb symptoms is 1.5.[75]

Cervical Range of Motion (CROM)

A common problem among patients with neck pain is decreased cervical mobility.[76] In this trial, cervical range of motion (CROM) will be measured using the CROM device.[77] The CROM device is reported as a highly valid and reliable ($ICC_{3,3}$ ranging 0.89-0.98 for all neck movement directions) device in assessing CROM.[78] In the assessment process, participants will sit on a comfortable chair with both hips and knees flexed to 90º and be attached by the CROM device to the head.[79-81] The average of 3 measurements will be performed for data analysis. The MCID of CROM for non-specific neck pain is 10°.[82]

Fear-Avoidance Beliefs Questionnaire

Fear-Avoidance Beliefs Questionnaire (FABQ) is a valid and reliable tool to predict prolonged disability in patients with neck pain.[83 84] It consists of 16 items (each scored 0 to 6) covering both work and physical activity.[85] The FABQ has been translated into several languages (e.g. Chinese, Persian and Greek) for patients with neck pain.[86-88] In Thailand, the translation and cross-cultural adaptation of the FABQ was conducted and tested the psychometric properties for Thai patients with non-specific neck pain (n=129) by TW and his colleagues. The findings reveal that the FABQ version Thai is a valid (Cronbach α=0.80-0.87 for all items) and reliable ($ICC_{2,1}$=0.98) tool (preparing for publication) to quantify fear and avoidance

beliefs in patients with non-specific neck pain. The minimum detectable change of the Thai version is 5.85. Unfortunately, the MCID of the FABQ is not available for patients with non-specific neck pain.

EuroQol-5 Dimensions (EQ-5D-5L)

The EQ-5D-5L is a valid and reliable self-report quality of life (QoL) questionnaire.[89-91] It is recommended as a useful tool for measuring generic QoL in order to provide information for cost-effectiveness analysis.[92] The EQ-5D-5L has been translated into many languages including Thai and is valid and reliable tool ($ICC_{2,1}$=0.70).[93-95] Unfortunately, the MCID of the EQ-5D-5L for non-specific neck pain is not available.

Assessment of outcome

All participants will be assessed at baseline and at 3-months post baseline. Participants who continue with symptoms and problems after 3 months will be defined as chronic.[23] The number of fully recovered patients with non-specific neck pain at 3 months will be evaluated using a cut-off of NDI ≤ 4.[62] Telephone contact will be used by assessors in case of participants do not attend the 3-month follow-up assessment and they will be asked if they would like to make a new appointment. When participants cannot make a new appointment, the assessors will ask them to complete the NDI, NRS, FABQ and EQ-5D via telephone interview; these outcomes have established reliability and validity via telephone.[96-98]

Feasibility of cost-effectiveness analysis

In order to assess the feasibility of data collection for the planned cost-effectiveness analysis in the definitive trial, direct and indirect medical costs will be collected and recorded. The diary pocket book of the previous AWIS trial [30] will be modified to Thai in order to record any activities related to non-specific neck pain

management such as using medication, consulting other health professionals; along with any health care costs they incurred, and days of sick leave. The information will be collected by the blinded assessors each week replacing self-record which was unsuccessful in the previous trial.[31] Furthermore, general information of participants (e.g. work status, income and distance between home and hospital) will be collected at the baseline assessment. Costs related to physiotherapy management will be collected from the physiotherapy departments throughout the trial. Training costs of physiotherapists in the ABPI arm will be also included.

Sample size

According to a pilot and feasibility trial, a power calculation is not required and targeted sample sizes for pilot/feasibility trials is still controversial.[36] However, 30 participants can be safely assumed to be normal distribution. Therefore, 60 participants (30 per arm, 10 from each department) will be recruited in order to provide parameters for designing a high quality of a definitive RCT.[99]

Randomisation

Stata software version 12 with block sampling will be used by TW to randomise 6 physiotherapy departments to either SPI (n=3 departments) or ABPI (n=3 departments) in order to minimise selection bias at cluster level. The allocation will be concealed before assignment and only TW will involve in the process. Cluster randomisation will be performed prior to participant recruitment (**Figure 1: CONSORT flow diagram**).

Data analysis

Phase I: Quantitative data will be analysed and summarised to evaluate eligibility, recruitment and follow-up rates, using IBM SPSS version 22. The feasibility of the ABPI for non-specific neck pain management will be assessed using descriptive statistics (e.g. frequencies, percentages, means, standard deviations, medians and interquartile ranges depending on data).[37] Intention-to-treat analyses will be used in this trial and missing data will be reported descriptively. The evaluation of the number of fully recovered participants will be performed by consideration of NDI ≤4 at 3-month follow-up.[62] The intra-cluster correlation coefficient (ICC) will be provided to calculate the sample size within a clustered definitive trial. The analyses and findings of the trial will be discussed with the research team at each stage, and by the trial steering and data monitoring committee.

After trial completion, the following are the possible decisions for progressing to a definitive trial: (i) stop if the main trial is not possible or valuable, (ii) continue but modify the protocol if the main trial is possible and valuable, (iii) continue without modifications but monitor closely if the main trial is possible and valuable with close monitoring, (iv) continue without modifications if the main trial is possible and valuable.[37] **Table 1** shows the criteria to consider a future definitive trial.

Table 1: Considerations for a future definitive trial

Objectives	Criteria for success
To evaluate the feasibility of procedures for a cluster randomised controlled trial in the public physiotherapy sector in Thailand (i.e. randomisation, recruitment, data collection, adherence, trial management and follow-up)	Feasible to conduct a phase III trial • No major obstruction issue and/or serious adverse event (assessed by trial monitoring) • Feasible for the type of study (randomised design) (assessed by trial monitoring) • Feasible for procedures of data collection, trial management and follow-up (assessed by trial monitoring) • At least 3 participants a month per hospital
To explore the acceptability of the ABPI among Thai physiotherapists and patients with acute non-specific neck pain	• The ABPI can be acceptable to Thai physiotherapists and patients with acute

	non-specific neck pain (explored by qualitative study). • Acceptable rate ≥60% of participants in each group
To estimate sample size in order to conduct an adequately powered definitive trial	• All parameters can be provided to calculate sample size for an adequately powered definitive trial

Phase II: All interviews will be transcribed verbatim and analysed in line with IPA.[48] All participants will be anonymous using a pseudonym. Transcripts will be read a number of times to enable familiarisation. Qualitative data will be coded and grouped by TW and a coder to minimise potential bias. Related themes of the acceptability of the ABPI for non-specific neck pain management will be identified by QRS Nvivo 10. The analyses will be performed case by case in both deductively (to identify themes) and inductively (to identify additional themes).[100 101] After the completion of the initial coding, similarities of the themes between coders will be examined. Then, a table of emergent themes will be established. The process will be used throughout the study. The analysis and findings from the qualitative data will be reviewed and discussed with the research team and the trial management group to ensure the accuracy of data analysis and provide other interpretations and suggestions.

Trial management and monitoring

The Trial Management Group (combing The Trial Steering Committee and the Data Monitoring Committee consistent with the pilot and feasibility nature of the trial) consisting of TW (the lead researcher), AR (the experienced trialist), SU (the neck expert), a non-specific neck pain patient, an external member, and an independent chair will meet at the start of recruitment, after 3 months of recruitment, and at the completion of data collection.

Adverse events

This trial can be considered as a low risk trial for adverse event owing to no reporting of any adverse/ serious adverse event in using the ABPI in physiotherapy setting of the previous AWIS trial.[30 31] Moreover, patients with non-specific neck pain have reported less severity than patients with WAD. Both interventions are conservative treatments without existing reporting of serious adverse events in managing neck pain.[31 102-104] From the literature, the most common adverse event after physiotherapy intervention is muscle soreness and it can recover within 1-2 days.[105]

Serious adverse events

Serious adverse event can be evaluated as a very low risk owing to the nature of patient pathology and treatment management. This trial is designed to exclude patients with high severity using experienced physiotherapists who will be trained further in screening participants. Furthermore, the International Federation of Orthopaedic Manipulative Physical Therapists (IFOMPT) cervical framework [53], which has provided guidance for clinical reasoning to identify the risk of adverse events regarding vascularity and instability of the neck, will be used to inform examination for eligibility. However, a serious adverse event will be defined if participants have worsening symptoms within 3 days and been admitted to the hospital due to non-specific neck pain problems.[30]

Procedures for reporting adverse and serious adverse events

An adverse event reporting form will be provided to all physiotherapy departments. Participants will be required to report any unpleasant symptoms to their physiotherapists by completing the form. Then, physiotherapists will report any event to TW within 24 hours, and TW will report to the trial steering

committee within 24 hours to enable analysis of the event and any required action. Any unexpected serious adverse events (e.g. a life-threatening situation, inpatient hospitalisation and/or significant disability) will be immediately reported with a written form and verbal contact by physiotherapists to TW. Subsequently, TW will report any event to the trial steering committee; immediately to discuss for an action.

Data management

A participant's data will be assigned an ID code, and the key relating participant to ID code will be stored securely and separately to the project files. All information of participants will be preserved safely from any third party to maintain the participants' privacy at the Faculty of Allied Health Sciences, Naresuan University. All collected documents will be stored in a secure place and electronic data will be confidentially stored in a password-protected computer. Only members of the research team can access the data. All data will be securely destroyed after being kept for 10 years.

Patient and public involvement

The trial is designed by a team of researchers using a part of the results from the previous pilot and feasibility trial which a patient was a member of the trial steering committee.[30 32] A patient will be planned to involve in this trial as a member of the trial management group. He/she will be thanked in the contributorship statement/acknowledgements in a full article.

Ethics and dissemination

The trial will be conducted in accordance with the Declaration of Helsinki and the ethical guidelines for medical human research and is approved by the Naresuan University Institutional Review Board

(NUIRB_0380/61). The findings of the trial (completely unattributable format or at an aggregate level) will be submitted to medical journals and presented at international and/or local conferences/lectures.

DISCUSSION

The findings of the previous AWIS trial reported that the ABPI was feasible for acute WADII management to prevent the transition to chronicity (e.g. 95% of the participants fully recovered by the ABPI within 3 months whereas ~17% by the standard physiotherapy) and was acceptable to physiotherapists and patients.[30 31] Furthermore, physiotherapists have applied the ABPI to manage other neck pathologies and regions owing to the possible success of this management approach.[31] According to the similarity of the situations and symptom characteristics between the WAD and non-specific neck pain populations,[25 27] it is interesting to investigate if the ABPI is feasible for managing non-specific neck pain in the acute stage to prevent chronicity. Therefore, this phase II trial will be conducted to evaluate feasibility and acceptability of the ABPI for acute non-specific neck pain in a Thai physiotherapy setting and/or to prepare information in designing an adequately powered, high quality definitive trial.

This trial is designed to prevent potential problems resulting from some limitations of the previous AWIS trial.[30-32] First, this trial will provide one blinded assessor at each site to accelerate the recruitment rate and logistical convenience. Second, the trial will use individual semi-structured in-depth interviews to explore the acceptability of the participants replacing a focus group. In the previous trial, only one participant could attend the focus group (3 participants verbally agreed previously) although the research team tried to use several strategies (e.g. contacting all participants, arranging based on their preference and convenience, reminding (2 days) for the date and location of the meeting prior to the date of the focus group and providing convenient facilities (e.g. the nearest parking area and meals). Subsequently,

the focus group was modified to an individual interview. Third, the qualitative data will be analysed using two independent coders to establish higher trustworthiness.

In Thailand, neck pain is a substantial health problem among musculoskeletal disorders leading to socioeconomic burden. Owing to the similar conditions and clinical characteristics between WAD and non-specific neck pain [25 27] and the findings of the AWIS trial,[31 32] the ABPI may be potentially effective intervention to manage acute non-specific neck pain. Thus, this trial will be conducted to evaluate feasibility of the ABPI in patients with acute non-specific neck pain and its procedures. This trial is the first investigation of the ABPI in Thai clinical setting and the first time in conducting a cluster randomised design in Thai physiotherapy setting.

Trial status

Recruiting commenced 01/02/2019.

Competing interests

No competing interests.

Authors' contributions

TW is the chief investigator and guarantor leading to drafting the initial manuscript, protocol development, analyses and dissemination. TW, SU and AR have contributed to clinical and methodological decisions to ensure the trial quality and will contribute to data interpretation, conclusions and dissemination. All authors have read and agreed the final manuscript.

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Supporting information

Figure 1: CONSORT flow diagram (adapted from CONSORT 2010)

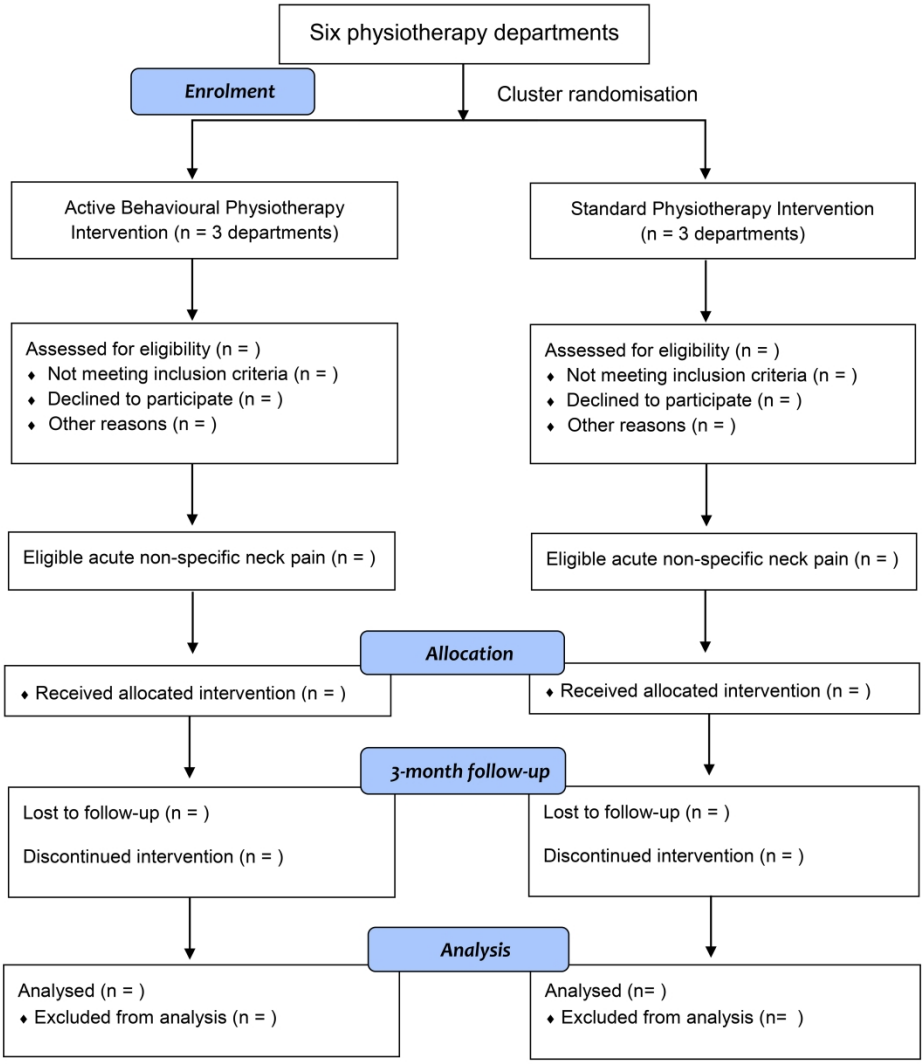

Figure 1: CONSORT flow diagram (adapted from CONSORT 2010).

Figure 1: CONSORT flow diagram (adapted from CONSORT 2010)

175x224mm (600 x 600 DPI)

TIDieR Template for Intervention Description and Replication

The TIDieR (Template for Intervention Description and Replication) Checklist*:

Information to include when describing an intervention and the location of the information

Item number	Item	Where located **	
		Primary paper (page or appendix number)	Other † (details)
	BRIEF NAME		
1.	Provide the name or a phrase that describes the intervention.	1, 5-6, 10-11	
	WHY		
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.	5-6, 10-11	
	WHAT		
3.	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).	10-11	
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	10-11	
	WHO PROVIDED		
5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.	10-11	
	HOW		
6.	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	10-11	
	WHERE		
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	10-11	

	WHEN and HOW MUCH		
8.	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.	___10-11___	_____
	TAILORING		
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.	___10-11___	_____
	MODIFICATIONS		
10.‡	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).	____-____	__protocol__
	HOW WELL		
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.	___10-11___	_____
12.‡	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	____-____	__ protocol __

** **Authors** - use N/A if an item is not applicable for the intervention being described. **Reviewers** – use '?' if information about the element is not reported/not sufficiently reported.

† If the information is not provided in the primary paper, give details of where this information is available. This may include locations such as a published protocol or other published papers (provide citation details) or a website (provide the URL).

‡ If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.

* We strongly recommend using this checklist in conjunction with the TIDieR guide (see *BMJ* 2014;348:g1687) which contains an explanation and elaboration for each item.

* The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study. Other elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist. When a **randomised trial** is being reported, the TIDieR checklist should be used in conjunction with the CONSORT statement (see www.consort-statement.org) as an extension of **Item 5 of the CONSORT 2010 Statement.** When a **clinical trial protocol** is being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement as an extension of **Item 11 of the SPIRIT 2013 Statement** (see www.spirit-statement.org). For alternate study designs, TIDieR can be used in conjunction with the appropriate checklist for that study design (see www.equator-network.org).

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Pages
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	-
Protocol version	3	Date and version identifier	-
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 22
	5b	Name and contact information for the trial sponsor	1, 22
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	18-20
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7-9

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8-9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9-10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	18-20
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11-12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10-12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	16
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8, 21
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	15

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	15
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	15
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8, 18-20
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12-15, 18
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	20
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17-18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	-
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18-20

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	18-20
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	18-20
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	18-20
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	20
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	7, 20
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8-9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	20
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	20
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	19-20
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
	31b	Authorship eligibility guidelines and any intended use of professional writers	22
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	-
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Pragmatic cluster randomised double-blind pilot and feasibility trial of an active behavioural physiotherapy intervention for acute non-specific neck pain: a mixed methods protocol

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Pragmatic cluster randomised double-blind pilot and feasibility trial of an active behavioural physiotherapy intervention for acute non-specific neck pain: a mixed methods protocol

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ABSTRACT

Introduction: Non-specific neck pain causes pain and disability and contributes substantial socio-economic burden internationally. Up to 50% of adults experience neck pain annually, leading to reduced quality of life. An active behavioural physiotherapy intervention (ABPI) may be feasible to manage patients with acute non-specific neck pain to prevent transition to chronicity. A recent pilot and feasibility trial investigating an acute whiplash-associated disorder population found potential value of the ABPI with 95% of participants fully recovered (neck disability index: NDI≤4, compared to 17% in the standard physiotherapy arm); supporting a definitive trial. Qualitative findings from the physiotherapists supported the potential of the ABPI in a non-specific neck pain population.

Methods and analysis: Two phases. (1) Pragmatic cluster randomised double-blind, parallel 2-arm (ABPI versus standard physiotherapy intervention) pilot and feasibility trial to evaluate procedures and feasibility of the ABPI for the management of acute non-specific neck pain. Six physiotherapy departments from 6 public hospitals in Thailand will be recruited and cluster randomised by a computer-generated randomisation sequence with block sampling. Sixty participants (30 each arm, 10 per hospital) will be assessed at baseline and 3-month following baseline for neck disability index, numerical rating scale for pain intensity, cervical range of motion, fear-avoidance beliefs questionnaire and EQ-5D-5L outcomes. (2) Embedded qualitative study using semi-structured interviews to explore acceptability of the ABPI to participants (n=12) and physiotherapists (n=3). Descriptive analysis of quantitative data and interpretative phenomenological analysis to code and analyse qualitative data (deductive and inductive) will inform feasibility for a future definitive trial.

Ethics and dissemination: This trial is approved by the Naresuan University Institutional Review Board (NUIRB_0380/61).

Trial registration: TCTR20180607001

Keywords (3-5 words): Non-specific neck pain, active behavioural physiotherapy intervention, complex intervention, pilot and feasibility trial, cluster randomisation

Strengths and limitations

- This trial is the first investigation of the active behavioural physiotherapy intervention (ABPI) in patients with acute non-specific neck pain after finding potential benefits in patients with acute Whiplash-Associated Disorder (WAD) in the previous Acute Whiplash Injury Study (AWIS) trial.
- A mixed method (quantitative and qualitative) trial will be performed to evaluate procedures, feasibility and acceptability of the ABPI in managing acute non-specific neck pain within the Thai public hospitals.
- The quantitative phase will be conducted using a cluster randomised double-blind (participants and assessors) design to avoid treatment contaminations and for administrative convenience.
- The qualitative phase is designed to explore the treatment perceptions from all stakeholders, specifically patients and physiotherapists.
- Although the ABPI was originally developed for managing patients with acute WAD, it may be helpful in patients with acute non-specific neck pain owing to the similar characteristics of both conditions.

INTRODUCTION

Background and rationale

Neck pain is the 4th cause of disability [1] and the second biggest contributor to disability-adjusted life years (DALYs) among musculoskeletal disorders in the world.[2] Each year, approximately 50% of adults experience neck pain,[3] leading to a reduced quality of life.[4] Furthermore, the pain and disability associated with neck pain has a substantial impact contributing to social and economic burden (e.g. health-care utilisation, work absenteeism and lost productivity).[1 5] In the USA, the health-care spending on neck and back pain is approximately $86.7 billion, following diabetes and ischemic heart disease.[6] For sickness absence in the UK, approximately 31 million days were lost due to musculoskeletal problems (mostly neck and back pain) among workers in 2016.[7] In Thailand, the 4th greatest health problem is musculoskeletal diseases (n=22 million people in 2015),[8] and up to 50% of these individuals' problems can be caused by neck pain,[8 9] leading to a socioeconomic burden of approximately 11 billion Thai baht.[10] Therefore, an effective intervention for managing neck pain is required to improve quality of life and reduce socioeconomic burden.

Physical (e.g. pain and disability)[1 2] and psychological (e.g. anxiety, depression and fear avoidance)[11-13] problems are observed in patients with non-specific neck pain. The current clinical guidelines [14 15] and low-moderate quality evidence [16 17] suggest that manual and exercise therapy may be useful in managing patients with non-specific neck pain. However, high recurrence and chronicity amongst patients with non-specific neck pain are reported, suggesting limited success of existing interventions.[1 2 18 19] For drug therapy, the recent systematic review and meta-analysis of randomised placebo controlled trials found that there were no effects of paracetamol for pain reduction, reducing disability and improving quality of life,[20] and no clinical importance of Nonsteroidal Anti-inflammatory

Drugs (NSAIDs) for spinal pain.[21] Additionally, use of paracetamol (3000-4000 mg total) and NSAIDs (the median duration of included trial=7 days) are documented to contribute a 4 times increase in abnormal liver function [20] and 2.5 times increased risk of gastrointestinal reactions, respectively.[21] Owing to these unwanted side effects from pharmacological management, non-specific neck pain is commonly managed by physiotherapists,[14 15 22] and effective conservative management in the acute stage (≤4 weeks) [11 23] is required to prevent the transition to chronicity and recurrence.

According to the current evidence, non-specific neck pain is a complex biopsychosocial disorder.[1 2 11-13] Subsequently, the management of patients with non-specific neck pain can be complex, encompassing both physical and psychological perspectives. All individuals with acute non-specific neck pain can be variously impacted by psychological problems which can lead to poor recovery.[11] Unfortunately, using multimodal therapy or multifaceted implementation strategies to date have not been useful.[24] Although whiplash-associated disorders (WAD) and non-specific neck pain can be different in mechanism of injury and severity, their conditions and clinical characteristics are similar.[24-27] An active behavioural physiotherapy intervention (ABPI) may therefore be useful in managing patients with non-specific neck pain based on the findings of the previous Acute Whiplash Injury Study (AWIS) pilot and feasibility trial.[28-32] The findings demonstrated that 95% of patients who received the ABPI fully recovered at 3 months follow-up whereas ~17% of patients who received standard physiotherapy fully recovered using a cut-off on the neck disability index ≤ 4.[30-32] This suggests that the ABPI could prevent chronicity among patients with WADII (≥3 months is classified as chronic stage).[33] Moreover, the ABPI appeared better than standard physiotherapy in terms of pain reduction (visual analogue scale for pain intensity), cervical range of motion (cervical range of motion device), pressure pain threshold (digital pressure algometer) and general health status (EQ-5D-5L). Furthermore, the number of physiotherapy sessions and the costs of management in the ABPI arm were lower than standard physiotherapy.[32] The

ABPI was acceptable to physiotherapists and patients, leading to the possibility for it enhancing physiotherapy practice in the future.[31]

Originally, the ABPI was developed through a sequential multiphase project using rigorous, precise and transparent methodologies in order to manage patients with acute WAD.[28-32] The ABPI is a flexible complex intervention combining active physiotherapy and behavioural intervention (underpinned by social cognitive theory focusing self-efficacy enhancement).[28-31] It contains logical concept and phases (i.e. understanding, maturity, stamina and coping) covering both physical and psychological management [29-31] which seems to be suitable to address the problems in the patients with non-specific neck pain. Owing to no report of WAD as a health problem in Thailand but non-specific neck pain being a substantial problem [34] and possible value of the ABPI, the ABPI is therefore first investigate as a pilot and feasibility clinical trial in order to manage patients with acute non-specific neck pain in a public Thai physiotherapy setting.

AIM

To evaluate procedures, feasibility and acceptability of an active behavioural physiotherapy intervention for the management of patients experiencing acute non-specific neck pain in a Thai public physiotherapy setting in order to inform the design and sample size requirements for a future definitive randomised controlled trial.

Objectives

- To evaluate the feasibility of procedures for a cluster randomised controlled trial in the public physiotherapy sector in Thailand (i.e. randomisation, recruitment, data collection, adherence, trial management and follow-up) [35-38]
- To explore the acceptability of the ABPI among Thai physiotherapists (e.g. ABPI contents, barriers to use, distinctiveness and acceptance) and patients (e.g. received treatment and acceptance) with acute non-specific neck pain [36]
- To synthesise parameters to inform the sample size of an adequately powered definitive trial [36-40]

METHODS

Trial design and setting

The protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) to ensure adequate transparency.[41] This protocol contains 2 phases: 1) a quantitative study to evaluate the procedures and feasibility of the ABPI will follow research methods and reporting in line with the CONSORT 2010 statement: extension to cluster randomised trials [42] and the CONSORT 2010 statement: extension to randomised pilot and feasibility trials [43]; and 2) an embedded exploratory qualitative study to investigate the acceptability of the ABPI of patients and physiotherapists in the ABPI arm will follow research methods and reporting of the Consolidated criteria for Reporting Qualitative research (COREQ): a 32-item checklist for interviews and focus groups.[44] Subsequent deviations of the protocol will be submitted to the Naresuan University Institutional Review Board for an amendment and reported in the full trial.

Phase I: pilot and feasibility trial

A pilot and feasibility trial of a pragmatic cluster randomised double-blind (assessors and participants), parallel two-arm design, comparing ABPI with standard physiotherapy intervention (SPI), will be conducted to evaluate procedures and feasibility of the ABPI for acute non-specific neck pain management. Six physiotherapy departments from 6 public hospitals in Thailand will be recruited. The cluster randomisation design has several benefits in terms of reducing treatment contamination, enhancing participant adherence,[42 45-47] participant blinding,[42] administrative convenience [45] and logistical conveniences.[45]

The heads of 6 physiotherapy departments or their hospital directors will be invited to participate by signing consent forms (cluster-level consent) prior to cluster randomisation.[42] One physiotherapist and one blinded assessor (another physiotherapist who will be familiar with and trained for outcome measurements) will be provided by our research team in each hospital. Only physiotherapists, who will treat participants, will be informed their intervention arm. However, they will not be allowed to talk or discuss any concepts/treatments with the assessors, colleagues or other physiotherapists/people during the trial to ensure blinding assessors and participants. The physiotherapists can discuss with other physiotherapists within their intervention arm to provide an opportunity to exchange their experiences. Following randomisation, consecutive potential participants will be screened and recruited by physiotherapists. The participant information sheet and consent form will be given to potential participants. The recruiting physiotherapists will then discuss any issues relating to the trial, provide an opportunity to ask questions, confirm eligibility and obtain written consent (individual-level consent). After giving informed written consent, participants will be assessed on all outcome measures by blinded assessors at each site using standardised instruments with established measurement properties. Assessments will be performed at this baseline and at 3-months follow-up post baseline. All outcome assessments will be

independent from treatment sessions to ensure the blinding of the assessors from treatment allocation. Additionally, the assessors will not be permitted to ask any question related to participants' received treatment from participants and treating physiotherapists throughout the trial. Both assessors and participants will not know to which intervention arm the participants are allocated. To evaluate blinding, at the end of the 3-month follow-up, participants and assessors will be asked which intervention they/their department have been allocated to in order to consider the blinded procedures of definitive phase III trial. The participants will receive a reminder 2 days prior to the 3-month follow-up appointment using e-mail, message or telephone calling depending on their preference.

Phase II: qualitative semi-structured interviews

An embedded qualitative study using interpretative phenomenological analysis (IPA) [48] will explore the acceptability of the ABPI for participants (n=12) and physiotherapists (all physiotherapists, n=3) in the ABPI arm.[30] There are several advantages of the IPA in terms of exploring personal experience, concerning personal perception, producing an objective statement and emphasising an active role for a research in dynamic process.[49] For convenience to interviewer and interviewees, semi-structured interviews will be conducted by TW (a key person with physiotherapy background in developing the ABPI) who is the key to data quality from the interviews. His previous experiences and involvements are seen as positive rather than negative (e.g. understanding of the context or the experiences of the interviewees).[50] Topic guides adapted from the AWIS trial [30] will be pilot tested 2-3 times prior to conducting the first interview. Potential participants will be recruited via telephone. The information sheet and consent form will be sent to them via e-mail or post depending on their preference in order to provide an opportunity to decide whether they wish to complete the consent form in advance. Demographic characteristics of the participants (e.g. age, gender, occupation and ethnicity) will be recorded and reported.[44] The participants will be interviewed for 30-90 minutes in a private room of their local

hospital. In the Thai context, we are not sure that the interviewees can provide a private room for the interviews in their homes. However, the interviewees will be paid for their journey to ensure that they are reimbursed for any expenses that they incur. The interviews will be recorded using a digital recorder.

Participants

Participants will be recruited from the physiotherapy departments of 6 public hospitals. Demographic characteristics, including age, gender, present medications, and information regarding non-specific neck-pain symptoms will be collected by the blinded assessors at the baseline assessment.

Eligibility criteria for clusters: Physiotherapy departments in public hospitals in Thailand.

Inclusion criteria: Participants aged 20-60 years presenting with non-specific neck pain within the previous 4 weeks.[11 23]

Exclusion criteria: Signs and symptoms WAD or traumatic neck pain,[51] upper cervical instability,[52] cervical artery dysfunction,[53] suspected serious spinal pathology, active inflammatory arthritis, tumours, infection of the skin and soft tissue, bleeding disorders or using anti-coagulant medication,[52] any current or previous treatment from any other third party, or presenting with any serious injuries, history of cervical surgery,[54] previously symptomatic degenerative diseases of the cervical spine or neck pain within 6 months prior to the recruitment,[55] neurological conditions, alcohol abuse,[55 56] dementia,[55 56] serious mental diseases,[55 56] psychiatric diseases,[57 58] osteoporosis, serious medical conditions (e.g. severe diabetes and hypertension), pregnant and/or non-Thai speaking and reading.

Interventions

Intervention details are provided in line with the Template for Intervention Description and Replication (TIDieR).[59] All participants will attend face-to-face physiotherapy for up to 10 sessions in a

physiotherapy department based on their physiotherapist's clinical judgement. The frequency of appointment will depend on their physiotherapists' strategies but each session will be limited to 30 minutes. A minimum of a Bachelor Degree in Physiotherapy with 5 years of post-registration experience will be required for the qualifications of all physiotherapists. TW will randomly select treatment sessions to observe in the experimental arm to evaluate fidelity of the ABPI. Also, this will enable provide an opportunity to monitor and provide feedback regarding the intervention to the treating physiotherapists.[30]

Standard Physiotherapy Intervention (SPI)

Patients will be managed according to current practice reflecting the recommendations provided in the non-specific neck pain clinical guidelines.[14 19 23 60] The SPI will consist of cervical or thoracic mobilisation/manipulation, exercises (e.g. stretching, coordination, strengthening and endurance), upper quarter and nerve mobilisation, appropriate advice (e.g. remain active as possible, restore their neck movement as pain allows using neck range of motion exercises, correct poor posture, sleep with one pillow which provides lateral support and also gives support to hollow of the neck), simple analgesia and other physiotherapy interventions (e.g. manual therapy and modalities). All physiotherapists in the control arm will be trained and updated for the existing clinical guidelines to reach the standard physiotherapy management. Appropriate interventions will be selected depending on the physiotherapist's decision-making for the individual patient based on examination findings and clinical reasoning.[53] Treatment sessions and notes will be randomly observed by TW to ensure adhering to the guidelines. Feedback and discussion will be provided throughout the trial.

Active Behavioural Physiotherapy Intervention (ABPI)

The ABPI has been developed through a systematic review,[28] a modified Delphi study internationally,[29] use of social cognitive theory focusing on self-efficacy enhancement [61] and has been tested for WAD patients in a AWIS pilot and feasibility trial.[30] Full details of the ABPI (e.g. concept, phases and strategies) are provided by the previous published articles.[29 30] The ABPI is delivered within a flexible framework, and will be modified to manage individuals with acute non-specific neck pain based on clinical examination findings. The intervention will focus on reducing psychological stress and increasing confidence in exercises and/or home programmes using self-efficacy enhancement at the beginning prior to improving physical functions based on the concept, phases and strategies of the ABPI.

Physiotherapists in the experimental arm will be trained to deliver the ABPI in advance of data collection. Training will consist of a group tutorial (1 day) and workshop followed by individual training sessions (4 weeks) to enable them to tailor the intervention to an individual patients with acute non-specific neck pain based on the findings from the patient history and physical examination data, and their evidence-informed clinical reasoning.[53] Physiotherapists and their treatment notes will be randomly observed by TW during data collection to ensure fidelity of the intervention and to provide feedback throughout the trial. Treatment fidelity will also be assessed by interviews from all physiotherapists (n=3) and participants (n=12) in the experiment group in an embedded qualitative study (phase II of this study).

Outcomes

Planned definitive trial primary outcome measure

The Neck Disability Index (NDI) is a patient-reported questionnaire with 10 sections to evaluate pain intensity and functional activities (e.g. personal care, lifting, reading, headache, concentration, work, driving, sleeping and recreation.[62] Each section is scored from 0 to 5 (the highest score representing the

greatest disability). The NDI is a valid, reliable and responsive tool in assessing pain and disability in both acute and chronic neck problems.[62-65] The level of participant's disability will be indicated by the overall score.[62] The NDI version Thai has been reported as a reliable tool (Cronbach α=0.85, Intra-class Correlation Coefficient (ICC)=0.85) in assessing patients with neck pain, and will be used in this trial.[66] The minimum clinically importance difference (MCID) of the NDI in patients with neck pain is 8.[66-68]

Secondary outcome measures

Numerical Rating Scale for pain intensity

Pain will be measured using a 0 (no pain) to 10 (worst possible pain) by the Numerical Rating Scale (NRS).[69 70] It is a simple and the preferred tool for assessing pain intensity, with high validity and reliability (ICC=0.76).[71-74] The MCID of NRS for patients with mechanical neck pain without upper limb symptoms is 1.5.[75]

Cervical Range of Motion (CROM)

A common problem among patients with neck pain is decreased cervical mobility.[76] In this trial, cervical range of motion (CROM) will be measured using the CROM device.[77] The CROM device is reported as a highly valid and reliable ($ICC_{3,3}$ ranging 0.89-0.98 for all neck movement directions) device in assessing CROM.[78] In the assessment process, participants will sit on a comfortable chair with both hips and knees flexed to 90º and be attached by the CROM device to the head.[79-81] The average of 3 measurements will be performed for data analysis. The MCID of CROM for non-specific neck pain is 10°.[82]

Fear-Avoidance Beliefs Questionnaire

Fear-Avoidance Beliefs Questionnaire (FABQ) is a valid and reliable tool to predict prolonged disability in patients with neck pain.[83 84] It consists of 16 items (each scored 0 to 6) covering both work and physical

activity.[85] The FABQ has been translated into several languages (e.g. Chinese, Persian and Greek) for patients with neck pain.[86-88] In Thailand, the translation and cross-cultural adaptation of the FABQ was conducted and tested the psychometric properties for Thai patients with non-specific neck pain (n=129) by TW and his colleagues. The findings reveal that the FABQ version Thai is a valid (Cronbach α=0.80-0.87 for all items) and reliable ($ICC_{2,1}$=0.98) tool (preparing for publication) to quantify fear and avoidance beliefs in patients with non-specific neck pain. The minimum detectable change of the Thai version is 5.85. Unfortunately, the MCID of the FABQ is not available for patients with non-specific neck pain.

EuroQol-5 Dimensions (EQ-5D-5L)

The EQ-5D-5L is a valid and reliable self-report quality of life (QoL) questionnaire.[89-91] It is recommended as a useful tool for measuring generic QoL in order to provide information for cost-effectiveness analysis.[92] The EQ-5D-5L has been translated into many languages including Thai and is valid and reliable tool ($ICC_{2,1}$=0.70).[93-95] Unfortunately, the MCID of the EQ-5D-5L for non-specific neck pain is not available.

Assessment of outcome

All participants will be assessed at baseline and at 3-months post baseline. Participants who continue with symptoms and problems after 3 months will be defined as chronic.[23] The number of fully recovered patients with non-specific neck pain at 3 months will be evaluated using a cut-off of NDI ≤ 4.[62] Telephone contact will be used by assessors in case of participants do not attend the 3-month follow-up assessment and they will be asked if they would like to make a new appointment. When participants cannot make a new appointment, the assessors will ask them to complete the NDI, NRS, FABQ and EQ-5D via telephone interview; these outcomes have established reliability and validity via telephone.[96-98]

Feasibility of cost-effectiveness analysis

In order to assess the feasibility of data collection for the planned cost-effectiveness analysis in the definitive trial, direct and indirect medical costs will be collected and recorded. The diary pocket book of the previous AWIS trial [30] will be modified to Thai in order to record any activities related to non-specific neck pain management such as using medication, consulting other health professionals; along with any health care costs they incurred, and days of sick leave. The information will be collected by the blinded assessors each week replacing self-record which was unsuccessful in the previous trial.[31] Furthermore, general information of participants (e.g. work status, income and distance between home and hospital) will be collected at the baseline assessment. Costs related to physiotherapy management will be collected from the physiotherapy departments throughout the trial. Training costs of physiotherapists in the ABPI arm will be also included.

Sample size

According to a pilot and feasibility trial, a power calculation is not required and targeted sample sizes for pilot/feasibility trials is still controversial.[36] However, 30 participants can be safely assumed to be normal distribution. Therefore, 60 participants (30 per arm, 10 from each department) will be recruited in order to provide parameters for designing a high quality of a definitive RCT.[99]

Randomisation

Stata software version 12 with block sampling will be used by TW to randomise 6 physiotherapy departments to either SPI (n=3 departments) or ABPI (n=3 departments) in order to minimise selection bias at cluster level. The allocation will be concealed before assignment and only TW will involve in the

process. Cluster randomisation will be performed prior to participant recruitment (**Figure 1: CONSORT flow diagram**).

Data analysis

Phase I: Quantitative data will be analysed and summarised to evaluate eligibility, recruitment and follow-up rates, using IBM SPSS version 22. The feasibility of the ABPI for non-specific neck pain management will be assessed using descriptive statistics (e.g. frequencies, percentages, means, standard deviations, medians and interquartile ranges depending on data).[37] Intention-to-treat analyses will be used in this trial and missing data will be reported descriptively. The evaluation of the number of fully recovered participants will be performed by consideration of NDI ≤4 at 3-month follow-up.[62] The intra-cluster correlation coefficient (ICC) will be provided to calculate the sample size within a clustered definitive trial. The analyses and findings of the trial will be discussed with the research team at each stage, and by the trial steering and data monitoring committee.

After trial completion, the following are the possible decisions for progressing to a definitive trial: (i) stop if the main trial is not possible or valuable, (ii) continue but modify the protocol if the main trial is possible and valuable, (iii) continue without modifications but monitor closely if the main trial is possible and valuable with close monitoring, (iv) continue without modifications if the main trial is possible and valuable.[37] **Table 1** shows the criteria to consider a future definitive trial.

Table 1: Considerations for a future definitive trial

Objectives	Criteria for success
To evaluate the feasibility of procedures for a cluster randomised controlled trial in the public physiotherapy sector in Thailand (i.e.	Feasible to conduct a phase III trial • No major obstruction issue and/or serious adverse event (assessed by trial monitoring) • Feasible for the type of study (randomised

randomisation, recruitment, data collection, adherence, trial management and follow-up)	design) (assessed by trial monitoring) • Feasible for procedures of data collection, trial management and follow-up (assessed by trial monitoring) • At least 3 participants a month per hospital
To explore the acceptability of the ABPI among Thai physiotherapists and patients with acute non-specific neck pain	• The ABPI can be acceptable to Thai physiotherapists and patients with acute non-specific neck pain (explored by qualitative study). • Acceptable rate ≥60% of participants in each group
To estimate sample size in order to conduct an adequately powered definitive trial	• All parameters can be provided to calculate sample size for an adequately powered definitive trial

Phase II: All interviews will be transcribed verbatim and analysed in line with IPA.[48] All participants will be anonymous using a pseudonym. Transcripts will be read a number of times to enable familiarisation. Qualitative data will be coded and grouped by TW and a coder to minimise potential bias. Related themes of the acceptability of the ABPI for non-specific neck pain management will be identified by QRS Nvivo 10. The analyses will be performed case by case in both deductively (to identify themes) and inductively (to identify additional themes).[100 101] After the completion of the initial coding, similarities of the themes between coders will be examined. Then, a table of emergent themes will be established. The process will be used throughout the study. The analysis and findings from the qualitative data will be reviewed and discussed with the research team and the trial management group to ensure the accuracy of data analysis and provide other interpretations and suggestions.

Trial management and monitoring

The Trial Management Group (combing The Trial Steering Committee and the Data Monitoring Committee consistent with the pilot and feasibility nature of the trial) consisting of TW (the lead

researcher), AR (the experienced trialist), SU (the neck expert), a non-specific neck pain patient, an external member, and an independent chair will meet at the start of recruitment, after 3 months of recruitment, and at the completion of data collection.

Adverse events

This trial can be considered as a low risk trial for adverse event owing to no reporting of any adverse/ serious adverse event in using the ABPI in physiotherapy setting of the previous AWIS trial.[30 31] Moreover, patients with non-specific neck pain have reported less severity than patients with WAD. Both interventions are conservative treatments without existing reporting of serious adverse events in managing neck pain.[31 102-104] From the literature, the most common adverse event after physiotherapy intervention is muscle soreness and it can recover within 1-2 days.[105]

Serious adverse events

Serious adverse event can be evaluated as a very low risk owing to the nature of patient pathology and treatment management. This trial is designed to exclude patients with high severity using experienced physiotherapists who will be trained further in screening participants. Furthermore, the International Federation of Orthopaedic Manipulative Physical Therapists (IFOMPT) cervical framework [53], which has provided guidance for clinical reasoning to identify the risk of adverse events regarding vascularity and instability of the neck, will be used to inform examination for eligibility. However, a serious adverse event will be defined if participants have worsening symptoms within 3 days and been admitted to the hospital due to non-specific neck pain problems.[30]

Procedures for reporting adverse and serious adverse events

An adverse event reporting form will be provided to all physiotherapy departments. Participants will be required to report any unpleasant symptoms to their physiotherapists by completing the form. Then, physiotherapists will report any event to TW within 24 hours, and TW will report to the trial steering committee within 24 hours to enable analysis of the event and any required action. Any unexpected serious adverse events (e.g. a life-threatening situation, inpatient hospitalisation and/or significant disability) will be immediately reported with a written form and verbal contact by physiotherapists to TW. Subsequently, TW will report any event to the trial steering committee; immediately to discuss for an action.

Data management

A participant's data will be assigned an ID code, and the key relating participant to ID code will be stored securely and separately to the project files. All information of participants will be preserved safely from any third party to maintain the participants' privacy at the Faculty of Allied Health Sciences, Naresuan University. All collected documents will be stored in a secure place and electronic data will be confidentially stored in a password-protected computer. Only members of the research team can access the data. All data will be securely destroyed after being kept for 10 years.

Patient and public involvement

The trial is designed by a team of researchers using a part of the results from the previous pilot and feasibility trial which a patient was a member of the trial steering committee.[30 32] A patient will be planned to involve in this trial as a member of the trial management group. He/she will be thanked in the contributorship statement/acknowledgements in a full article.

Ethics and dissemination

The trial will be conducted in accordance with the Declaration of Helsinki and the ethical guidelines for medical human research and is approved by the Naresuan University Institutional Review Board (NUIRB_0380/61). The findings of the trial (completely unattributable format or at an aggregate level) will be submitted to medical journals and presented at international and/or local conferences/lectures.

DISCUSSION

The findings of the previous AWIS trial reported that the ABPI was feasible for acute WADII management to prevent the transition to chronicity (e.g. 95% of the participants fully recovered by the ABPI within 3 months whereas ~17% by the standard physiotherapy) and was acceptable to physiotherapists and patients.[30 31] Furthermore, physiotherapists have applied the ABPI to manage other neck pathologies and regions owing to the possible success of this management approach.[31] According to the similarity of the situations and symptom characteristics between the WAD and non-specific neck pain populations,[25 27] it is interesting to investigate if the ABPI is feasible for managing non-specific neck pain in the acute stage to prevent chronicity. Therefore, this phase II trial will be conducted to evaluate feasibility and acceptability of the ABPI for acute non-specific neck pain in a Thai physiotherapy setting and/or to prepare information in designing an adequately powered, high quality definitive trial.

This trial is designed to prevent potential problems resulting from some limitations of the previous AWIS trial.[30-32] First, this trial will provide one blinded assessor at each site to accelerate the recruitment rate and logistical convenience. Second, the trial will use individual semi-structured in-depth interviews to explore the acceptability of the participants replacing a focus group. In the previous trial, only one participant could attend the focus group (3 participants verbally agreed previously) although the research team tried to use several strategies (e.g. contacting all participants, arranging based on their

preference and convenience, reminding (2 days) for the date and location of the meeting prior to the date of the focus group and providing convenient facilities (e.g. the nearest parking area and meals). Subsequently, the focus group was modified to an individual interview. Third, the qualitative data will be analysed using two independent coders to establish higher trustworthiness.

In Thailand, neck pain is a substantial health problem among musculoskeletal disorders leading to socioeconomic burden. Owing to the similar conditions and clinical characteristics between WAD and non-specific neck pain [25 27] and the findings of the AWIS trial,[31 32] the ABPI may be potentially effective intervention to manage acute non-specific neck pain. Thus, this trial will be conducted to evaluate feasibility of the ABPI in patients with acute non-specific neck pain and its procedures. This trial is the first investigation of the ABPI in Thai clinical setting and the first time in conducting a cluster randomised design in Thai physiotherapy setting.

Trial status

Recruiting commenced 01/02/2019.

Competing interests

No competing interests.

Authors' contributions

TW is the chief investigator and guarantor leading to drafting the initial manuscript, protocol development, analyses and dissemination. TW, SU and AR have contributed to clinical and methodological decisions to ensure the trial quality and will contribute to data interpretation, conclusions and dissemination. All authors have read and agreed the final manuscript.

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Data sharing plan

Data sharing will be provided where legally and ethically possible. The data will be made available upon reasonable request.

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Supporting information

Figure 1: CONSORT flow diagram (adapted from CONSORT 2010)

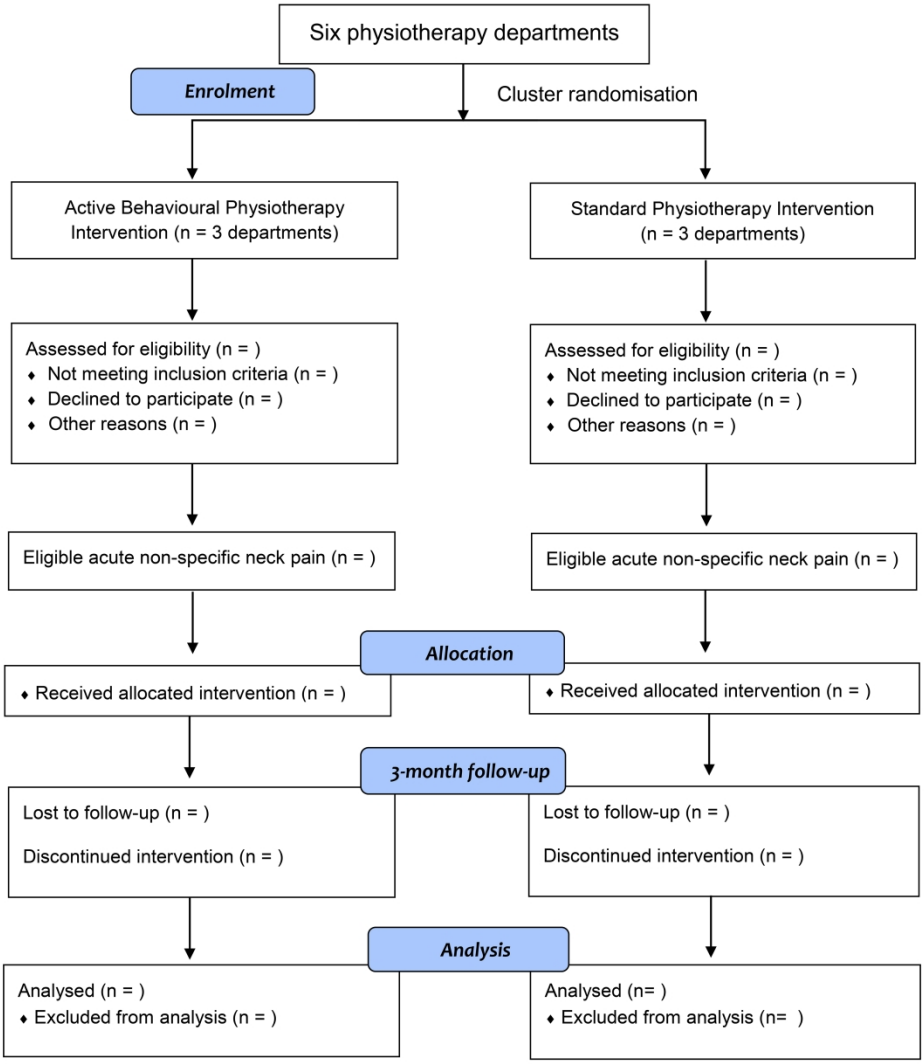

Figure 1: CONSORT flow diagram (adapted from CONSORT 2010).

Figure 1: CONSORT flow diagram (adapted from CONSORT 2010)

175x224mm (600 x 600 DPI)

TIDieR Template for Intervention Description and Replication

The TIDieR (Template for Intervention Description and Replication) Checklist*:

Information to include when describing an intervention and the location of the information

Item number	Item	Where located **	
		Primary paper (page or appendix number)	Other † (details)
	BRIEF NAME		
1.	Provide the name or a phrase that describes the intervention.	1, 5-6, 10-11	
	WHY		
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.	5-6, 10-11	
	WHAT		
3.	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).	10-11	
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	10-11	
	WHO PROVIDED		
5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.	10-11	
	HOW		
6.	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	10-11	
	WHERE		
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	10-11	

	WHEN and HOW MUCH		
8.	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.	___10-11___	_____
	TAILORING		
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.	___10-11___	_____
	MODIFICATIONS		
10.‡	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).	____-____	__protocol__
	HOW WELL		
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.	___10-11___	_____
12.‡	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	____-____	__ protocol __

** **Authors** - use N/A if an item is not applicable for the intervention being described. **Reviewers** – use '?' if information about the element is not reported/not sufficiently reported.

† If the information is not provided in the primary paper, give details of where this information is available. This may include locations such as a published protocol or other published papers (provide citation details) or a website (provide the URL).

‡ If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.

* We strongly recommend using this checklist in conjunction with the TIDieR guide (see *BMJ* 2014;348:g1687) which contains an explanation and elaboration for each item.

* The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study. Other elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist. When a **randomised trial** is being reported, the TIDieR checklist should be used in conjunction with the CONSORT statement (see www.consort-statement.org) as an extension of **Item 5 of the CONSORT 2010 Statement.** When a **clinical trial protocol** is being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement as an extension of **Item 11 of the SPIRIT 2013 Statement** (see www.spirit-statement.org). For alternate study designs, TIDieR can be used in conjunction with the appropriate checklist for that study design (see www.equator-network.org).

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Pages
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	-
Protocol version	3	Date and version identifier	-
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 22
	5b	Name and contact information for the trial sponsor	1, 22
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	18-20
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7-9

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8-9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9-10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	18-20
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11-12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10-12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	16
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8, 21
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	15

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	15
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	15
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8, 18-20
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12-15, 18
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	20
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17-18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	-
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18-20

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	18-20
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	18-20
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	18-20
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	20
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	7, 20
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8-9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	20
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	20
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	19-20
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
	31b	Authorship eligibility guidelines and any intended use of professional writers	22
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	-
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.