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Keywords:	Chronic non-malignant pain, Opioids, behavioural interventions, tapering, RCT, process evaluation

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Abstract

Introduction: Chronic non-malignant pain has a major impact on the wellbeing, mood and productivity of those affected. Opioids are increasingly being prescribed to manage this type of pain, but the increasing risk of other disabling symptoms, and their effectiveness for this type of pain has been questioned. This trial is designed to implement and evaluate a patient-centred intervention targeting withdrawal of strong opioids in chronic pain patients.

Methods and analysis: A pragmatic, multi–centre, randomised controlled trial will assess the clinical and cost-effectiveness of a group-based multicomponent intervention combined with individualised clinical facilitator led support for the management of chronic non-malignant pain. An embedded process evaluation will examine fidelity of delivery and investigate experiences of the intervention. The co-primary outcomes are activities of daily living (measured by PROMIS Pain Interference Short Form (8A)) and opioid use. The secondary outcomes are pain severity, quality of life, sleep quality, self-efficacy, adverse events, and NHS health care resource use. Patients are followed up at four, eight, and 12 months, with a primary

endpoint of 12 months. Between-group differences will indicate effectiveness; we are looking for a difference of 3.5 points on our primary outcome (scale 40-77). We will undertake an NHS perspective cost-effectiveness analysis using Quality Adjusted Life Years.

Ethics: Full approval was given by Yorkshire & The Humber - South Yorkshire Research Ethics Committee on September 13th, 2016 (16/YH/0325). Appropriate local approvals were sought for each area in which recruitment was undertaken. The current protocol version is 1.5, date 24th October 2018.

Dissemination: Publication of results in peer reviewed journals, including the development and theoretical framework of the intervention, will inform the scientific and clinical community. We will disseminate results to patient participants and study facilitators in a study newsletter as well as a lay summary of results on the study website.

Trial registration: This trial is registered with an International Standard Randomised Controlled Trial Number (ISRCTN) Register. ISRCTN number: 49470934 (06 Feb 2017)

Strengths and limitations

- A randomised controlled trial, participants are randomised to either the active intervention (group plus one-to-one support) or control (self-help booklet and relaxation CD).
- Participants meeting the inclusion criteria, including use of strong opioids for the management of chronic non-malignant pain, are recruited mainly from primary care.
- Data collection will include weekly diaries, self-report questionnaires and qualitative interviews.
- The embedded process evaluation will help us understand people's experiences of the intervention and what helped or hindered its use (compared to the control group).
- Long term economic modelling will include potential impact of reduced opioid use on long-term harms such as sedation, nausea, respiratory depression/sleep apnoea, depression, abdominal pain, overdose and death.

Keywords: Chronic non-malignant pain, Opioids, Self-management, behavioural interventions, tapering, RCT, process evaluation

Introduction

Chronic non-malignant pain is defined as pain that persists past normal healing time of around 12 weeks.(1, 2) and affects eight million people (15%) in England alone.(3) Around 20% of those aged 34 years old or over, and around 40% in those aged 75 years old or over, report high levels of interference with their lives from pain.(3)The common disorders contributing to this include low back pain, neck pain, osteoarthritis, neuropathic pain, fibromyalgia, chronic widespread pain, and post-surgical pain. Individuals may live with more than one of these pain disorders.

While opioids are regularly prescribed for the management of chronic non-malignant pain, they are not always effective in the long term and can cause a range of adverse effects such as sedation, nausea, respiratory depression/sleep apnoea, depression, abdominal pain, overdose and even death.(4, 5) Furthermore, people on long-term opioid treatment (three months or more) report inadequate analgesia, in spite of high doses, due to the development of tolerance with reduced function, quality of life, or absence of progress toward therapeutic goals.(6-8) Yet, prescription data from the UK show that over an 11 year period (2002 to 2013) there was an increase in prescribing of the more potent controlled and long-acting, long-term opioids for those with musculoskeletal conditions within the first 90 days of their long term episode (2.3% to 9.9%).(9) There is a pressing need for interventions to help people withdraw from strong opioids used for chronic non-malignant pain.

While much is known about the adverse effects of long-term opioid treatment (10), little is known about the economic impact of these adverse events. There are few evaluations of interventions designed to support opioid reduction. Cochrane reviews (11, 12) and randomised controlled trials (13, 14) offer some support for interventions supporting opioid withdrawal, including interdisciplinary pain management programmes, use of behavioural strategies,

motivational interviewing, mindfulness and pain education, however, this is of low quality with short follow up (≤ 4 months).(15)

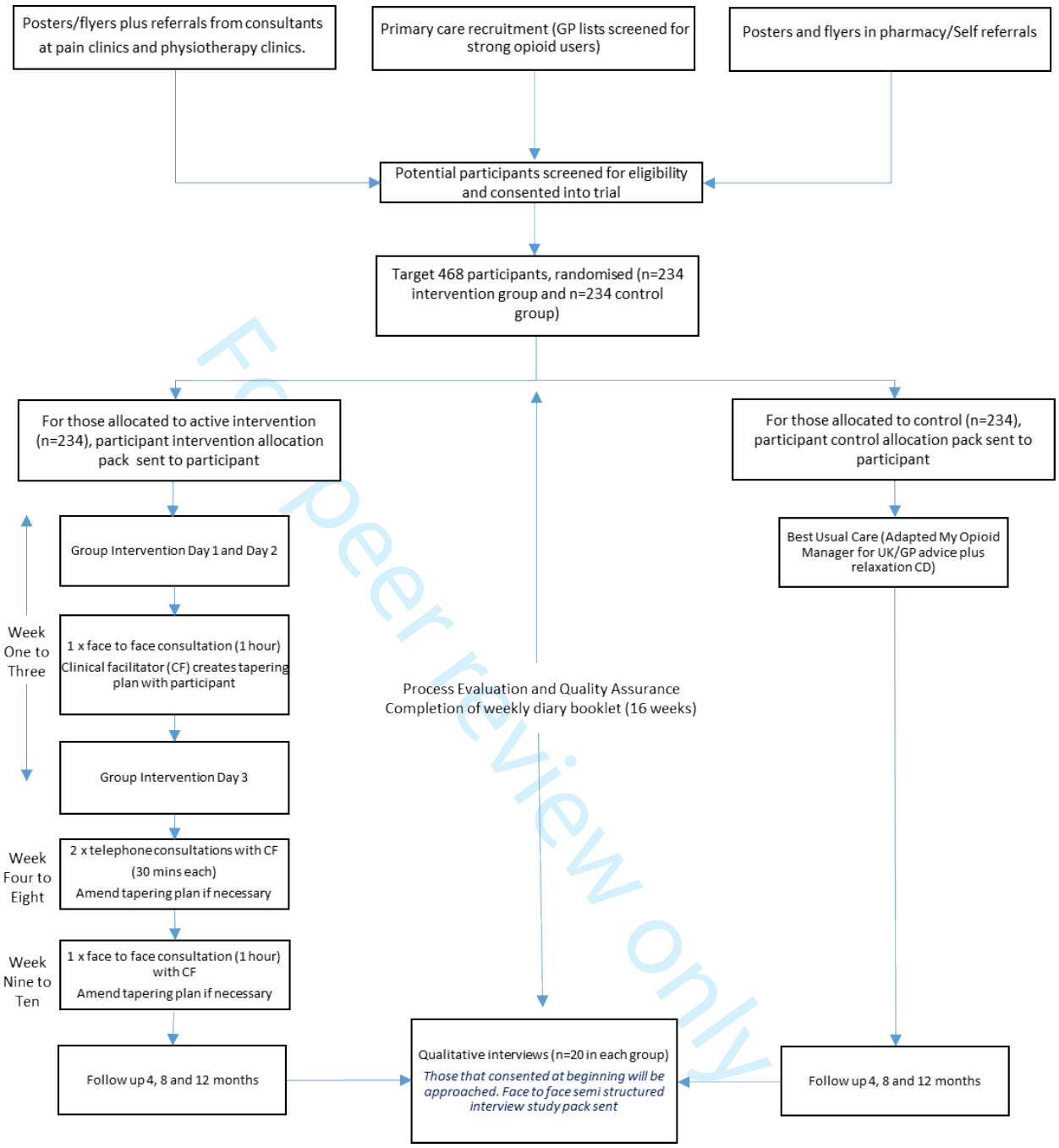
There are no formal UK guidelines for opioid reduction in this population. While such recommendations are currently emerging in North America (16, 17), these are based on expert consensus rather than data. There is also no clear evidence to support a particular speed of opioid tapering or the use of particular opioid drug(s) or rotating from one opioid to another. Overall, data substantiating the role of self-management and cognitive behavioural interventions in support of opioid tapering is weak and mostly applicable to the North American health systems.(18) Consequently, this trial will test an evidence-based intervention among chronic non-malignant samples. The intervention is designed to help patients manage pain interference, reduce individuals' opioid consumption and enhance quality of life.

Methods/Design

Trial design and objectives

The primary objective is to test the clinical and cost effectiveness of a patient-centred, group-based, multicomponent, self-management intervention for people living with chronic non-malignant pain, compared to a best usual care (i.e. the control group intervention) in a two-arm pragmatic randomised controlled trial. The intervention will target withdrawal of strong opioids to assess the impact of their withdrawal on pain interference with daily living. We are running an embedded process evaluation (publication in preparation) to test fidelity, inform the interpretation of the findings and implications for the implementation of the intervention across the NHS, if indicated.

I-WOTCH Flow chart – For original sample calculation



Trial setting

The trial is taking place in the North East, East Midlands, West Midlands and South Central areas of England. When originally planned we also intended to recruit in London. However, operational barriers meant we were unable to deliver the trial in London. The populations from which participants are drawn are broadly representative of the UK. We are recruiting participants from general practices, community pain services, local musculoskeletal services, and pharmacies. We also accept self-referrals. Recruitment sites are clustered by reasonable geographical proximity to a treatment site and people in one locality are approached accordingly so that the intervention groups can be populated in a timely manner.

Box 1 Eligibility criteria

Inclusion criteria	*Exclusion criteria*
• Provision of written informed consent • Aged 18 years old or above • Using opioid for chronic non-malignant pain • Report using one or more prescriptions for strong opioid treatment in the previous three to six months and on most days in the preceding month • One or more prescriptions for strong opioid treatment in the previous three months • Fluent in written and spoken English • Willingness for GP to be informed of participation	• Regular use of injected opioid drugs • Report chronic headache as the dominant painful disorder • Serious mental health problems that preclude participation in a group intervention • Previous entry or randomisation in the present trial • Participation in a clinical trial of an investigational medicinal product in the last 90 days • Pregnant at time of eligibility assessment, or actively trying to become pregnant. • Methadone use as part of substance abuse management • People receiving strong opioid for the management of pain due to active malignant disease • Housebound status (this limits participation in group sessions)

For the purpose of this study, we define strong opioids using the British National Formulary. Thus, we are recruiting participants taking any of the following analgesia: buprenorphine, dipipanone, morphine, diamorphine, fentanyl, hydromorphone, methadone, oxycodone,

papaveretum, pentazocine, pethidine, tapentadol or tramadol.(19) Although in some jurisdictions tramadol is considered to be a weak opioid the BNF classifies it as a strong opioid.

Recruitment procedures

1. (Primary care) electronic screening of GP records: GP practice lists are searched electronically to identify people who have been prescribed strong opioids on more than one occasion in the previous six months as indicated by their health record. The practice then screens the list of those identified from the first search to exclude patients taking strong opioids for malignant pain or who should not be approached for other reasons, including those at risk, vulnerable, or not suitable for a group-based intervention. Recreational drug users being prescribed methadone are not approached.

2. Referred to the study by their GP or healthcare professionals at pain clinics and musculoskeletal physiotherapy clinics. GPs and healthcare professionals at pain clinics and musculoskeletal physiotherapy clinics can also refer potential participants by giving them an information pack on the study and an expression of interest form.

3. Posters advertising details of the study are displayed in prominent areas of GP surgeries, pharmacies, pain clinics and musculoskeletal physiotherapy clinics. The posters contain information about the study, including contact details for the study team.

Eligibility and informed consent

Once we receive an expression of interest form from a potential participant (with contact details), a member of the study team contacts them by telephone to check their eligibility for the study, using the inclusion and exclusion criteria as a checklist. An anonymised screening

log is kept, detailing all those screened and reasons for exclusion. Potential participants (those who are eligible) are then sent a study pack in the post containing an I-WOTCH cover letter, participant information sheet, trial consent form, baseline questionnaire, and pre-addressed envelope. Upon receipt of a signed consent form and completed questionnaire, a designated member of the study team performs a final telephone eligibility check on medications reported by the patient in the baseline questionnaire. If the medications meet the eligibility criteria and consent is deemed to be valid and informed, the consent form is counter-signed by the appropriately trained member of the study team and a copy of the completed form is sent to the participant and to the participant's GP.

Experimental intervention

I-WOTCH is an 8-10 week programme with a mixture of group sessions (facilitated by a trained I-WOTCH clinical facilitator, usually a nurse, and a trained lay person with chronic pain and experience of opioid tapering, or an I-WOTCH trained allied health-care professional), two one-to-one consultations and two telephone calls with the I-WOTCH trained clinical facilitator. The course is adapted from a previously tested intervention used for the self-management of chronic pain.(20, 21) The I-WOTCH group intervention is described (in preparation).

One to one clinical facilitator consultations

Between Day Two and Day Three of the group based sessions, participants attend a face to face, one to one consultation with the I-WOTCH trained clinical facilitator. This is an opportunity for the clinical facilitator to explore opioid tapering experiences with participants, including thoughts, motivation, perceived challenges and opportunities, and to collaboratively develop realistic tapering goals adapted to the participant's circumstances. The clinical facilitators will be trained to use motivational interviewing skills to facilitate discussion. After

Day Three participants receive two telephone consultations (approximately 30 minutes each) to discuss progress with the tapering and to identify the need for other support during withdrawal. They also receive a final face face-to to-face consultation to (i) reflect on progress, (ii) recap over self-management skills covered in the group sessions, (iii) review and re-set goals and objectives, and (iv) assess future needs for support.

I-WOTCH tapering app to generate the opioid tapering plan

We have developed a tapering app to be used by the I-WOTCH clinical facilitators in the one to one consultations to generate the tapering plan. The app was developed within the programming team at Warwick Clinical Trials Unit with clinical expertise guided by SE. The App facilitates calculations of tapering regimes, as well equianalgesic doses of systemic opioids when switching between opioid preparations is necessary. During our preparation for the study and design of the app we uncovered a discrepancy between a number of existing equianalgesic opioid tables.(22) For the purposes of opioid tapering we used the Faculty of Pain Medicine Equianalgesic table (https://www.rcoa.ac.uk/faculty-of-pain-medicine/opioids-aware/structured-approach-to-prescribing/dose-equivalents-and-changing-opioids) for our calculation.(23) We supplemented this with reviews of the individual drugs' Summary of product characteristics (SPC) and other sources where needed.(24, 25) For the purposes of managing changes in medication during the taper, individual variability is taken into account. Once the tapering plan is generated a paper copy is given to the participant and the electronic data is sent to the study team for checking and filing. All tapering plans generated are checked by a clinician for accuracy (SE or JN). A paper copy is sent to the participant's GP for their records.

Opioid tapering procedures

Participants are tapered on their drug of presentation. Opioid rotation is only recommended for participants who have reached the lowest dose of a transdermal patch preparation. For example, in cases of participants presenting on fentanyl transdermal patches these are tapered in decrement of 12 mcg/hr patches, and an oral formulation of alternative opioid with equianalgesic potency introduced when the lowest increment of the patch is reached.(18) Participants on buprenorphine patches are weaned using decreasing increments of the patches with no substitution due to its agonist/ antagonist action.(26)

We are using a regimen based on the Mayo Clinic experience as it provides some evidence to support the notion of slow tapering and is unlikely to be associated with severe withdrawal symptoms and therefore likely to facilitate adherence.(18) This consists of a 10% decrease of the original dose every 5-7 days until 30% of the original dose is reached. This is followed by a weekly decrease by 10% of the remaining dose. The 10% may be rounded up or down to suit prescribing.

We are providing training in equianalgesic dose calculation as well as an electronic means of calculating. People utilising opioids as rescue analgesia, at a frequency of less than one dose per day, do not require a formal tapering regime but are still being supported to completely withdraw from opioids.

Facilitator training

I-WOTCH facilitators attend a two day training course delivered by HS and JS (experienced in the design and delivery of the intervention) to deliver the intervention. Over the two days the facilitators are taught how to deliver each of the topics, as well as given an opportunity to

experience the mindfulness and relaxation practice which is a part of the programme. In addition they are also taught group facilitation skills and procedures to follow within the study. The I-WOTCH clinical facilitators also attend a third day of training, during which they are given further opioid education, and trained in how to taper, use of the I-WOTCH APP, motivational interviewing and study procedures for the one-to-one consultations.

We have adapted a comprehensive facilitator's manual and training programme used in a previous trial on the management of chronic pain (21) to facilitate delivery of the I-WOTCH intervention (in preparation). The adaptations have been formed through literature, piloting of the intervention and input from lay people (those with chronic pain and experience of opioid use). The manual is acting as a guide and a reference point for the all facilitators throughout the intervention.

Adaptations and development of the intervention has included: structuring the programme to include opioid education as well as pain education, and integrating these throughout the programme. Specific examples and case studies related to opioid tapering and pain have been used, mindfulness and relaxation CDs created, and a DVD (focused on pain and opioid education) has been produced for participants to take home and watch and again, integrated throughout the programme for reference. Specially designed handouts are given to participants at the end of each group day summarising key topics discussed. Further details of the intervention and theoretical framework used to design are reported elsewhere (to be published).

Control intervention

Those randomised to the control group will receive augmented usual care, including two participant-facing components: a hard copy of the I-WOTCH adapted 'My Opioid Manager'

booklet, and a relaxation CD with instructions on its use. 'My Opioid Manager' was developed in Canada (Toronto Rehabilitation Institute) specifically for people using opioid drugs for chronic non-cancer pain. It is a self-help guide that contains information about opioids and provides guidance about setting goals, issues the participant may encounter, tapering, and non-opioid options for management of chronic pain. It is based on the 2010 Canadian Opioid guideline of opioids for chronic non-cancer pain.(27)

Compliance

For the intervention, we are recording the number of sessions that each participant attends, including the follow-up calls completed. Other quality assurance checks include the integrity of randomisation, study entry procedures and data collection.

Study outcomes

Primary outcome: activities of daily living

Our primary clinical outcome is the Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Interference Short Form (8A) (PROMIS-PI-SF-8A) (28). This is an eight-item generic self-reported measure, which assesses the consequences of pain on relevant aspects of an individual's life and key activities of daily living: engagement with social, cognitive, emotional, physical, and recreational practices. The PROMIS-PI-SF-8A raw score ranges from 4-80 which is then standardised to give a score ranging from 40.7-77, with higher scores indicating worse outcome. The PROMIS-PI measures the same construct as two legacy pain interference measures (Brief Pain Inventory Pain Interference subscale and the SF-36 Bodily Pain subscale), supporting the calculation of a common metric.(29, 30)

As originally designed, we proposed pain interference as a single primary outcome to ensure

we could recruit sufficient participants. However, how the intervention might affect this directly through its behavioural and educational component and how there might be indirect effects through changing opioid use is unclear. It is possible, for example, that the intervention has a good effect upon opioid use but little effect on pain interference. In this situation the potential long-term benefits of opioid reduction might justify claiming a positive result from the trial. During the later stages of recruitment, it became clear we had capacity, and sufficient interest from practices and potential participants to exceed our planned target.

Our main outcome measure for opioid use is the mean difference in morphine equivalent dose in the four weeks prior to one-year follow-up expressed as mg equivalents of morphine per day. In ongoing work we are reviewing morphine equivalence tables before making a final decision on which set of equivalence values to use for this analysis. For sensitivity analyses, we will use alternative published values for equianalgesic doses of opioids to ensure that our findings are robust if different weightings are used. For secondary analyses, we are comparing proportions achieving a complete withdrawal and proportions of responders, defined as ≥50% reduction in morphine equivalent doses taken, between intervention and control groups.

While our study entry criterion is participant reported use of strong opioids on most days in the preceding four weeks, our continuous measure of opioid use is mean morphine equivalents of opioid used in the preceding four weeks. This includes all opioids consumed, including any weak or as required opioids.

Self-reported data on opioid use are being collected at baseline, four, eight, and 12 months following randomisation via postal follow-up. At baseline, one postal reminder is sent. At four, eight, and 12 months a postal reminder is sent. In the event that no response is obtained from

the postal reminder at four, eight, or 12 months, we contact the participant by phone and collect our primary clinical outcome, opioid use, and EQ-5D-5L over the phone. Participants complete a weekly diary that includes the EQ-5D-5L and the Short Opioid Withdrawal Scale for the first four months after randomisation.

Secondary outcomes

Our package of other secondary outcomes and process measures is informed by the consensus recommendations for core outcome domains for trials of the efficacy and effectiveness of treatments for chronic pain by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group.(31) All outcome measures are presented in Table 1 with data collection time points.

Table 1 Outcomes measures and time points

Outcome measure	Baseline	4 months	8 months	12 months
Demographic data	x			
PROMIS Pain Interference Short Form (8A)	x	x	x	x
Self-reported opioid use (mean morphine equivalents of opioid used in the preceding four weeks)	x	x	x	x
Opioid prescription from GP records				x
EQ-5D-5L	x	x	x	x
SF 12 V2	x	x	x	x
Short Opioid Withdrawal Scale (ShOWS)	x	x	x	x
PROMIS Pain Intensity Short-Form (3A)	x	x	x	x
Pittsburgh Sleep Quality Index (PSQI)	x	x	x	x
Hospital Anxiety and Depression Scale (HADS)	x	x	x	x
Pain Self Efficacy Questionnaire (PSEQ)	x	x	x	x

Participant ratings of global improvement and satisfaction with treatment Patient Global Impression of Change	x	x	x	x
Symptoms and adverse events Passive capture of spontaneously reported adverse events and symptoms and use of open-ended prompts	x	x	x	x

Power and sample size

For the purposes of our original sample size calculation we used our primary clinical outcome measure, the PROMIS-PI-SF-8A.(28) Using the PROMIS primary outcome, participants in the control arm are likely to obtain a mean score of 50, SD 10.(32) A sample size of 346 participants is required to show a difference of 3.5 points on PROMIS-PI-SF-8A (standardised mean difference of 0.35) at 5% significance with 90% power There may, however, be clustering effects by groups in the intervention arm. We do not have any data from similar studies to inform an estimate of the intra-cluster correlation (ICC). Our recent experience across multiple studies of group interventions has been that such effects are trivial or negligible. (20, 33, 34) Despite this, assuming a relatively modest ICC of 0.01 and assuming, on average, that 10 participants per group provide one year outcome data, we would require 374 patients. Allowing for 20% loss to follow-up (whilst striving for 10%) we planned to recruit 468 participants. We subsequently changed the significance level to 2.5% to allow for two primary outcomes (PROMIS –PI-SF-8A and opioid use) with effect size of similar magnitude, and adjusted the inflation factor for clustering to reflect actual group sizes. Our final recruitment target was 542 participants. Experience in similar studies is that, towards the end of recruitment, there can be a need to over-recruit slightly more people than originally projected to ensure the final intervention groups are adequately populated.

Randomisation methods and blinding procedures

Patients are randomised in a 1:1 ratio to either the I-WOTCH intervention or best usual care arms. Randomisation procedures are being performed at The Warwick Clinical Trials Unit (WCTU). Where possible randomisations are carried out by a member of staff who is not a core member of the I-WOTCH team. The method of randomisation is computer generated using WCTU randomisation systems developed by the WCTU Programmers. There is no allocation concealment as the person conducting the randomisation is also entering baseline data prior to randomisation. All baseline data are being collected prior to randomisation. Where possible any data collected from GP records is being done by staff blind to treatment allocation. Routine data sources such as GP prescribing data are also collected.

To ensure that we populate the groups, we are clustering groups of four-five geographically proximate practices with approximately 50,000 patients to launch recruitment at around the same time. We are then randomising participants when we have sufficient participants to populate a group in batches of around 24 participants to delay time between randomisation and the start of the intervention. Randomisation has been stratified by group, baseline pain severity and baseline opioid use.

Data management

Data for individual participants are being collected via participant-completed questionnaires, by clinical facilitator-completed Case Report Forms (CRF), or by collection from participants' GP records by a member of the I-WOTCH research team or local clinical research network support team.

Participant identification in the CRF is done through their initials and unique research number allocated at the point of entering into the study. Data are being collected from the time the potential participant is considered for entry into the research through to completion of the intervention and follow-up period (interviews are conducted after the 12 month follow up). Data is subject to a full set of validation checks and additional data checking procedures to assure quality of data entry.

All (paper) data are being held securely by the research team at WCTU for the baseline questionnaires, intervention evaluation sheets, postal questionnaires at four, eight and 12 months, weekly diary booklets, and any ad-hoc CRFs required. The database has been developed by the Programming Team at WCTU and all specifications (i.e. database variables, validation checks, screens) have been agreed between the programmer and appropriate trial staff including the trial statistician.

All essential documentation and trial records are being stored by WCTU in conformance with the applicable regulatory requirements. Access to stored information is restricted to authorised personnel only.

We will develop questionnaires to record relevant information. CRFs have been designed by Research Fellows and the Trial Manager in conjunction with our TMG (Trial Management Group) building on the expertise of the applicants. The TMG consists of project staff and co-investigators involved in the running of the day-to-day trial. Significant issues arising from management meetings are referred to the Group.

The Trial Steering Committee (TSC) has an independent chairperson. The Committee is responsible for major decisions such as a need to change the protocol for any reason, monitoring and supervising the progress of the trial, reviewing relevant information from other sources, considering recommendations from the Committee and informing and advising on all aspects of the trial.

The Data Monitoring Committee consists of independent experts with relevant clinical research and statistical experience. Confidential reports containing recruitment, protocol compliance, safety data and interim assessments of outcomes are being reviewed by the Committee. It advises the TSC as to whether there is evidence or reason why the trial should be amended or terminated.

All electronic participant-identifiable information are held on a secure, password-protected database accessible only to essential personnel. Paper forms with participant-identifiable information are held in secure, locked filing cabinets within a restricted area of WCTU. Participants are identified by a unique research number only. Direct access to source data/documents is required for trial-related monitoring. For quality assurance, the data and results are statistically checked. A full data management plan has been produced by the Trial Manager and statistician to outline the data monitoring checks required. Trial documentation and data will be archived for at least 10 years after completion of the trial.

Adverse event management

Any adverse events are reported to the trial coordinating centre by the clinical facilitators in each region within 24 hours of them becoming aware of the event. Participants will be asked if they have experienced any adverse effects while tapering opioid use at the clinical facilitator

consultations, in the weekly diaries and in questionnaire follow-up at four, eight, and 12 months; and if so, which symptoms they have experienced. Participants GP's will not be informed of any adverse events unless there are serious safety concerns and there is a chance of significant harm to the participant or others. In accordance with WCTU standard operating procedures risk assessment is completed and a trial monitoring plan produced commensurate to the risks identified.

Statistical analysis

The data will be summarised and reported in accordance with C*on*solidated *S*tandards *o*f *R*eporting *T*rials (CONSORT) guidelines for RCTs. We are using intention-to-treat analyses.(35) Hierarchical linear regression models are used to estimate the treatment effects (with 95% confidence intervals), and are adjusted for important patient-level covariates. These will be defined in the final approved statistical analysis plan which will include specific methods of analysis for all outcome variables. We have included estimation of and adjustment for group effects. If there is negligible group effect, then the usual linear regression will be used for the analysis. Any categorical data is assessed in a similar way, using logistic regression models. Pre-specified sub-group analyses examine the interaction of treatment assignment with symptoms of anxiety/depression and baseline opioid use. Analysis is conducted using formal tests of interaction.(36) This trial is not powered to identify interactions. Thus, whilst pre-specified, these analyses should be considered as no more than exploratory. We are exploring the extent to which change in opioid use, or changes in self-efficacy, mediate change in activities of daily living to gain some understanding as to whether any effects seen are the non-specific effects of the behavioural component of the intervention or they are specifically due to change in opioid usage.

Health Economic Evaluation

Published evidence and data from the COPERS study [add ref] informed the process of conceptualising the structure of a decision analytic model - representing the treatment pathway of individual's on long-term opioid therapy for non-malignant chronic pain. Data requirements to populate our model structure were used to inform the data collection strategy of the main I-WOTCH trial. The economic analysis of the I-WOTCH study will be in three stages. Firstly, published evidence and individual patient level data from the I-WOTCH internal pilot and COPERS studies will be used to populate the model structure and conduct a Bayesian value of information analysis to identify those parameters for which additional data collection is warranted. Secondly, we will conduct a *within-trial* cost-consequences analysis from the perspective of the NHS and social services. Thirdly, a *model-based* cost-utility analysis will be conducted to estimate the long-term cost-effectiveness of the I-WOTCH intervention versus best usual care. This *comprehensive iterative approach* has been tested and successfully implemented by one of the applicants in the context of a number of previous National Institute Health Research (NIHR) and Medical Research Council (MRC) funded studies.(37, 38)

Process evaluation and intervention fidelity

The process evaluation will investigate any barriers and enablers to the intervention recommendations becoming part of everyday behaviour patterns, from both the perspective of those delivering and receiving the intervention. We will collect observational data by digitally audio-recording all intervention interactions. We will analyse 10% of the recordings to assess fidelity to protocol and further investigate interaction between facilitators and participants.

We will conduct semi-structured interviews with approximately 20 participants in the intervention and 20 in the control arms. To ensure a diverse range of views, participants will

be selected purposively by age, gender, geographical location, baseline and follow-up opioid use. We will also undertake interviews with a sample of staff delivering the intervention about their experiences of teaching it including enablers and barriers.

End of trial

The end of the trial is defined as the date when the last participant completes their 12 month follow-up after randomisation. However, follow up data collection will proceed beyond this date, in particular interviews with participants contributing to the process evaluation.

Ethics and Dissemination

The University of Warwick (Research Impact Services, University of Warwick, Coventry CV4 7AL) is the Sponsor for the study. The study is being conducted in full adherence with the principles of the Declaration of Helsinki and MRC Good Clinical Practice principles and guidelines. It also complies with all applicable UK legislation and Warwick Standard Operating Procedures. All data are being stored securely and held in accordance with the Data Protection Act 2018. All identifiable data is pseudo-anonymised and treated as confidential. Patients have the choice of whether or not to participate and are given all relevant information about the study to make an informed decision. Participants are informed that they are free to withdraw from the trial at any time during any phase of the work without providing a reason and without prejudice, if they so wish. The findings will be disseminated in peer reviewed journals. We will also publish results on the study website and produce a newsletter for the study facilitators and patient participants. We will engage with NHS organisations, managers, policy makers and clinical commissioning groups to ensure effective dissemination of the findings and inform national, and international, guidance on opioid reduction in this population. Ethics approval was given by Yorkshire & The Humber - South Yorkshire Research Ethics Committee on

September 13th, 2016 (16/YH/0325). Appropriate local approvals were sought for each area in which recruitment was undertaken. The trial is being co-ordinated by the WCTU, University of Warwick.

References

1. Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. A classification of chronic pain for ICD-11. Pain. 2015;156(6):1003-7.
2. Bonica JJ. The management of pain. Philadelphia: Lea & Febiger; 1953.
3. Bridges S. Chronic Pain In: Craig, R. Mindell, J. editors. Health Survey for England 2011. Leeds: Health and Social Care Information Centre; 2012. https://catalogueicnhsuk/publications/public-health/surveys/heal-surv-eng-2011/HSE2011-Ch9-Chronic-Painpdf.
4. Els C, Kunyk D, Lappi VG, Sonnenberg B, Hagtvedt R, Sharma S, et al. Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane Reviews. Cochrane Database of Systematic Reviews. 2017(1).
5. Wersocki E, Bedson J, Chen Y, LeResche L, Dunn KM. Comprehensive systematic review of long-term opioids in women with chronic noncancer pain and associated reproductive dysfunction (hypothalamic-pituitary-gonadal axis disruption). Pain. 2017;158(1):8-16.
6. Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P, et al. Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain. The Journal of Pain. 2009;10(2):113-30.e22.
7. Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2006;174(11):1589-94.
8. Noble M, Treadwell JR, Tregear SJ, Coates VH, Wiffen PJ, Akafomo C, et al. Long-term opioid management for chronic noncancer pain. The Cochrane database of systematic reviews. 2010(1):CD006605.
9. Bedson J, Chen Y, Hayward RA, Ashworth J, Walters K, Dunn KM, et al. Trends in long-term opioid prescribing in primary care patients with musculoskeletal conditions: an observational database study. Pain. 2016;157(7):1525-31.
10. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Prescription of Long-Acting Opioids and Mortality in Patients With Chronic Noncancer Pain. JAMA. 2016;315(22):2415-23.
11. Gowing L, Ali R, White JM, Mbewe D. Buprenorphine for managing opioid withdrawal. Cochrane Database of Systematic Reviews. 2017(2).
12. Gowing L, Ali R, White JM. Opioid antagonists with minimal sedation for opioid withdrawal. Cochrane Database of Systematic Reviews. 2017(5).
13. Frank JW, Lovejoy TI, Becker WC, Morasco BJ, Koenig CJ, Hoffecker L, et al. Patient Outcomes in Dose Reduction or Discontinuation of Long-Term Opioid Therapy: A Systematic Review. Annals of internal medicine. 2017;167(3):181-91.
14. Sullivan MD, Turner JA, DiLodovico C, D'Appollonio A, Stephens K, Chan YF. Prescription Opioid Taper Support for Outpatients With Chronic Pain: A Randomized Controlled Trial. The journal of pain : official journal of the American Pain Society. 2017;18(3):308-18.

15. Sandhu H, Underwood M, Furlan AD, Noyes J, Eldabe S. What interventions are effective to taper opioids in patients with chronic pain? BMJ (Clinical research ed). 2018;362.
16. Prevention CfDCa. Guideline for Prescribing Opioids for Chronic Pain. U.S. Department of Health and Human Services.
17. Berna C, Kulich RJ, Rathmell JP. Tapering Long-term Opioid Therapy in Chronic Noncancer Pain. Mayo Clinic proceedings. 2015;90(6):828-42.
18. Berna C, Kulich RJ, Rathmell JP. Tapering Long-term Opioid Therapy in Chronic Noncancer Pain: Evidence and Recommendations for Everyday Practice. Mayo Clinic proceedings. 2015;90(6):828-42.
19. Excellence NIfHaC. British National Formulary (BNF) 2018. Available from: https://bnf.nice.org.uk/.
20. Taylor SJ, Carnes D, Homer K, Kahan BC, Hounsome N, Eldridge S, et al. Novel Three-Day, Community-Based, Nonpharmacological Group Intervention for Chronic Musculoskeletal Pain (COPERS): A Randomised Clinical Trial. 2016;13(6):e1002040.
21. Carnes D, Homer K, Underwood M, Pincus T, Rahman A, Taylor SJC. Pain management for chronic musculoskeletal conditions: the development of an evidence-based and theory-informed pain self-management course. BMJ Open. 2013;3(11).
22. Knotkova H, Fine PG, Portenoy RK. Opioid rotation: the science and the limitations of the equianalgesic dose table. Journal of pain and symptom management. 2009;38(3):426-39.
23. Medicine FoP. Dose Equivalent and Changing Opioids 2018. Available from: https://www.rcoa.ac.uk/faculty-of-pain-medicine/opioids-aware/structured-approach-to-prescribing/dose-equivalents-and-changing-opioids.
24. Ripamonti C, De Conno F, Groff L, Belzile M, Pereira J, Hanson J, et al. Equianalgesic dose/ratio between methadone and other opioid agonists in cancer pain: comparison of two clinical experiences. Annals of oncology : official journal of the European Society for Medical Oncology. 1998;9(1):79-83.
25. Lawlor PG, Turner KS, Hanson J, Bruera ED. Dose ratio between morphine and methadone in patients with cancer pain: a retrospective study. Cancer. 1998;82(6):1167-73.
26. Cowan A, Lewis JW, Macfarlane IR. Agonist and antagonist properties of buprenorphine, a new antinociceptive agent. British journal of pharmacology. 1977;60(4):537-45.
27. Furlan AD, Reardon R, Weppler C, National Opioid Use Guideline G. Opioids for chronic noncancer pain: a new Canadian practice guideline. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2010;182(9):923-30.
28. Amtmann D, Cook KF, Jensen MP, Chen WH, Choi S, Revicki D, et al. Development of a PROMIS item bank to measure pain interference. Pain. 2010;150(1):173-82.
29. Askew RL, Kim J, Chung H, Cook KF, Johnson KL, Amtmann D. Development of a crosswalk for pain interference measured by the BPI and PROMIS pain interference short form. Qual Life Res. 2013;22(10):2769-76.
30. Cook KF, Schalet BD, Kallen MA, Rutsohn JP, Cella D. Establishing a common metric for self-reported pain: linking BPI Pain Interference and SF-36 Bodily Pain Subscale scores to the PROMIS Pain Interference metric. Qual Life Res. 2015.
31. Turk DC, Dworkin RH, Allen RR, Bellamy N, Brandenburg N, Carr DB, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. Pain. 2003;106(3):337-45.
32. PAIN INTERFERENCE A brief guide to the PROMIS Pain Interference instruments. Available from:

https://www.assessmentcenter.net/documents/PROMIS%20Pain%20Interference%20Scoring%20Manual.pdf.
33. United Kingdom back pain exercise and manipulation (UK BEAM) randomised trial: effectiveness of physical treatments for back pain in primary care. BMJ (Clinical research ed). 2004;329(7479):1377.
34. Lamb SE, Hansen Z, Lall R, Castelnuovo E, Withers EJ, Nichols V, et al. Group cognitive behavioural treatment for low-back pain in primary care: a randomised controlled trial and cost-effectiveness analysis. Lancet (London, England). 2010;375(9718):916-23.
35. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ (Clinical research ed). 2010;340.
36. Brookes ST, Whitley E, Peters TJ, Mulheran PA, Egger M, Davey Smith G. Subgroup analyses in randomised controlled trials: quantifying the risks of false-positives and false-negatives. Health technology assessment (Winchester, England). 2001;5(33):1-56.
37. Ashby RL, Gabe R, Ali S, Adderley U, Bland JM, Cullum NA, et al. Clinical and cost-effectiveness of compression hosiery versus compression bandages in treatment of venous leg ulcers (Venous leg Ulcer Study IV, VenUS IV): a randomised controlled trial. Lancet (London, England). 2014;383(9920):871-9.
38. Soares MO, Dumville JC, Ashby RL, Iglesias CP, Bojke L, Adderley U, et al. Methods to assess cost-effectiveness and value of further research when data are sparse: negative-pressure wound therapy for severe pressure ulcers. Medical decision making : an international journal of the Society for Medical Decision Making. 2013;33(3):415-36.

Authors' contributions

All authors read and approved the manuscript. All authors have been involved in the study design and running of the study. HS and SE are Co-Chief Investigators and have been involved in the study design and oversee the running of the study. MU has provided input into all aspects of the study design. CT has provided input into study deign and intervention development and delivery. CA, KS and VN are leading the process evaluation. AM and CU are leading the health economics modeling and formulation. RL, KB and DM have developed the statistical analysis plan. ST, DC, JN, NT, AF and JS have provided input into the design of the I-WOTCH intervention, delivery, training and general study design. SB, ST and AR have provided input into the design of the study and clinical input. KH has provided input into study design with particular focus on outcome measures. SA, LB and EW have provided input into study design and day to day running of the study.

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Competing interests

HS is director of Health Psychology Services Ltd, providing psychological services for a range of health related conditions.

MU was Chair of the NICE accreditation advisory committee until March 2017 for which he received a fee. He is chief investigator or co-investigator on multiple previous and current research grants from the UK National Institute for Health Research, Arthritis Research UK and is a co-investigator on grants funded by the Australian NHMRC. He is an NIHR Senior Investigator. He has received travel expenses for speaking at conferences from the professional organisations hosting the conferences He is a director and shareholder of Clinvivo Ltd that provides electronic data collection for health services research. He is part of an academic partnership with Serco Ltd related to return to work initiatives. He is a co-investigator on a study receiving support in kind from Orthospace Ltd. He is an editor of the NIHR journal series, and a member of the NIHR Journal Editors Group, for which he receives a fee.

SE is investigator on a number of NIHR and industry sponsored studies. He received travel expenses for speaking at conferences from the professional organisations. SE consults for Medtronic, Abbott, Boston Scientific and Mainstay Medical, none in relation to opioids. SE is chair of the BPS Science and Research Committee. SE is deputy Chair of the NIHR CRN Anaesthesia Pain and Perioperative Medicine National Specialty Group. SE's department has received fellowship funding from Medtronic as well as nurse funding from Abbott.

AF developed an App that is sold in iTunes for US$9.99 (Opioid Manager). The App is owned by the hospital (UHN) where Dr. Furlan works, and Dr. Furlan does not retain any profits of the sales of this app for herself.

KS received grant funding as PI and CoI from NIHR for other projects. I was on the NIHR HS&DR Funding Board until January 2018.

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List of abbreviations

CONSORT - *Con*solidated *S*tandards *o*f *R*eporting *T*rials

CRF – Case Report Form

HRQoL – Health-Related Quality of Life

ICC – Inter-cluster correlation

IMMPACT - Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials

I-WOTCH – Improving the Wellbeing of People with CHronic Pain

MRC – Medical Research Council

NIHR – National Institute of Health Research

PROMIS-PI-SF-8A - Patient-Reported Outcomes Measurement Information System Pain Interference Short Form (8A)

PSA - Probabilistic Sensitivity Analysis

QALYs - Quality Adjusted Life Years

RCT – Randomised Controlled Trial

TMG – Trial Management Group

TSC – The Trial Steering Committee

WCTU – Warwick Clinical Trials Unit

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	Addressed on page number
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	5-6
	2b	All items from the World Health Organization Trial Registration Data Set	6
Protocol version	3	Date and version identifier	6
Funding	4	Sources and types of financial, material, and other support	30
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-4
	5b	Name and contact information for the trial sponsor	29
	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	26
	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)	23

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	8-9
	6b	Explanation for choice of comparators	9
Objectives	7	Specific objectives or hypotheses	9
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)	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	11
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)	11
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	13-16
	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)	15, 23
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	17
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	16-17
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	17-19
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)	10

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	20
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	20
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	21
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	21
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	21
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	21
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	21
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	15, 19 20
	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	22

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	22
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	24
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	24
	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)	24
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	23
	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	23
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	23 -24
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	24
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	27
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)	26

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	26
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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	26
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	30
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	27
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	27
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	27
	31b	Authorship eligibility guidelines and any intended use of professional writers	29
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
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	NA

*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

Testing a support programme for opioid reduction for people with chronic non-malignant pain: The I-WOTCH randomised controlled trial protocol

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Testing a support programme for opioid reduction for people with chronic non-malignant pain: The I-WOTCH randomised controlled trial protocol

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Abstract

Introduction: Chronic non-malignant pain has a major impact on the wellbeing, mood and productivity of those affected. Opioids are increasingly prescribed to manage this type of pain, but with a risk of other disabling symptoms, when their effectiveness has been questioned. This trial is designed to implement and evaluate a patient-centred intervention targeting withdrawal of strong opioids in people with chronic pain.

Methods and analysis: A pragmatic, multi–centre, randomised controlled trial will assess the clinical and cost-effectiveness of a group-based multicomponent intervention combined with individualised clinical facilitator led support for the management of chronic non-malignant pain against the control intervention (self-help booklet and relaxation CD). An embedded

process evaluation will examine fidelity of delivery and investigate experiences of the intervention. The two primary outcomes are activities of daily living (measured by PROMIS Pain Interference Short Form (8A)) and opioid use. The secondary outcomes are pain severity, quality of life, sleep quality, self-efficacy, adverse events, and NHS health care resource use. Participants are followed up at four, eight, and 12 months, with a primary endpoint of 12 months. Between-group differences will indicate effectiveness; we are looking for a difference of 3.5 points on our pain interference outcome (scale 40-77). We will undertake an NHS perspective cost-effectiveness analysis using Quality Adjusted Life Years.

Ethics: Full approval was given by Yorkshire & The Humber - South Yorkshire Research Ethics Committee on September 13th, 2016 (16/YH/0325). Appropriate local approvals were sought for each area in which recruitment was undertaken. The current protocol version is 1.6 date 19th December 2018.

Dissemination: Publication of results in peer reviewed journals will inform the scientific and clinical community. We will disseminate results to patient participants and study facilitators in a study newsletter as well as a lay summary of results on the study website.

Trial registration: This trial is registered with an International Standard Randomised Controlled Trial Number (ISRCTN) Register. ISRCTN number: 49470934 (06 Feb 2017)

Strengths and limitations

- First large multicentre randomised controlled trial in UK to test, active intervention (group based multi-component self-management programme plus one-to-one support) in comparison to control (self-help booklet and relaxation CD) in opioid tapering for those with chronic non-malignant pain.
- Recruitment is mainly through primary care, where a large population can be screened for use of strong opioids.

- The intervention is manualised, comprehensive and includes a specifically designed app used by the clinical facilitators to generate opioid tapering plans.
- The embedded process evaluation will help us understand people's experiences of the intervention and what helped or hindered its use (compared to the control group).
- The proposed best usual care method is not embedded in current NHS practice and may thus not represent usual care model.

Keywords: Chronic non-malignant pain, Opioids, Self-management, behavioural interventions, tapering, RCT, process evaluation

Introduction

Chronic pain is defined as pain that persists past normal healing time of around 12 weeks.(1, 2) and affects eight million people (15%) in England alone.(3) Around 20% of those aged 34 years old or over, and around 40% in those aged 75 years old or over, report high levels of interference with their lives from pain.(3) The common disorders contributing to this include low back pain, neck pain, osteoarthritis, neuropathic pain, fibromyalgia, chronic widespread pain, and post-surgical pain. Individuals may live with more than one of these pain disorders. While opioids are regularly prescribed for the management of chronic non-malignant pain, they are not always effective in the long term and can cause a range of adverse effects such as sedation, nausea, respiratory depression/sleep apnoea, depression, abdominal pain, overdose and even death.(4, 5) Furthermore, people on long-term opioid treatment (three months or more) report inadequate analgesia, in spite of high doses, due to the development of tolerance with reduced function, quality of life, or absence of progress toward therapeutic goals.(6-8) Yet, prescription data from the UK show that over an 11 year period (2002 to 2013) there was an increase in prescribing of the more potent controlled and long-acting, long-term opioids for

those with musculoskeletal conditions within the first 90 days of their long term episode (2.3% to 9.9%).(9) There is a pressing need for interventions to help people withdraw from strong opioids used for chronic non-malignant pain.

While much is known about the adverse effects of long-term opioid treatment (10), little is known about the economic impact of these adverse events. There are few evaluations of interventions designed to support opioid reduction. Cochrane reviews (11, 12) and randomised controlled trials (13, 14) offer some support for interventions supporting opioid withdrawal, including interdisciplinary pain management programmes, use of behavioural strategies, motivational interviewing, mindfulness and pain education, however, this is of low quality with short follow up (≤ 4 months).(15)

There are no formal UK guidelines for opioid reduction in this population. While such recommendations are currently emerging in North America (16, 17), these are based on expert consensus rather than data. There is also no clear evidence to support a particular speed of opioid tapering or the use of particular opioid drug(s) or rotating from one opioid to another. Overall, data substantiating the role of self-management and cognitive behavioural interventions in support of opioid tapering is weak and mostly applicable to the North American health systems.(17) Consequently, this trial will test an evidence-based intervention for people with chronic non-malignant pain. The intervention is designed to help patients manage pain interference, reduce individuals' opioid consumption and enhance quality of life.

Methods/Design

Trial design and objectives

The primary objective is to test the clinical and cost effectiveness of a patient-centred, group-based, multicomponent, self-management intervention for people living with chronic non-malignant pain, compared to a best usual care (i.e. the control group intervention) in a two-arm

pragmatic randomised controlled trial (Figure 1). The intervention targets withdrawal of strong opioids to assess the impact of their withdrawal on pain interference with daily living. We are running an embedded process evaluation (publication in preparation) to test fidelity to inform the interpretation of the findings and, if indicated, implications for the implementation of the intervention across the National Health Service (NHS).

Dates of study enrolment are: 17 May 2017 to 30 Jan 2019.

Trial setting

The trial is taking place in the North East, East Midlands, West Midlands and South Central areas of England. When originally planned we also intended to recruit in London. However, operational barriers meant we were unable to deliver the trial in London. The populations from which participants are drawn are broadly representative of the UK. We are recruiting participants from general practices, community pain services, local musculoskeletal services, and pharmacies. We also accept self-referrals (eligibility is checked over the phone once an expression of interest form is returned to check study criteria are met including non-cancer pain diagnosis and use of strong opioids). All medications reported on the baseline questionnaire are checked again with the participant at time to consent. Recruitment sites are clustered by reasonable geographical proximity to a treatment site and people in one locality are approached accordingly so that the intervention groups can be populated in a timely manner.

Box 1 Eligibility criteria

Inclusion criteria	*Exclusion criteria*
• Provision of written informed consent • Aged 18 years old or above • Using opioids for chronic non-malignant pain • Using strong opioids for at least three months • Using strong opioids on most days in the preceding month • Fluent in written and spoken English • Able to attend group sessions • Willingness for GP to be informed of participation	• Regular use of injected opioid drugs • Chronic headache as the dominant painful disorder • Serious mental health problems that preclude participation in a group intervention • Previous entry or randomisation in the present trial • Participation in a clinical trial of an investigational medicinal product in the last 90 days • Pregnant at time of eligibility assessment, or actively trying to become pregnant.[a] • People receiving strong opioid for the management of pain due to active malignant disease
[a a]Added as exclusion criteria from 15/11/2018	

For the purpose of this study, we define strong opioids using the British National Formulary. Thus, we are recruiting participants taking any of the following analgesia: buprenorphine, dipipanone, morphine, diamorphine, fentanyl, hydromorphone, methadone, oxycodone, papaveretum, pentazocine, pethidine, tapentadol or tramadol.(18) Although in some jurisdictions tramadol is considered to be a weak opioid the BNF classifies it as a strong opioid.

Recruitment procedures

1. (Primary care) electronic screening of GP records: GP practice lists are searched electronically to identify people (aged 18 years or over), who have been prescribed strong opioids on more than one occasion in the previous 3 to 6 months and in the previous 0 to 3 months as indicated by their health record and not in a care home or house bound. The practice then screens the list of those identified from the first search to exclude patients taking strong opioids for malignant pain or who should not be approached for other reasons, including those

at risk, vulnerable, or not suitable for a group-based intervention. Those who are using methadone for purposes other than to manage chronic pain are not approached.

2. Referred to the study by their GP or healthcare professionals at pain clinics and musculoskeletal physiotherapy clinics. GPs and healthcare professionals at pain clinics and musculoskeletal physiotherapy clinics can also refer potential participants by giving them an information pack on the study and an expression of interest form.

3. Posters advertising details of the study are displayed in prominent areas of GP surgeries, pharmacies, pain clinics and musculoskeletal physiotherapy clinics. The posters contain information about the study, including contact details for the study team.

Eligibility and informed consent

Once we receive an expression of interest form from a potential participant (with contact details), a member of the study team contacts them by telephone to check their eligibility for the study, using the inclusion and exclusion criteria as a checklist (Box 1). Pregnancy or actively trying for pregnancy was included as an exclusion from 15/11/2018. Following a query from a potential participant we identified some evidence, from the addiction literature that abrupt opioid withdrawal may trigger miscarriages and stillbirths.(19, 20) There is no clear evidence on how to taper opioids in pregnancy and detoxification is not recommended as a treatment intervention due to limited evidence available, low completion rates of detoxification and high rates of relapse.(21)

During this telephone check the study team give a brief background as to why the study is being done and specifically the aims of opioid reduction and study design. At this stage of enrolment commitment to opioid dose reduction is not mandatory, the aim is to give potential participants

as much information as possible and answer any questions they may have. An anonymised screening log is kept, detailing all those screened and reasons for exclusion. Potential participants (those who are eligible) are then sent a study pack in the post containing an I-WOTCH cover letter, participant information sheet, trial consent form (supplementary file), baseline questionnaire, and pre-addressed envelope. Upon receipt of a signed consent form and completed questionnaire, a designated member of the study team performs a final telephone eligibility check on medications reported by the patient in the baseline questionnaire. If the medications meet the eligibility criteria and consent is deemed to be valid and informed, the consent form is counter-signed by the appropriately trained member of the study team and a copy of the completed form is sent to the participant and to the participant's GP. Participants are informed that if they decline to take part in the study or are found to be ineligible there is no impact on their usual form of care or access to opioid medication. Where possible, participants are randomised in batches of 24 to ensure adequate group sizes. Once they are randomised they are sent a letter informing them of this with details of the group session (time and venue) if they are randomised into the intervention arm. There is no further checking or consent at this point.

Experimental intervention

I-WOTCH is an 8-10 week programme with a mixture of group sessions (facilitated by a trained I-WOTCH clinical facilitator, usually a nurse, and a trained lay person with chronic pain and experience of opioid tapering, or an I-WOTCH trained allied health-care professional), two one-to-one consultations and two telephone calls with the I-WOTCH trained clinical facilitator. The programme is adapted from a previously tested intervention used for the self-management of chronic pain.(22, 23) All those randomised to the I-WOTCH intervention in a locality are invited to join day one of the next available programme. Should

no group be available, or if a participant withdraws from the group based intervention, they are sent all of the written material that they would have received had they attended the group. Attendance at Day One is mandatory for accessing subsequent elements of the programme.

One to one clinical facilitator consultations

Between Day Two and Day Three of the group based sessions, participants attend a face to face, consultation with the I-WOTCH trained clinical facilitator. This is an opportunity for the clinical facilitator to explore opioid tapering experiences with participants, including thoughts, motivation, perceived challenges and opportunities, and to collaboratively develop realistic tapering goals adapted to the participant's circumstances. The clinical facilitators are trained to use motivational interviewing skills to facilitate discussion. After Day Three participants receive two telephone consultations (approximately 30 minutes each) to discuss progress with the tapering and to identify the need for other support during withdrawal. They also receive a final face face-to to-face consultation to (i) reflect on progress, (ii) recap over self-management skills covered in the group sessions, (iii) review and re-set goals and objectives, and (iv) assess future needs for support.

I-WOTCH tapering app to generate the opioid tapering plan

We have developed a tapering app to be used by the I-WOTCH clinical facilitators in the one to one consultations to generate the tapering plan. The app was developed within the programming team at Warwick Clinical Trials Unit with clinical expertise guided by SE. The App facilitates calculations of tapering regimes, as well equianalgesic doses of systemic opioids when switching between opioid preparations is necessary. During our preparation for the study and design of the app we uncovered a discrepancy between a number of existing equianalgesic opioid tables.(24) For the purposes of opioid tapering we used the Faculty of Pain Medicine Equianalgesic table (https://www.rcoa.ac.uk/faculty-of-pain-medicine/opioids-

aware/structured-approach-to-prescribing/dose-equivalents-and-changing-opioids) for our calculation.(25) We supplemented this with reviews of the individual drugs' Summary of product characteristics (SPC) and other sources where needed.(26, 27) For the purposes of managing changes in medication during the taper, individual variability is taken into account. Once the tapering plan is generated a paper copy is given to the participant and the electronic data is sent to the study team for checking and filing. All tapering plans generated are checked by a clinician for accuracy (SE or JN). A paper copy is sent to the participant's GP for their records.

Opioid tapering procedures

Participants are tapered on their drug of presentation. Opioid rotation is only recommended for participants who have reached the lowest dose of a transdermal patch preparation. For example, in cases of participants presenting on fentanyl transdermal patches these are tapered in decrement of 12 mcg/hr patches, and an oral formulation of alternative opioid with equianalgesic potency introduced when the lowest increment of the patch is reached.(28) Participants on buprenorphine patches are weaned in decrements of the patches with no substitution due to its agonist/ antagonist action.(29) The nurses make every effort to encourage participants to stick to the suggested tapering schedule. Nevertheless, there is an element of negotiation about speed, if any, of dose reduction.

We are using a regimen based on the Mayo Clinic experience as it provides some evidence to support the notion of slow tapering and is unlikely to be associated with severe withdrawal symptoms and therefore likely to facilitate adherence.(28) This consists of a 10% decrease of the original dose every 5-7 days until 30% of the original dose is reached. This is followed by a weekly decrease by 10% of the remaining dose. The 10% may be rounded up or down to suit

prescribing. We are providing training in equianalgesic dose calculation as well as an electronic means of calculating. People utilising opioids as rescue analgesia, at a frequency of less than one dose per day, do not require a formal tapering regime but are still being supported to completely withdraw from opioids.

Facilitator training

I-WOTCH facilitators (clinical and lay) attend a two day training course delivered by HS and JS (experienced in the design and delivery of the intervention) to deliver the intervention. Over the two days the facilitators are taught how to deliver each of the topics, as well as given an opportunity to experience the mindfulness and relaxation practice which is a part of the programme. In addition they are also taught group facilitation skills and procedures to follow within the study. The I-WOTCH clinical facilitators also attend a third day of training, during which they are given further opioid education, and trained in how to taper, use of the I-WOTCH APP, motivational interviewing and study procedures for the one-to-one consultations.

We have adapted a comprehensive facilitator's manual and training programme used in a previous trial on the management of chronic pain (23) to facilitate delivery of the I-WOTCH intervention (in preparation). The adaptations have been formed through literature, piloting of the intervention and input from lay people (those with chronic pain and experience of opioid use). The manual is acting as a guide and a reference point for the all facilitators throughout the intervention.

Adaptations and development of the intervention has included: structuring the programme to include opioid education as well as pain education, and integrating these throughout the programme. Specific examples and case studies related to opioid tapering and pain have been

used, mindfulness and relaxation Compact Discs (CDs) created, and a video (focused on pain and opioid education) has been produced for participants. Clips of the video are integrated into the group programme to illustrate specific topics such as pain education, challenging unhelpful thoughts and fear related to opioid tapering and withdrawal. Participants are given the full video on a Digital Versatile Disc (DVD) to watch with their friends and family. Having the DVD allows the participant to watch it in their own time and consolidate the information learnt on the programme. Specially designed handouts are given to participants at the end of each group day summarising key topics discussed. Further details of the intervention and its theoretical framework used to design are to be reported elsewhere.

Control intervention

Those randomised to the control group will receive augmented usual care, including two participant-facing components: a hard copy of the I-WOTCH adapted 'My Opioid Manager' booklet, and a relaxation CD with instructions on its use. 'My Opioid Manager' was developed in Canada (Toronto Rehabilitation Institute) specifically for people using opioid drugs for chronic non-cancer pain. It is a self-help guide that contains information about opioids and provides guidance about setting goals, issues the participant may encounter, tapering, and non-opioid options for management of chronic pain. It is based on the 2010 Canadian Opioid guideline of opioids for chronic non-cancer pain.(30)

Compliance

For the intervention, we are recording the number of sessions that each participant attends, including the follow-up calls completed. Assurance checks through the study also include the integrity of randomisation, study entry procedures and data collection.

Study outcomes

Primary outcome: activities of daily living

Our primary clinical outcome is the Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Interference Short Form (8A) (PROMIS-PI-SF-8A) (31). This is an eight-item generic self-reported measure, which assesses the consequences of pain on relevant aspects of an individual's life and key activities of daily living: engagement with social, cognitive, emotional, physical, and recreational practices. The PROMIS-PI-SF-8A raw score ranges from 4-80 which is then standardised to give a score ranging from 40.7-77, with higher scores indicating worse outcome. The PROMIS-PI measures the same construct as two legacy pain interference measures (Brief Pain Inventory Pain Interference subscale and the SF-36 Bodily Pain subscale), supporting the calculation of a common metric.(32, 33).

As originally designed, we proposed pain interference as a single primary outcome to ensure we could recruit sufficient participants. However, how the intervention might affect this directly through its behavioural and educational component and how there might be indirect effects through changing opioid use is unclear. It is possible, for example, that the intervention has a good effect upon opioid use but little effect on pain interference. In this situation the potential long-term benefits of opioid reduction might justify claiming a positive result from the trial. During the later stages of recruitment, it became clear we had capacity, and sufficient interest from practices and potential participants to exceed our planned target. This allowed us to add opioid use as a pre-specified second primary outcome.

Our main outcome measure for opioid use is the mean difference in morphine equivalent dose in the four weeks prior to one-year follow-up expressed as mg equivalents of morphine per day. In ongoing work we are reviewing morphine equivalence tables before making a final

decision on which set of equivalence values to use for this analysis. For sensitivity analyses, we will use alternative published values for equianalgesic doses of opioids to ensure that our findings are robust if different weightings are used. For secondary analyses, we are comparing proportions achieving a complete withdrawal and proportions of responders, defined as ≥50% reduction in morphine equivalent doses taken, between intervention and control groups.

While our study entry criterion is participant reported use of strong opioids on most days in the preceding four weeks, our continuous measure of opioid use is mean morphine equivalents of opioid used in the preceding four weeks. This includes all opioids consumed, including any weak or as required opioids.

Self-reported data on opioid use are being collected at baseline, four, eight, and 12 months following randomisation via postal follow-up. At baseline, one postal reminder is sent. At four, eight, and 12 months a postal reminder is sent. In the event that no response is obtained from the postal reminder at four, eight, or 12 months, we contact the participant by phone and collect our primary clinical outcome, opioid use, and EQ-5D-5L(34) over the phone. Participants complete a weekly diary that includes the EQ-5D-5L (34) and the Short Opioid Withdrawal Scale (35) for the first four months after randomisation.

Secondary outcomes

Our package of other secondary outcomes and process measures is informed by the consensus recommendations for core outcome domains for trials of the efficacy and effectiveness of treatments for chronic pain by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group.(36) All outcome measures are presented in Table 1 with data collection time points.

Table 1 Outcomes measures and time points

Outcome measure	Baseline	4 months	8 months	12 months
Demographic data	x			
PROMIS Pain Interference Short Form (8A) (31)	x	x	x	x
Self-reported opioid use (mean morphine equivalents of opioid used in the preceding four weeks)	x	x	x	x
Opioid prescription from GP records				x
EQ-5D-5L (34)	x	x	x	x
SF 12 V2 (37)	x	x	x	x
Short Opioid Withdrawal Scale (ShOWS) (35)	x	x	x	x
PROMIS Pain Intensity Short-Form (3A) (32, 33)	x	x	x	x
Pittsburgh Sleep Quality Index (PSQI) (38)	x	x	x	x
Hospital Anxiety and Depression Scale (39)	x	x	x	x
Pain Self Efficacy Questionnaire (PSEQ) (40)	x	x	x	x
Participant ratings of global improvement and satisfaction with treatment Patient Global Impression of Change	x	x	x	x
Symptoms and adverse events Passive capture of spontaneously reported adverse events and symptoms and use of open-ended prompts	x	x	x	x

Power and sample size

For the purposes of our original sample size calculation we used our primary clinical outcome measure, the PROMIS-PI-SF-8A.(31) Using the PROMIS primary outcome, participants in the control arm are likely to obtain a mean score of 50, SD 10.(41) A sample size of 346 participants is required to show a difference of 3.5 points on PROMIS-PI-SF-8A (standardised mean difference of 0.35) at 5% significance with 90% power. There may, however, be

clustering effects by groups in the intervention arm. We do not have any data from similar studies to inform an estimate of the intra-cluster correlation (ICC). Our recent experience across multiple studies of group interventions has been that such effects are trivial or negligible. (22, 42, 43) Despite this, assuming a relatively modest ICC of 0.01 and assuming, on average, that 10 participants per group provide one year outcome data, we would require 374 patients. Allowing for 20% loss to follow-up (whilst striving for 10%) we planned to recruit 468 participants. We subsequently changed the significance level to 2.5% to allow for two primary outcomes (PROMIS –PI-SF-8A and opioid use) with effect size of similar magnitude, and adjusted the inflation factor for clustering to reflect actual group sizes. Our final recruitment target was 542 participants. Experience in similar studies is that, towards the end of recruitment, there can be a need to over-recruit slightly more people than originally projected to ensure the final intervention groups are adequately populated.

Randomisation methods and blinding procedures

Patients are randomised in a 1:1 ratio to either the I-WOTCH intervention or best usual care arms. Randomisation procedures are being performed at The Warwick Clinical Trials Unit (WCTU). Where possible randomisations are carried out by a member of staff who is not a core member of the I-WOTCH team. The method of randomisation is computer generated using WCTU randomisation systems developed by the WCTU Programmers. There is no allocation concealment as the person conducting the randomisation is also entering baseline data prior to randomisation. All baseline data are being collected prior to randomisation. Where possible any data collected from GP records is being done by staff blind to treatment allocation. Routine data sources such as GP prescribing data are also collected.

To ensure that we populate the groups, we are clustering groups of four-five geographically proximate practices with approximately 50,000 patients to launch recruitment at around the same time. We are then randomising participants when we have sufficient participants to populate a group in batches of around 24 participants to minimise time between randomisation and the start of the intervention. We aim to randomise within two weeks of the start of the group. This ensures exposure time to the two interventions is as similar as possible. We anticipate the number of people in a group to between 10 and 12 participants. However due to the pragmatic nature of the trial and the possibility that participants may not turn up on the day of the group, we will run the group with a minimum of two people. We will record attendance and the number of people in each group for each day. Randomisation has been stratified by group (Groups 1-35), baseline pain severity (PROMIS 3A score: Low pain=3-8, High pain=9-15) and baseline opioid use (Morphine equivalent dose: 0-29, 30-59, 60-89, 90-119, 120-149, 150+).

Data management

Data for individual participants are being collected via participant-completed questionnaires, by clinical facilitator-completed Case Report Forms (CRF), or by collection from participants' GP records by a member of the I-WOTCH research team or local clinical research network support team.

Participant identification in the CRF is done through their initials and unique research number allocated at the point of entering into the study. Data are being collected from the time the potential participant is considered for entry into the research through to completion of the intervention and follow-up period (interviews are conducted after the 12 month follow up).

Data are subject to a full set of validation checks and additional data checking procedures to assure quality of data entry.

All (paper) data are being held securely by the research team at WCTU for the baseline questionnaires, intervention evaluation sheets, postal questionnaires at four, eight and 12 months, weekly diary booklets, and any ad-hoc CRFs required. The database has been developed by the Programming Team at WCTU and all specifications (i.e. database variables, validation checks, screens) have been agreed between the programmer and appropriate trial staff including the trial statistician.

All essential documentation and trial records are being stored by WCTU in conformance with the applicable regulatory requirements. Access to stored information is restricted to authorised personnel only.

We developed questionnaires to record relevant information. CRFs have been designed by Research Fellows and the Trial Manager in conjunction with our TMG (Trial Management Group) building on the expertise of the applicants. The TMG consists of project staff and co-investigators involved in the running of the day-to-day trial. Significant issues arising from management meetings are referred to the Group.

The Trial Steering Committee (TSC) has an independent chairperson. The Committee is responsible for major decisions such as a need to change the protocol for any reason, monitoring and supervising the progress of the trial, reviewing relevant information from other sources, considering recommendations from the Committee and informing and advising on all aspects of the trial.

The Data Monitoring Committee (DMC) consists of independent experts with relevant clinical research and statistical experience. Confidential reports containing recruitment, protocol compliance, safety data and interim assessments of outcomes are being reviewed by the Committee. The DMC is responsible for monitoring data and making recommendations to the TSC on whether there are any ethical or safety reasons why the trial should be amended or terminated. The DMC will determine if additional interim analyses of trial data should be undertaken, and if so, when. The DMC will meet early on in the trial and then annually or more frequently if necessary. The final DMC meeting will be held upon the availability of the final trial data.

Both the Trial Steering Committee and the Data Monitoring Committee follow Warwick CTU standard operating procedures.

All electronic participant-identifiable information are held on a secure, password-protected database accessible only to essential personnel. Paper forms with participant-identifiable information are held in secure, locked filing cabinets within a restricted area of WCTU. Participants are identified by a unique research number only. Direct access to source data/documents is required for trial-related monitoring. For quality assurance, the data and results are statistically checked. A full data management plan has been produced by the Trial Manager and statistician to outline the data monitoring checks required. Trial documentation and data will be archived for at least 10 years after completion of the trial.

Adverse event management

Any adverse events are reported to the trial coordinating centre by the clinical facilitators in each region within 24 hours of them becoming aware of the event. Participants will be asked if they have experienced any adverse effects while tapering opioid use at the clinical facilitator

consultations, in the weekly diaries and in questionnaire follow-up at four, eight, and 12 months; and if so, which symptoms they have experienced. Participants GP's will not be informed of any adverse events unless there are serious safety concerns and there is a chance of significant harm to the participant or others. In accordance with WCTU standard operating procedures risk assessment is completed and a trial monitoring plan produced commensurate to the risks identified.

Statistical analysis

The data will be summarised and reported in accordance with C*on*solidated *S*tandards *o*f *R*eporting *T*rials (CONSORT) guidelines for RCTs. We are using intention-to-treat analyses.(44) Hierarchical linear regression models are used to estimate the treatment effects (with 95% confidence intervals), and are adjusted for important patient-level covariates. These will be defined in the final approved statistical analysis plan which will include specific methods of analysis for all outcome variables. We have included estimation of and adjustment for group effects. If there is negligible group effect, then the usual linear regression will be used for the analysis. Any categorical data is assessed in a similar way, using logistic regression models. Pre-specified sub-group analyses examine the interaction of treatment assignment with symptoms of anxiety/depression and baseline opioid use. Analysis is conducted using formal tests of interaction.(45) This trial is not powered to identify interactions. Thus, whilst pre-specified, these analyses should be considered as no more than exploratory. We are exploring the extent to which change in opioid use, or changes in self-efficacy, mediate change in activities of daily living to gain some understanding as to whether any effects seen are the non-specific effects of the behavioural component of the intervention or they are specifically due to change in opioid usage.

Health Economic Evaluation

Published evidence and data from the COPERS study(23), informed the process of conceptualising the structure of a decision analytic model - representing the treatment pathway of individual's on long-term opioid therapy for non-malignant chronic pain. Data requirements to populate our model structure were used to inform the data collection strategy of the main I-WOTCH trial. The economic analysis of the I-WOTCH study will be in three stages. Firstly, published evidence and individual patient level data from the I-WOTCH internal pilot and COPERS studies will be used to populate the model structure and conduct a Bayesian value of information analysis to identify those parameters for which additional data collection is warranted. Secondly, we will conduct a within-trial cost-consequences analysis from the perspective of the NHS and social services. Thirdly, a model-based cost-utility analysis will be conducted to estimate the long-term cost-effectiveness of the I-WOTCH intervention versus best usual care. This comprehensive iterative approach has been tested and successfully implemented by one of the applicants in the context of a number of previous National Institute Health Research (46) and Medical Research Council (MRC) funded studies.(47, 48)

Process evaluation and intervention fidelity

The process evaluation will investigate any barriers and enablers to the intervention recommendations becoming part of everyday behaviour patterns, from both the perspective of those delivering and receiving the intervention. We will collect observational data by digitally audio-recording all intervention interactions. We will analyse 10% of the recordings to assess fidelity to protocol and further investigate interaction between facilitators and participants. Process evaluation includes outcomes around motivation, expectation and confidence in ability to reduce opioids.

We will conduct semi-structured interviews with approximately 20 participants in the intervention and 20 in the control arms. To ensure a diverse range of views, participants will be selected purposively by age, gender, geographical location, baseline and follow-up opioid use. We will also undertake interviews with a sample of staff delivering the intervention about their experiences of teaching it including enablers and barriers. More information can be found in the protocol for the process evaluation.(49)

End of trial

The end of the trial is defined as the date when the last participant completes their 12 month follow-up after randomisation. However, follow up data collection will proceed beyond this date, in particular interviews with participants contributing to the process evaluation.

Patient and Public involvement (PPI)

Two lay advisers with chronic pain, withdrawal of opioids and substantive experience of clinical trial research have been fully involved in the development of the study and intervention. One remains an active member of the study team (CT), the other took retirement from her role during the study (SB). Both lay advisors were recruited via Universities/User Teaching and Research Action Partnership (UNTRAP).

Additionally, prior to receiving funding for the study we ran two meetings at the North East and North Cumbria Clinical Research Network. The meetings included volunteers (n=19) who were people living with chronic non-malignant pain, some of whom had discontinued opioids without medical supervision, others who had discontinued with GP or pain clinic supervision. Both events allowed discussion and input into the design of the intervention structure; (group days and one to one support) length of the intervention and content to be covered based on education, motivation, support and providing alternative pain management techniques. The meetings also allowed discussion of the design of the study which included randomisation, best usual care intervention, recruitment processes as well as outcome measures to collect. PPI

participants did not feel the intervention or outcome measures were burdensome and welcomed both arms of the intervention as support for opioid tapering. They also supported the idea of having a lay person with chronic pain with experience of opioid withdrawal to deliver the group days in the active intervention alongside a clinician. In addition to the PPI events, and again prior to receiving funding for the study, we were able to pilot the facilitator training and delivery of the I-WOTCH intervention as part of the Hambleton and Richmond, clinical commissioning group funded community pain service in the North East. This allowed feedback into what worked well and recommendations for changes and improvements.

We will disseminate findings of the main study for the patient participants and group facilitators through a study newsletter and post a lay summary on the study website. In partnership with our PPI representatives we will also feedback to the organisations they represent such as UNTRAP and the PPI events as part of the North East and North Cumbria Clinical Research Network.

Ethics and Dissemination

The University of Warwick (Research Impact Services, University of Warwick, Coventry CV4 7AL) is the Sponsor for the study. The study is being conducted in full adherence with the principles of the Declaration of Helsinki and MRC Good Clinical Practice principles and guidelines. It also complies with all applicable UK legislation and Warwick Standard Operating Procedures. All data are being stored securely and held in accordance with the Data Protection Act 2018. All identifiable data are pseudo-anonymised and treated as confidential. Patients have the choice of whether or not to participate and are given all relevant information about the study to make an informed decision. Participants are informed that they are free to withdraw from the trial at any time during any phase of the work without providing a reason and without prejudice, if they so wish. The findings will be disseminated in peer reviewed journals. We will

also publish results on the study website and produce a newsletter for the study facilitators and patient participants. We will engage with NHS organisations, managers, policy makers and clinical commissioning groups to ensure effective dissemination of the findings and inform national, and international, guidance on opioid reduction in this population. Ethics approval was given by Yorkshire & The Humber - South Yorkshire Research Ethics Committee on September 13th, 2016 (16/YH/0325). Appropriate local approvals were sought for each area in which recruitment was undertaken. The trial is being co-ordinated by the WCTU, University of Warwick.

References

1. Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. A classification of chronic pain for ICD-11. Pain. 2015;156(6):1003-7.
2. Bonica JJ. The management of pain. Philadelphia: Lea & Febiger; 1953.
3. Bridges S. Chronic Pain In: Craig, R. Mindell, J. editors. Health Survey for England 2011. Leeds: Health and Social Care Information Centre; 2012. https://catalogueicnhsuk/publications/public-health/surveys/heal-surv-eng-2011/HSE2011-Ch9-Chronic-Painpdf.
4. Els C, Kunyk D, Lappi VG, Sonnenberg B, Hagtvedt R, Sharma S, et al. Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane Reviews. Cochrane Database of Systematic Reviews. 2017(1).
5. Wersocki E, Bedson J, Chen Y, LeResche L, Dunn KM. Comprehensive systematic review of long-term opioids in women with chronic noncancer pain and associated reproductive dysfunction (hypothalamic-pituitary-gonadal axis disruption). Pain. 2017;158(1):8-16.
6. Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P, et al. Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain. The Journal of Pain. 2009;10(2):113-30.e22.
7. Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2006;174(11):1589-94.
8. Noble M, Treadwell JR, Tregear SJ, Coates VH, Wiffen PJ, Akafomo C, et al. Long-term opioid management for chronic noncancer pain. The Cochrane database of systematic reviews. 2010(1):CD006605.
9. Bedson J, Chen Y, Hayward RA, Ashworth J, Walters K, Dunn KM, et al. Trends in long-term opioid prescribing in primary care patients with musculoskeletal conditions: an observational database study. Pain. 2016;157(7):1525-31.
10. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Prescription of Long-Acting Opioids and Mortality in Patients With Chronic Noncancer Pain. JAMA. 2016;315(22):2415-23.

11. Gowing L, Ali R, White JM, Mbewe D. Buprenorphine for managing opioid withdrawal. Cochrane Database of Systematic Reviews. 2017(2).
12. Gowing L, Ali R, White JM. Opioid antagonists with minimal sedation for opioid withdrawal. Cochrane Database of Systematic Reviews. 2017(5).
13. Frank JW, Lovejoy TI, Becker WC, Morasco BJ, Koenig CJ, Hoffecker L, et al. Patient Outcomes in Dose Reduction or Discontinuation of Long-Term Opioid Therapy: A Systematic Review. Annals of internal medicine. 2017;167(3):181-91.
14. Sullivan MD, Turner JA, DiLodovico C, D'Appollonio A, Stephens K, Chan YF. Prescription Opioid Taper Support for Outpatients With Chronic Pain: A Randomized Controlled Trial. The journal of pain : official journal of the American Pain Society. 2017;18(3):308-18.
15. Sandhu H, Underwood M, Furlan AD, Noyes J, Eldabe S. What interventions are effective to taper opioids in patients with chronic pain? BMJ (Clinical research ed). 2018;362.
16. Prevention CfDCa. Guideline for Prescribing Opioids for Chronic Pain. U.S. Department of Health and Human Services.
17. Berna C, Kulich RJ, Rathmell JP. Tapering Long-term Opioid Therapy in Chronic Noncancer Pain. Mayo Clinic proceedings. 2015;90(6):828-42.
18. Excellence NIfHaC. British National Formulary (BNF) 2018 [Available from: https://bnf.nice.org.uk/.
19. McCarthy JJ, Leamon MH, Finnegan LP, Fassbender C. Opioid dependence and pregnancy: minimizing stress on the fetal brain. American journal of obstetrics and gynecology. 2017;216(3):226-31.
20. Saia KA, Schiff D, Wachman EM, Mehta P, Vilkins A, Sia M, et al. Caring for Pregnant Women with Opioid Use Disorder in the USA: Expanding and Improving Treatment. 2016;5(3):257-63.
21. Terplan M, Laird HJ, Hand DJ, Wright TE, Premkumar A, Martin CE, et al. Opioid Detoxification During Pregnancy: A Systematic Review. Obstetrics and gynecology. 2018;131(5):803-14.
22. Taylor SJ, Carnes D, Homer K, Kahan BC, Hounsome N, Eldridge S, et al. Novel Three-Day, Community-Based, Nonpharmacological Group Intervention for Chronic Musculoskeletal Pain (COPERS): A Randomised Clinical Trial. 2016;13(6):e1002040.
23. Carnes D, Homer K, Underwood M, Pincus T, Rahman A, Taylor SJC. Pain management for chronic musculoskeletal conditions: the development of an evidence-based and theory-informed pain self-management course. BMJ Open. 2013;3(11).
24. Knotkova H, Fine PG, Portenoy RK. Opioid rotation: the science and the limitations of the equianalgesic dose table. J Pain Symptom Manage. 2009;38(3):426-39.
25. Medicine FoP. Dose Equivalent and Changing Opioids 2018 [Available from: https://www.rcoa.ac.uk/faculty-of-pain-medicine/opioids-aware/structured-approach-to-prescribing/dose-equivalents-and-changing-opioids.
26. Ripamonti C, De Conno F, Groff L, Belzile M, Pereira J, Hanson J, et al. Equianalgesic dose/ratio between methadone and other opioid agonists in cancer pain: comparison of two clinical experiences. Annals of oncology : official journal of the European Society for Medical Oncology. 1998;9(1):79-83.
27. Lawlor PG, Turner KS, Hanson J, Bruera ED. Dose ratio between morphine and methadone in patients with cancer pain: a retrospective study. Cancer. 1998;82(6):1167-73.
28. Berna C, Kulich RJ, Rathmell JP. Tapering Long-term Opioid Therapy in Chronic Noncancer Pain: Evidence and Recommendations for Everyday Practice. Mayo Clinic proceedings. 2015;90(6):828-42.

29. Cowan A, Lewis JW, Macfarlane IR. Agonist and antagonist properties of buprenorphine, a new antinociceptive agent. British journal of pharmacology. 1977;60(4):537-45.
30. Furlan AD, Reardon R, Weppler C, National Opioid Use Guideline G. Opioids for chronic noncancer pain: a new Canadian practice guideline. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2010;182(9):923-30.
31. Amtmann D, Cook KF, Jensen MP, Chen WH, Choi S, Revicki D, et al. Development of a PROMIS item bank to measure pain interference. Pain. 2010;150(1):173-82.
32. Askew RL, Kim J, Chung H, Cook KF, Johnson KL, Amtmann D. Development of a crosswalk for pain interference measured by the BPI and PROMIS pain interference short form. Qual Life Res. 2013;22(10):2769-76.
33. Cook KF, Schalet BD, Kallen MA, Rutsohn JP, Cella D. Establishing a common metric for self-reported pain: linking BPI Pain Interference and SF-36 Bodily Pain Subscale scores to the PROMIS Pain Interference metric. Qual Life Res. 2015.
34. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.
35. Gossop M. The development of a Short Opiate Withdrawal Scale (SOWS). Addictive behaviors. 1990;15(5):487-90.
36. Turk DC, Dworkin RH, Allen RR, Bellamy N, Brandenburg N, Carr DB, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. Pain. 2003;106(3):337-45.
37. Gandek B, Ware JE, Aaronson NK, Apolone G, Bjorner JB, Brazier JE, et al. Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. International Quality of Life Assessment. J Clin Epidemiol. 1998;51(11):1171-8.
38. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry research. 1989;28(2):193-213.
39. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta psychiatrica Scandinavica. 1983;67(6):361-70.
40. Nicholas MK. The pain self-efficacy questionnaire: Taking pain into account. European journal of pain (London, England). 2007;11(2):153-63.
41. PAIN INTERFERENCE A brief guide to the PROMIS Pain Interference instruments [Available from: https://www.assessmentcenter.net/documents/PROMIS%20Pain%20Interference%20Scoring%20Manual.pdf.
42. United Kingdom back pain exercise and manipulation (UK BEAM) randomised trial: effectiveness of physical treatments for back pain in primary care. BMJ (Clinical research ed). 2004;329(7479):1377.
43. Lamb SE, Hansen Z, Lall R, Castelnuovo E, Withers EJ, Nichols V, et al. Group cognitive behavioural treatment for low-back pain in primary care: a randomised controlled trial and cost-effectiveness analysis. Lancet (London, England). 2010;375(9718):916-23.
44. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ (Clinical research ed). 2010;340.
45. Brookes ST, Whitley E, Peters TJ, Mulheran PA, Egger M, Davey Smith G. Subgroup analyses in randomised controlled trials: quantifying the risks of false-positives and false-negatives. Health technology assessment (Winchester, England). 2001;5(33):1-56.

46. Pilkington SA, Emmett C, Knowles CH, Mason J, Yiannakou Y, group NCw, et al. Surgery for constipation: systematic review and practice recommendations: Results V: Sacral Nerve Stimulation. Colorectal Dis. 2017;19 Suppl 3:92-100.
47. Ashby RL, Gabe R, Ali S, Adderley U, Bland JM, Cullum NA, et al. Clinical and cost-effectiveness of compression hosiery versus compression bandages in treatment of venous leg ulcers (Venous leg Ulcer Study IV, VenUS IV): a randomised controlled trial. Lancet (London, England). 2014;383(9920):871-9.
48. Soares MO, Dumville JC, Ashby RL, Iglesias CP, Bojke L, Adderley U, et al. Methods to assess cost-effectiveness and value of further research when data are sparse: negative-pressure wound therapy for severe pressure ulcers. Medical decision making : an international journal of the Society for Medical Decision Making. 2013;33(3):415-36.
49. Nichols V, Abraham C, Eldabe S, Sandhu H, Underwood M, Seers K, et al. Process evaluation protocol for the IWOTCH study: An opioid tapering support programme for people with chronic non-malignant pain. . BMJ Open. 2019;Submitted to BMJopen awaiting editorial decision 14-5-19.

Authors' contributions

All authors read and approved the manuscript. All authors have been involved in the study design and running of the study. HS and SE are Co-Chief Investigators and have been involved in the study design and oversee the running of the study. MU has provided input into all aspects of the study design. CT has provided input into study deign and intervention development and delivery. CA, KS and VN are leading the process evaluation. AM and CU are leading the health economics modeling and formulation. RL, KB and DM have developed the statistical analysis plan. ST, DC, JN, NT, AF and JS have provided input into the design of the I-WOTCH intervention, delivery, training and general study design. SB, ST and AR have provided input into the design of the study and clinical input. KH has provided input into study design with particular focus on outcome measures. SA, LB and EW have provided input into study design and day to day running of the study.

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those of the authors and do not necessarily reflect those of the HTA, NIHR, NHS or the Department of Health.

Data Availability:

The final trial dataset will be available for sharing with other research teams after publication of the main trial paper. All data will be anonymised and provided after assessment of any further research proposals and evidence of ethical approvals.

Competing interests

HS is director of Health Psychology Services Ltd, providing psychological services for a range of health related conditions.

MU was Chair of the NICE accreditation advisory committee until March 2017 for which he received a fee. He is chief investigator or co-investigator on multiple previous and current research grants from the UK National Institute for Health Research, Arthritis Research UK and is a co-investigator on grants funded by the Australian NHMRC. He is an NIHR Senior Investigator. He has received travel expenses for speaking at conferences from the professional organisations hosting the conferences He is a director and shareholder of Clinvivo Ltd that provides electronic data collection for health services research. He is part of an academic partnership with Serco Ltd related to return to work initiatives. He is a co-investigator on a study receiving support in kind from Orthospace Ltd. He is an editor of the NIHR journal series, and a member of the NIHR Journal Editors Group, for which he receives a fee.

SE is investigator on a number of NIHR and industry sponsored studies. He received travel expenses for speaking at conferences from the professional organisations. SE consults for Medtronic, Abbott, Boston Scientific and Mainstay Medical, none in relation to opioids. SE is chair of the BPS Science and Research Committee. SE is deputy Chair of the NIHR CRN

Anaesthesia Pain and Perioperative Medicine National Specialty Group. SE's department has received fellowship funding from Medtronic as well as nurse funding from Abbott.

AF developed an App that is sold in iTunes for US$9.99 (Opioid Manager). The App is owned by the hospital (UHN) where Dr. Furlan works, and Dr. Furlan does not retain any profits of the sales of this app for herself.

KS received grant funding as PI and CoI from NIHR for other projects. I was on the NIHR HS&DR Funding Board until January 2018.

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We would like to thank Ms Sally Brown for her valuable input in the early stages of the study. We would also like to thank all of our PPI volunteers and the North East and North Cumbria clinical research network for hosting the events. We would like to thank our clinical and lay facilitators who delivered the intervention and the Clinical Research Networkswho assisted in recruitment for the study (North East & North Cumbria; West Midlands; East Midlands; Thames Valley & South Midlands. We would also like to thank Dr Alison Hipwell for her contribution to the intervention development and Dr Celia Bernstein for her contribution to the I-WOTCH study. .

List of abbreviations

CD – Compact Disc

CONSORT - *Con*solidated *S*tandards *o*f *R*eporting *T*rials

CRF – Case Report Form

DMC - Data Monitoring Committee

DVD - Digital Versatile Disc

HRQoL – Health-Related Quality of Life

ICC – Inter-Cluster Correlation

IMMPACT - Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials

I-WOTCH – Improving the Wellbeing of People with CHronic Pain

MRC – Medical Research Council

NHS – National Health Service

NIHR – National Institute of Health Research

PPI – Patient and Public Involvement

PROMIS-PI-SF-8A - Patient-Reported Outcomes Measurement Information System Pain Interference Short Form (8A)

PSA - Probabilistic Sensitivity Analysis

QALYs - Quality Adjusted Life Years

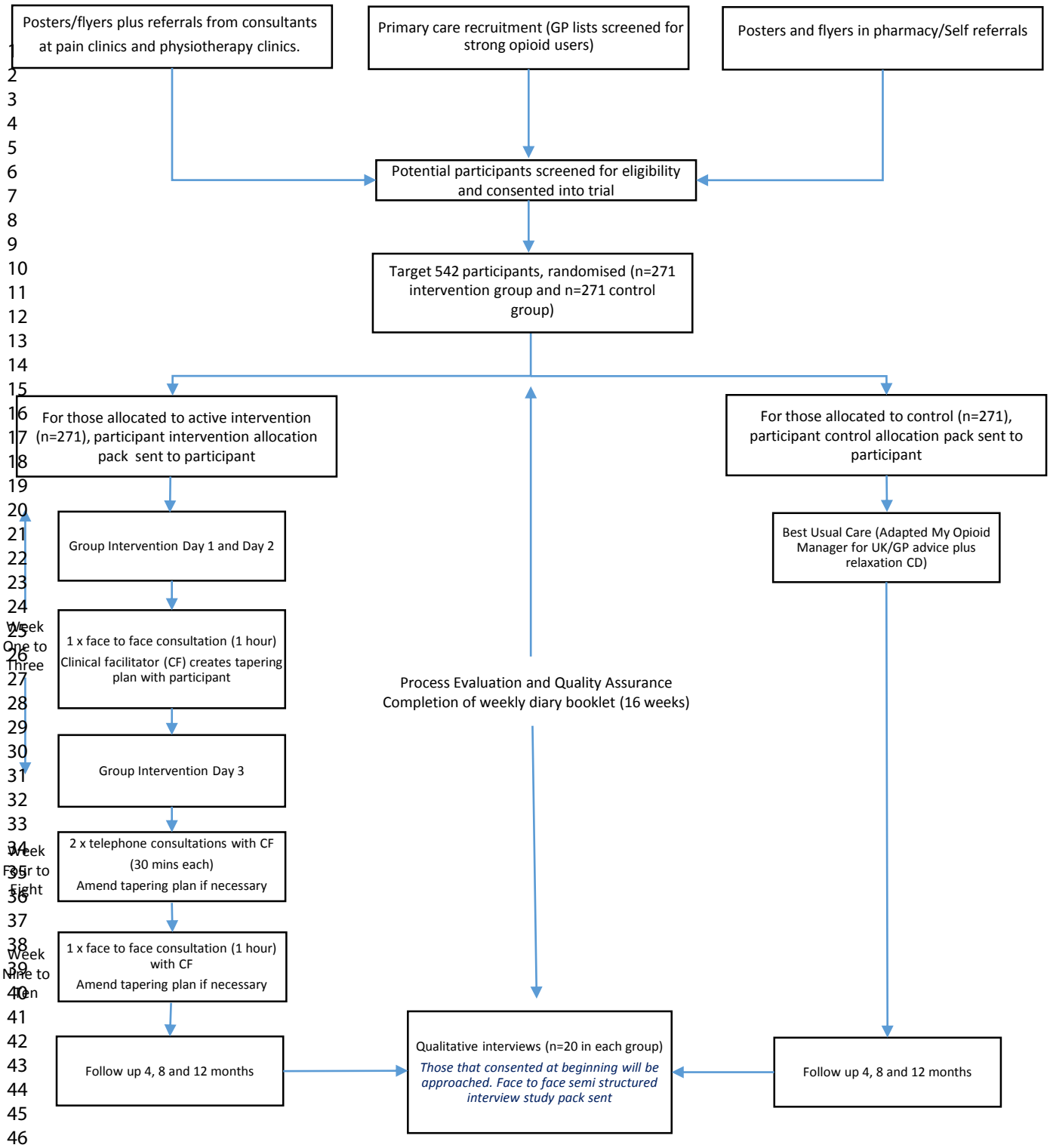
RCT – Randomised Controlled Trial

TMG – Trial Management Group

TSC – The Trial Steering Committee

UNTRAP - Universities/User Teaching and Research Action Partnership

WCTU – Warwick Clinical Trials Unit


Posters/flyers plus referrals from consultants at pain clinics and physiotherapy clinics.
Primary care recruitment (GP lists screened for strong opioid users)
Posters and flyers in pharmacy/Self referrals
Potential participants screened for eligibility and consented into trial
Target 542 participants, randomised (n=271 intervention group and n=271 control group)
For those allocated to active intervention (n=271), participant intervention allocation pack sent to participant
For those allocated to control (n=271), participant control allocation pack sent to participant
Group Intervention Day 1 and Day 2
Best Usual Care (Adapted My Opioid Manager for UK/GP advice plus relaxation CD)
Week One to Three
1 x face to face consultation (1 hour) Clinical facilitator (CF) creates tapering plan with participant
Process Evaluation and Quality Assurance
Completion of weekly diary booklet (16 weeks)
Group Intervention Day 3
Week Four to Eight
2 x telephone consultations with CF (30 mins each)
Amend tapering plan if necessary
Week Nine to Ten
1 x face to face consultation (1 hour) with CF
Amend tapering plan if necessary
Follow up 4, 8 and 12 months
Qualitative interviews (n=20 in each group)
Those that consented at beginning will be approached. Face to face semi structured interview study pack sent
Follow up 4, 8 and 12 months

I-WOTCH CONSENT FORM

Study	Improving the Wellbeing of people with Opioid Treated Chronic pain (I-WOTCH)	**Name of Investigator**	Dr Harbinder Sandhu Prof Sam Eldabe
Practice Name		**Participant ID number**	

Please tick the boxes below if you agree

1. I confirm that I have read the information sheet dated [DATE AND VERSION] for the above study and I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	☐
3. I agree for my contact details to be held at Warwick Clinical Trials Unit for the purpose of sending me questionnaires and other study related material.	☐
4. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the I-WOTCH research team, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐
5. I understand that all information that is collected during the study will be kept confidential at all times and held in compliance with the Data Protection Act 1998.	☐
6. I agree to my General Practitioner being informed of my participation in the study.	☐
7. I give permission for the study team to use data from my GP records, where it is relevant to my taking part in this research.	☐
8. I agree to being sent text messages in relation to the study	☐
9. I understand that if allocated to the support programme I will be asked to attend a 3 day support programme and partake in face to face consultations and phone consultations with a nurse.	☐
10. I understand and agree that all of the support programme will be audio recorded and may be transcribed for quality control purposes and to understand more about the issues discussed. I understand that some of the support programme may be observed. I understand transcripts will be held securely and only accessed by authorised study personnel.	☐

Please turn over….

This project was funded by the National Institute for Health Research, Health Technology Assessment (project number 14/224/04).
The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA, NIHR, NHS or the Department of Health.

11. I understand that that these transcripts will be made anonymous by a member of the research team or a third party transcription service contracted to work on the study. I understand anonymised transcripts may be shared with other carefully selected researchers for further analyses.	☐
12. I understand that brief, anonymous, extracts from the transcripts may be reproduced in academic and non-academic presentations and publications.	☐
13. I understand that the information held and maintained by The Health and Social Care Information Centre and other central UK NHS bodies may be used to help contact me or provide information about my health status.	☐
14. I understand and agree I may subsequently be contacted by the research team to take part in an interview to explore the experience of being in either the 'support programme' group or the 'self-learning manual' group.	☐
15. I agree to take part in the above study.	☐

Name of participant (please print)	**Date**	**Signature**

Name of person taking consent (please print)	**Date**	**Signature**

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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	Addressed on page number
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	6
	2b	All items from the World Health Organization Trial Registration Data Set	6
Protocol version	3	Date and version identifier	6
Funding	4	Sources and types of financial, material, and other support	33
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-5
	5b	Name and contact information for the trial sponsor	29
	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	29,33
	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)	24

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	___8-9_____
	6b	Explanation for choice of comparators	_____9_____
Objectives	7	Specific objectives or hypotheses	_____9_____
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)	_____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	_____11____
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)	_____ 12-13_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____14-18_____
	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)	__15, 24-25____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_____18____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	___14-17_____
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	____18-21_____
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)	_____10_____

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	___21-22_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	____21-22_____
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	_____22_____
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	_____22_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____22-23____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	____22-23_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	____22-23____
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	18, 21-22____
	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	20-21, 25_____

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	25-26
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	25-26
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	25-26
	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)	25-26
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	24
	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	24
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	24-25
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	2-25
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	29
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)	28-29

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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	23
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	33-34
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	29
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	29
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	29
	31b	Authorship eligibility guidelines and any intended use of professional writers	33
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix1
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	NA

*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.