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PROTOCOL

Improving the Wellbeing of people with Opioid Treated CHronic pain (I-WOTCH)

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Abbreviation	Explanation
AE	Adverse Event
BNF	British National Formulary
CI	Chief Investigator
CONSORT	*Con*solidated *S*tandards *o*f *R*eporting *T*rials
CCG	Clinical Commissioning Group
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
ICC	Inter-cluster correlation
ICF	Informed Consent Form
IRAS	Integrated Research Application System
ISRCTN	International Standard Randomised Controlled Trial Number
MRC	Medical Research Council
PI	Principal Investigator
PPI	Patient & Public Involvement
QoL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R&D	Research and Development
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TSC	Trial Steering Committee
WCTU	Warwick Clinical Trials Unit

1. BACKGROUND

1.1 Epidemiology and burden of the condition

Nearly eight million people (15%) in England have moderate to severe chronic non-malignant pain.(1) The condition has a major impact on the wellbeing and productivity of those affected with its prevalence reported to be higher among older people and those from socio-economically deprived areas.(13-15) Around 20% of those aged 34 or over and around 40% in those aged 75 or over report high levels of interference with their lives from pain.(1)

With an aging population the absolute number of those affected is set to increase substantially. The common disorders contributing to this epidemic include low back pain, neck pain, osteoarthritis, neuropathic pain, fibromyalgia, chronic widespread pain, and post-surgical pain. Individuals may be affected by more than one of these disorders. Strong opioids, including expensive transdermal preparations, are increasingly being prescribed and there is increasing regional variation in prescribing rates. There are limited data supporting the effectiveness of long-term strong opioids for chronic non-malignant pain.(2-4) Adverse effects often outweigh the benefits of long-term opioid treatment on pain: sedation, decreased concentration and memory, drowsiness, changes in mood, constipation, dry mouth, abdominal pain, nausea, hormonal changes with consequences such as sexual dysfunction, and osteopenia may limit treatment tolerability. People on long-term opioid treatment (defined here as three months or longer) report inadequate analgesia; despite high doses due to development of tolerance with reduced function, quality of life, or absence of progress toward therapeutic goals.(4-6) Opioid related adverse effects occur in 18% of subjects receiving moderate and low dose opioids. These side effects can all have profound impact on quality of life. Substance use disorders are common in this population with rates as high as 50% reported in those using opioids for back pain.(7, 8) In older adults there can be specific problems with drowsiness, poor balance, impaired coordination, altered perception, unsteady mobility, and falls leading to increased risk of fractures and deaths.(8) Furthermore, these problems are likely to increase 'fear of falling' which has been associated with a greater loss in quality of life than fractures themselves.(9)

1.2 Existing knowledge

Much is known about the adverse effects of long-term opioid treatment (10), however little is known about the economic impact of these adverse events. Also, there is sparse evidence supporting interventions that assist patients to reduce opioid doses. A Cochrane review found one RCT of acupuncture (N=35) and one of computerised therapeutic voice support (N=51).(11) The reviewers were unable to make recommendations for practice. This review also identified five observational studies (N=1,800) from one unit suggesting that an intensive three-week pain management programme can substantially reduce opioid use. We are not aware of any studies measuring the cost-effectiveness of opioid withdrawal in people using strong opioids.

Less intense self-management interventions for people with chronic low back pain that do not target opioid use, can have sustained benefits on pain and disability.(12) For the COPERS trial, we designed a three-day group programme based on cognitive behavioural principles and behaviour change for people with chronic musculoskeletal pain. We found that this complex intervention had a clinically important effect on mood (depression and anxiety) but no effect on pain and pain-related disability compared to a best usual care package; a relaxation CD.(13) Twenty three percent (162/703) of participants were prescribed strong opioids at baseline. Opioid use was not a target of the intervention and this did not change substantially over the duration of the study. However

interventions targeting reduction in opioid use in patients often lack face validity with patients who anticipate increased pain and consequent reduced quality of life. Thus, any intervention aimed at reducing opioid use must address optimisation of daily living with chronic pain as well as medication use.

There are no formal UK guidelines for opioid reduction in this population, while such guidelines are currently emerging in North America these are based on expert consensus rather than evidence. There is no clear evidence to support a particular speed of opioid tapering or the use of particular opioid drug (s) or switches. Although intuitive, the evidence supporting the role of self-management and cognitive behavioural interventions in support of opioid tapering remains low level and mostly applicable to North American health service.(14) We aim to use and test an evidence based intervention (COPERS) in the chronic pain population, adapted to include additional material on use of opioids, as an adjunct to an opioid tapering regime. If our intervention is shown to be effective then the results of our trial will feed into the development of much needed national, and international, guidance on opioid reduction in this group of subjects. Demonstrating whether such an intervention can be effective, and cost-effective is a key addition to current knowledge. Even if our trial fails to impact on our primary outcome our process evaluation will enable us to track why it might not have been effective informing future developments in the field.

1.3 Hypothesis

In the I WOTCH study we will test the hypothesis that a group multicomponent self-management intervention combined with individual support will improve activities of daily living, for people using strong opioids for chronic non-malignant pain.

1.4 Need for a trial

The extensive misuse of prescription drugs has brought into sharp focus the role of opioids for persistent pain. This has been paralleled by an increase in deaths from these drugs. Despite their popularity in the treatment of chronic pain opioids are neither an easy, or necessarily, effective solution to the problem. More often than not opioids are prescribed at higher doses and for longer than can be predicted by their natural efficacy in people living with non-malignant pain. In light of the epidemic of opioid use there is a pressing need to develop interventions to help people withdraw from strong opioids used for chronic non-malignant pain.

Prescription data from the UK show substantial increases in the use of opioids for non-cancer pain with a 466% increase in the number of strong opioid users between 2000 and 2010. During this decade only 12% of the opioid prescribing in the UK was cancer related while 88% of prescriptions were issued to non-malignant chronic pain patients. While morphine remained the most frequently prescribed drug both for cancer and non-cancer pain, the greatest increase in annual number of prescriptions was for oxycodone in both the non-cancer (11,265%, from 764 to 86,833 daily doses/1,000 of population) and cancer groups (8939%, from 124 to 11,209 daily doses/1,000 of population).(15) Data for the National Drug Treatment Monitoring System (NDTMS) 2011/2012 suggest a recent increase (around 8%) in the number of patients seeking help for analgesic dependency, with or without additional use of illicit drugs.(16) Our clinical experience is that there are a people who use illicit drugs for chronic pain instead of, or in addition to, prescribed medication.

There is an increased risk of serious harm occurring from opioid use. Mortality related to prescription opioids is increasing in various jurisdictions.(17) Between 1999 and 2007, the rate of unintentional overdose death in the United States increased by 124%, largely because of increases

in prescription opioid overdoses. A study examining the association between opioid prescribing patterns and opioid overdose-related deaths reported the incidence of fatal overdose over the 4-year study period among individuals treated with opioids to be 0.04%. The risk of overdose death was found to be directly related to the maximum prescribed daily dose of opioid medication.(18)

There are substantial potential benefits to individuals and to the health and social care system from reducing opioid use. Despite an overwhelming message of restraint, opioid prescribing continues to increase. This is in spite of guidelines on the prescription of opioids being produced in many countries including the UK such as the British Pain Society guidelines Opioids for Persistent Pain Good Practice.(19)

In addition to disseminating best practice guidelines to clinicians there is a pressing need to develop patient-centred interventions to manage this epidemic of opioid prescribing. Only by doing this will we be able to reduce the longer term consequences of opioid use; best practice guidelines may reduce incidence of long-term opioid use but are unlikely to help people withdraw from long-term opioids. In this context understanding the benefits of the intervention is much broader than simply assessing the effect of the intervention on the primary outcome. We will be seeking to improve activities of daily living as our primary patient-centred outcome. Nevertheless, we suggest that the benefits from this intervention may include a reduction in longer-term opioid related adverse events. Even with one-year follow up, within the trial, we are unlikely to identify the consequences of the longer term adverse events of opioids such as endocrine disturbances, osteopenia, increased risk of falls and fractures. Benefits on these longer term outcomes may continue to accrue if we reduce opioid use even if we show no difference on our primary outcome; activities of daily living at one year. For this reason there is a need to use data collected within the trial to model the long-term effects of the intervention on health outcomes and consequentially its long term cost-effectiveness.

1.5 Ethical considerations

The study will be conducted in full adherence with the principles of the Declaration of Helsinki and to MRC Good Clinical Practice (GCP) principles and guidelines. It will also comply with all applicable UK legislation and Warwick Standard Operating Procedures (SOPs). All data will be stored securely and held in accordance with Data Protection Act 2018.

We will ensure that all CRFs and questionnaires are anonymised and treated as confidential. Any identifiable data will be stored separately. Participants will be informed that they are free to withdraw at any time during any phase of the work.

We will only recruit patients who are fluent in English. We are excluding people who are not fluent in written and spoken English so that we can ensure comprehension of the study materials (e.g. patient information sheet) and ensure informed consent. In a previous systematic review we found that one of the few identified predictors of lack of success of a self-management intervention was attending courses that were not run in the patient's mother tongue.(20)

We are excluding patients who are either pregnant or aiming to become pregnant in the next 12 months at time of eligibility assessment. There is an absence of research in this area, and although the risk in tapering prescription opioids for chronic non-malignant pain patients was deemed low, it is unclear what impact that opioid reduction may have on their pregnancy, and may require more specialist support than provided in the I-WOTCH study.(21)

Ethical considerations for recruitment are minimal and are predominately to do with access to patient information. For searching of GP registers only clinical staff and the Local Clinical Research

Network (LCRN) along with any research staff (with appropriate permissions) will have access to such information. Patients will have the choice of whether or not to participate and will be given all relevant information about the study to make an informed decision. The general risks to the participants in this study are low, however the study team are aware of implications related to opioid withdrawal such as emotional reactions. We will therefore ensure all facilitators are trained in recognising and managing distress should a situation occur and furthermore each group session will have two facilitators to ensure appropriate management should a patient become distressed: one facilitator can see to the patient and the other continue the group session. For additional support we will ensure a clinical member of the study team is available for consultation by telephone if required. The study team will have a list of clinically qualified personnel to call on should it be necessary. Prof Eldabe is a pain physician and Profs Underwood and Taylor are General Practitioners with experience of research trials. GCP-trained personnel will conduct the trial.

1.6 Consort

The trial will be reported in line with the CONSORT (*Con*solidated *S*tandards *o*f *R*eporting *T*rials) statement.(22)

2. TRIAL DESIGN

2.1 Trial summary and flow diagram

Our overarching aim is to conduct a definitive randomised controlled trial to test the effectiveness and cost effectiveness of a multicomponent self-management intervention targeting withdrawal of strong opioids in comparison to best usual care (i.e. the control intervention) for people living with chronic pain. We will aim to run the intervention in three locations (North East England, North East London, and West Midlands). We will adapt our existing search algorithms to identify people living with chronic non-malignant pain who have been prescribed strong opioids on more than one occasion in the previous year from GP records. Our initial intention is to recruit 468 participants from between 100 to 200 general practices, community pain/musculoskeletal services and pharmacies across the three locations. The number of groups required will be calculated to ensure that low recruitment to individual groups will not prevent us from reaching our target of 468. As recruitment to these groups has been better than anticipated, then we will continue recruitment until all patients approached have been provided the opportunity to participate. An amended recruitment target of 542 would allow us to consider pain interference and opioid use as two primary outcomes. The clinical and cost-effectiveness of the I-WOTCH intervention will be compared to best usual care. Study outcomes include activities of daily living (including engagement with social, cognitive, emotional, physical and recreational activities), pain severity, generic preference based health related quality of life, sleep quality, self-efficacy, compliance/opioid freedom (percentage opioid free at one year, prescribed medication from GP records expressed as defined daily doses; converted morphine equivalents for opioids), adverse events and resource use (using a combination of routinely collected NHS data, such as hospital episode statistics & GP records, and patient self-reported data, such as over the counter medication and other non-pharmacological pain related costs). Follow up data will be collected at four, eight and 12 months. As well as a within trial economic analysis we will model the long term impact of the intervention. We will carry out a process evaluation, using the MRC guidance on developing and evaluating complex interventions including an assessment of intervention fidelity.(23)

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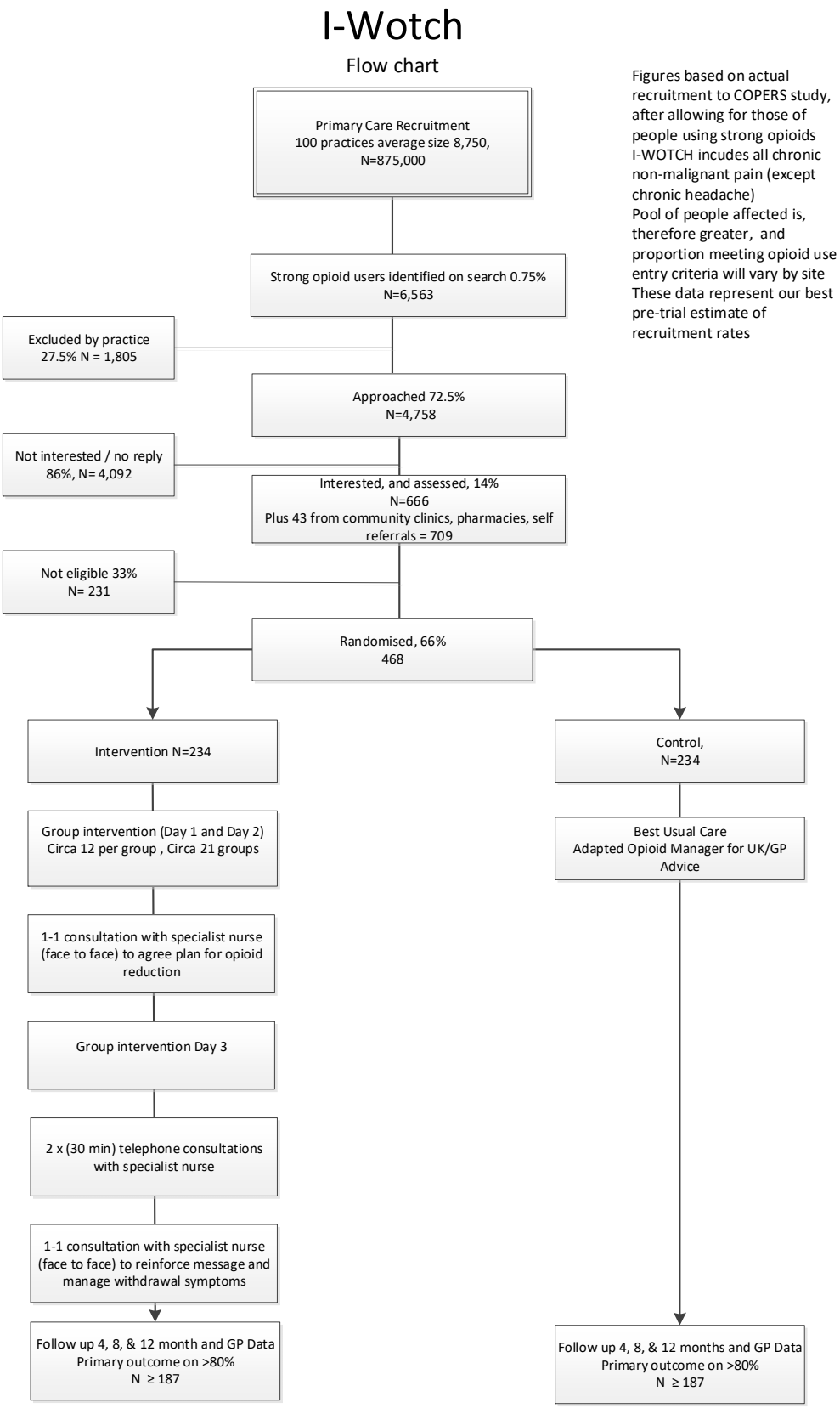
275 **Figure 1: Recruitment flow diagram *(original estimates based on the COPERS study)***



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2.2 Aims and objectives

2.2.1 Primary objective

The primary objective of this trial is to test the effectiveness and cost effectiveness of a patient-centred multicomponent self-management intervention targeting withdrawal of strong opioids on activities of daily living for people living with chronic non-malignant pain.

2.2.2 Secondary objectives

The secondary objectives of the trial are:

1. To run an internal pilot, with formative process evaluation, to confirm successful recruitment;

2. To run a definitive multi-centre trial to assess the clinical effectiveness and resource use implications of the I-WOTCH intervention versus usual care over a 12 month follow up; and related to this, develop an initial decision analytic cost effectiveness model and value of information analysis based on existing evidence.

3. To run a parallel process evaluation of the trial which will inform interpretation of the trial findings and the implementation of the intervention across the NHS, if indicated.

4. To update the decision analytic cost effectiveness model and value of information analysis with the data from the definitive trial and model the long term cost effectiveness of the I-WOTCH intervention versus usual care.

5. To disseminate the results. If appropriate, this will include providing materials to support roll-out of the intervention.

2.3 Outcome measures

2.3.1 Efficacy

Primary outcome; activities of daily living

Increasing or maintaining function is a key long-term goal in treating those with chronic pain. People maintained on opioids often report poor pain control with reduced function and quality of life. Experimental pain testing protocols suggest that sensory hyperalgesia may appear immediately after discontinuation of opioid with consequent worsening of pain. Studies of long term opioid tapering have overall shown an improvement in function without an associated worsening of pain.(24, 25)

We will use the Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Interference Short Form (8A)(PROMIS-PI-SF-8A) as the primary outcome measure (26) for activities of daily living. This is an eight- item, generic, self-report measure which assesses the consequence of pain on relevant aspects of an individual's life and key activities of daily living: engagement with social, cognitive, emotional, physical, and recreational activities. Full details of the measure are available from the Assessment Centre [SM] website http://www.assessmentcenter.net/. 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. (27, 28) Furthermore the Pain Interference Short Form is a universal rather than disease-specific scale. We consider that measurement of pain interference is the most appropriate measure for assessment of activities of daily living in this study.

If we achieve a positive result in our trial then evidence that we can reduce the extent that pain

interferes with usual activities will be a strong incentive for patients to join such a programme. Even, a negative result on this outcome, in the context of reduced overall opioid use may still be an important stimulus for patients to join such a programme;

'We can reduce your dependence on opioids, you avoid long term opioid side effects and how your pain affects your life will be no worse'

Data will be collected at baseline and four, eight and 12 months following randomisation.

Primary outcome; opioid use

The aim of our intervention is complete withdrawal from all immediate and long term release opioids. Our main analysis for opioid use will be the mean difference in morphine equivalent dose in the four weeks prior to one-year follow-up expressed as mg of morphine per day. We will calculate this using equianalgesic doses of opioids using the same values we provided to the nurses delivering the intervention (see below). By doing this we will achieve greater statistical power than using a categorical outcome of opioid free. 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 will compare proportions achieving a complete withdrawal and proportions of responders, defined as ≥50% reduction in morphine equivalent doses taken, between intervention and control groups.

Whilst for the purposes of identification of potential participants we will use general practice prescribing data for the purposes of outcome assessment it is medication used rather than medication prescribed that is of interest. We will therefore base our outcome assessment on participant self-report of opioid medications used in the preceding four weeks. In contrast to some other therapeutic areas we anticipate participants to have good recall of their current medication and doses. Our clinical experience is that this group of patients using strong opioids have very good recall for medication used. This is helped by their only being a limited number of products to consider.

Whilst our study entry criterion is participant reported use of using strong opioids on most days in the preceding four weeks, our continuous measure of opioid use will be mean morphine equivalents of opioid used in the preceding four weeks. This will include all opioids used; including any weak opioids used.

Self-reported data on opioid use will be collected at baseline, 4, 8 and 12 months following randomisation via postal follow-up. At baseline, one postal reminder will be sent. At 4, 8 and 12 months a postal reminder will be sent. In the event that no response is obtained from the postal reminder at 4, 8 or 12 months, we will contact the participant by phone and collect our primary clinical outcome, opioid use, and EQ-5D-5L over the phone. For those that have given consent for receiving study related text messages, texts will be used to facilitate return of questionnaires. Whilst we anticipate long term benefits from opioid withdrawal during the actual period of opioid withdrawal this may be a negative health impact. Any such early negative effects will not captured using a questionnaire at four months; when tapered withdrawal should have finished. For this reason we will ask participants to complete a weekly diary that includes the EQ-5D-5L and the Short Opioid Withdrawal Scale for the first four months after randomisation. For those that have given consent for receiving study related text messages, texts will be used to prompt participants to complete their weekly diary once a week.

Opioid use was originally intended as a main secondary outcome. Our amended recruitment target of 542 would allow these to be considered as two separate primary outcomes.

Other 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.(29) All outcome measures are presented in Table 1 with data collection time points. In the event that questionnaires are not returned by the participant, one postal reminder will be sent after 10-14 day intervals. Following this, if there is still no response, they will receive a telephone call from a member of the trial coordinating team to collect data on the primary clinical outcome (i.e. activities of daily living), opioid use, and EQ-5D-5L.

Table 1: Summary of outcome measures and delivery time points

Type of Data	Outcome measures	Time points				
		1 [a]	2 [b]	3 [c]	4 [d]	5[e]
Demographic	Age, gender, ethnic group, age at leaving full time education, current work status	X				
Activities of daily living*	Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Interference Short Form (8A)(PROMIS-PI-SF-8A).(26)	X	X	X	X	
Opioid use*	We will collect opioid consumption over the last 4 weeks by questionnaire. The dosage of opioids will be expressed as average daily morphine equivalent.	X	X	X	X	
Opioid prescriptions	Prescribed opioid medication from GP records expressed as average daily morphine equivalent.	X	X	X	X	
Pain severity	PROMIS Scale v1.0 - Pain Intensity Short-Form 3a (30, 31)	X	X	X	X	
Symptoms	Severity of Opioid Withdrawal (Symptoms): Short Opiate Withdrawal Scale (ShOWS).(32)	X	X	X	X	X
Health Related Quality of Life	SF-12 V2, and EQ-5D-5L.(33, 34)	X	X	X	X	X EQ5D – DL only
Sleep quality	Pittsburgh Sleep Quality Index.(35)	X	X	X	X	
Emotional well-being:	Hospital Anxiety and Depression Scale (HADS).(36)	X	X	X	X	

Self-Efficacy	Pain Self Efficacy Questionnaire.(37)	X	X	X	X	
Resource use	Combination of routinely collected NHS data, such as hospital admissions (including A&E) and duration of inpatient stay, specialists and primary care visits, prescriptions, over the counter medications and other non-pharmacological pain related costs (e.g. acupuncture, physiotherapy). NHS costs, Deaths and fractures will be collected using a combination of routine records (GP) and patients self-reported. The latter will be used also to collect non-NHS costs such as over the counter medications.	X	X	X	X	

1 [a]. Baseline
2 [b]. 4 month after randomisation
3 [c]. 8 months after randomisation
4 [d]. 12 months after randomisation
5 [e]. Weekly from allocation to 4 months
*Primary outcome measure

2.3.2 Safety

There will be a system for reporting adverse events and serious adverse events in addition to the trial outcomes by participating clinicians (see Section 4).

2.4 Eligibility criteria

Potential participants are adults living with chronic non-malignant pain who have been prescribed strong opioids for three months or more and are eligible to be included in the trial if they meet the following criteria:

2.4.1 Inclusion criteria

1. Provision of written informed consent
2. Aged 18 years old or above
3. Using opioids for chronic non-malignant pain
4. Report using strong opioids for at least three months and on most days in the preceding month
5. Fluent in written and spoken English
6. Willingness for General Practitioner to be informed of participation

2.4.2 Exclusion criteria

1. Regular use of injected opioid drugs
2. Report chronic headache as the dominant painful disorder
3. Serious mental health problems that preclude participation in a group intervention
4. Using opioids for malignant pain

5. Unable to attend group sessions

6. Previous entry or randomisation in the present trial.

7. Participation in a clinical trial of an investigational medicinal product in the last 90 days.

8. Pregnant at time of eligibility assessment, or actively trying to become pregnant.

For the purposes of this study we use the British National Formulary (BNF) definition of strong opioids; we will thus recruit participants who are using any of the following drugs; Buprenorphine, Dipipanone, Morphine, Diamorphine, Fentanyl, Methadone, Oxycodone, Papavertum, Pentazocine, Pethidine, Tapentadol, or Tramadol for the relief of pain. People using Methadone for reasons other than the management of chronic pain will not be included. People regularly using injected opioids will be excluded as they will need a different approach to the one we are testing here. We will include people using oral or transdermal preparations. Whilst we have provided a comprehensive list of strong opioids we anticipate that the vast majority of subjects will be using one or more of Buprenorphine, Fentanyl, Morphine, Oxycodone, or Tramadol.(15)

Any adult with chronic non-malignant pain who is using strong opioids will be eligible to join the study; this includes, but is not limited to people with: back pain, fibromyalgia, osteoarthritis, rheumatoid arthritis, post-surgical pain, non-cardiac chest pain, and chronic widespread pain. We will exclude people for whom chronic headache is the dominant painful disorder because there are some specific differences to the approach to the management of chronic migraine and medication overuse headache that do not fit in the treatment model proposed here.

We have used the definition of strong/weak opioids used in the BNF. We have not set an upper age limit to ensure that those at greatest risk of serious opioid-related adverse events are included. We have excluded those aged under eighteen as few adolescents are living with chronic non-malignant pain for which they are prescribed strong opioids.

We have considered in detail our definition of use of strong opioids. For the intervention to be meaningful it needs to be targeted at current regular opioid users. There is no accepted definition of regular opioid use. In epidemiological studies, definitions such as ‘several days a week for a month or more’, or ‘at least five days per week for at least four continuous weeks’ have been used.(38, 39) These definitions, however, may not capture our population of interest; those who are long-term users of strong opioids. These definitions may identify people who are taking opioids for an acute problem who will soon stop using opioids. We have, therefore, set our time frame for regular opioid use as three months to reflect the conventional definition of time for pain to become chronic. This will ensure that everyone we include is using opioids for chronic pain. We have, however, used the preceding four weeks to define the frequency of use to reflect previous definitions and for use to be on at least half the days for each of those four weeks. We recognise that some people using opioids for chronic pain may be sourcing some of their supplies outside conventional medical services. This group will also be eligible for the study.

Ability to participate in the group sessions is an essential criterion for joining the study. People who are physically unable to travel or are unable to arrange transport to the intervention venues will be excluded. Venues will be as accessible as possible by public transport. People with serious mental health problems, or other substance abuse problems (e.g. alcohol abuse) will not be excluded unless

their problems mean they will be disruptive in the group or otherwise unable to engage with group process.

If more than one person from the same household return an expression of interest form to prevent cross-contamination the study team would offer to complete the eligibility assessment with both potential participants. If both were eligible the study team will ask the potential participants to select who they would like to proceed to participate in the study.

2.5 Informed consent

There are two consent stages:

1) Expression of interest

2) Consent to be part of the study

1) Expression of interest

Potential participants will be sent an invitation letter with the patient information sheet and an 'expression of interest' form if they meet the eligibility criteria following: (a) electronic screening of GP records; or (b) telephone interview completed by a member of the study team. Those interested in participating can return this form along with contact details back to the study team using a pre-addressed envelope. There will be a single postal reminder after 10-14 days.

2) Consent to be part of the study

Following return of the 'expression of interest' form, a study package will be sent out to the potential participant. The study package will consist of an I-WOTCH cover letter, participant information sheet, trial consent form, baseline questionnaires and pre-addressed envelope. The consent form will include consent for participating in the trial, the use of anonymised data, audio recording group days, observation of the group days, participating in one-to-one consultations, permission to access health and GP records and permission to receive text messages in relation to the study. Contact details of the study team will also be provided should the potential participants have any questions before they consent.

For those entering the study following interest in posters in pharmacies or via self-referral, the patient will contact WCTU directly. A member of the study team will conduct an eligibility screen over the phone and collect patient and GP details for those that are eligible and would like to receive further information. The study pack as described above will be sent to these individuals.

If the potential participant wishes to participate in the study, they will return the signed consent form and completed baseline questionnaires using the pre-addressed envelope. A postal reminder will be sent after 10-14 days. If a signed consent form and completed questionnaire are received, a designated member of the study team will then contact the participant via telephone. A final eligibility check will be conducted based on the medications the patient self-reports in the baseline questionnaire, and any queries on the questionnaire will be resolved at this point. If the medications meet the eligibility criteria and consent is deemed to be valid and informed, the member will countersign the consent form after the patient has had the opportunity to ask questions and have these answered satisfactorily. Potential participants will be informed of their

withdrawal rights and, if they would like more time to consider their participation in the research study, they will be given the opportunity to consent at a later date. The potential participant will be able to do this by getting in touch with a member of the research team (contact details will be displayed on the participant information sheet) within two weeks of initial contact with the researcher. Once the consent form has been signed by the potential participant and countersigned by a member of the research team, they will be formally enrolled in the study. A copy of the fully signed consent will be sent to the participant and a copy to their GP.

In the unlikely scenario that new information becomes available that may be relevant to the participant's willingness to continue in the research, the participant will be contacted by the relevant researcher and asked whether they still wish to continue participating in the study. Should they wish to do this a revised written information sheet and consent form will be sent to the participant with a pre-paid envelope and the participant will be asked to read, sign and send this back to the research team.

Willingness to continue will also be monitored throughout the intervention period by researchers conducting the intervention.

Additional consent for qualitative interviews

For those that consent at the beginning of the study to be included as potential participants for the qualitative interviews (and are selected to be interviewed) a letter, information sheet and consent form specific for the interview part of the study will be sent by post. Participants will be contacted by phone approximately 7 – 10 days after the information and consent form have been posted to check whether participants would like to be interviewed, answer any questions they may have and to arrange a date. The consent form will be checked and countersigned by the interviewer before the interview.

Additional consent for missing data calls

The four and eight month questionnaires contain a Missing Data section, which will serve for participants to provide explicit consent for a member of the study team to contact them to discuss any unclear or missing data over the duration of the study.

2.6 Recruitment and randomisation

2.6.1 Recruitment

Potential participants will be identified via:

a) **Electronic screening of GP records, pain clinic records and musculoskeletal physiotherapy clinics**

We will adapt our existing search algorithms to identify people living with chronic non-malignant pain to identify those who have been prescribed strong opioids on more than one occasion in the previous six months from GP records, pain clinic records and musculoskeletal physiotherapy offices.

Inclusion criteria will include: (a) one or more prescriptions for strong opioid treatment in the previous 3 to 6 months and (b) one or more prescriptions for strong opioid treatment in the previous 0 to 3 months. Exclusion criteria will include: (a) methadone use as part of substance abuse management, (b) People receiving strong opioid for the management of pain due to active malignant disease (c) housebound status (this limits participation in group sessions). Eligible potential participants with cancer code(s) will be flagged for review.

Not all of the individuals identified through this screening process will meet our opioid use criteria. Practices, with support from the Clinical Research Network will, search their records, and screen the list for those who are taking opioids for malignant pain or who should not be approached for other reasons. No one who is considered vulnerable will be approached. The study team will be provided with a pooled anonymous data set to allow response rates to be calculated. This list will contain, gender, age (not date of birth) and ethnicity (if recorded).

b) **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 will be able to refer potential participants by giving them an information pack which will provide information on the study, expression of interest form and contact information for the study team.

c) **Posters advertising details of the study will be displayed in prominent areas of GP surgeries, pharmacies, pain clinics and musculoskeletal physiotherapy clinics**

GP surgeries, pain clinics, musculoskeletal physiotherapy clinics and pharmacies will display posters in prominent areas. The posters provide information on the study and contact details of the study team.

The eligibility of a participant will be determined by (i) electronic screening of health records and verification from the GP and/or healthcare professional; and (ii) telephone interview by a member of the study team. Any clinical queries raised during the telephone interview will be referred to a clinical member of the study team.

<u>GP Recruitment (Initial Plan):</u>

We will recruit in three locations (North East England, North East London, and West Midlands) whose populations are broadly representative of the UK as a whole. Our recruitment strategy is based on our experience of successful recruitment to multiple large community based studies of people living with chronic pain (BEAM, BEST, COPERS).(40-42). We seek to recruit from around 100 general practices in total with approximately 33 from each of the three geographical locations which will provide around 850,000-900,000 potential participants. This will be supplemented by recruitment from community pain services, community musculoskeletal services and pharmacies. We will recruit practices in waves with clusters of practices in reasonable geographical proximity so that we can populate groups in a timely manner.

<u>GP Recruitment (Amended Plan):</u>

Recruitment will be undertaken in two locations (North East England and the Midlands), as no funding was available in the London area – a larger proportion of recruitment will be from the Midlands, as this now incorporates East Midlands, West Midlands and the Thames Valley region.

Response rates to mail-outs were also lower than anticipated, so we now seek to recruit from around 200 general practices, providing around 2,000,000 potential participants.

We will also take direct referrals to the study from general practitioners and healthcare professionals in participating practices, pain clinics and musculoskeletal physiotherapy clinics and will provide posters for waiting rooms including in pharmacies; although our experience is that this is not a very productive route of recruitment. Those who find out about the study from their healthcare professional or via the waiting room advertisement will contact the study team directly

or pick up an invitation pack from the practice or clinic receptionists. We will also take self-referrals to the study following interest from media sources such as the study website or study press releases.

When participants contact the study team, they will then be screened and checked for suitability to participate by using the inclusion and exclusion criteria as a checklist. Eligibility forms will be completed for every participant assessed, detailing reasons for exclusion. To ensure that we meet our recruitment targets in a timely manner, where possible we will also recruit people attending relevant community services in the same localities as our participating practices. We will approach community based musculoskeletal services, community pain services and pharmacies serving similar geographical areas after we have identified our clusters of practices. Including these recruitment sites will ensure we can achieve our recruitment targets even if practice based recruitment is not as good as projected. We will use a broadly similar approach to recruitment in these sites to the general practices. We may not, however, be able to easily access data on opioid prescribing for this group and will therefore need to approach all those with chronic pain and establish current opioid use as part of the recruitment process.

2.6.2 Randomisation

The Warwick Clinical Trials Unit service will be used.

Initial Plan:

Assuming recruitment is similar in each locality, we will randomise around 75-80 people to the intervention in each locality (i.e. sequentially at a site level). We will need to provide around seven courses in each locality. To ensure we populate the groups we will cluster groups of 4-5 geographically proximate practices with 40,000 – 50,000 patients to launch recruitment at around the same time. We will then randomise participants when we have sufficient participants to populate a group in batches of around 24 participants. This will help reduce any delay between randomisation and start of the intervention. Randomisation will be stratified by geographical locality, baseline pain severity and baseline opioid use. These data will be collected via self-reported postal questionnaires while obtaining consent.

There are, of course, good reasons to think there will be regional differences in percentage of population using strong opioids but this may not translate into it being easier to recruit either practices or participants in different locations. We will revisit these estimates as part of the value of information analysis at the end of the pilot phase (described in more detail later in the document) and, if appropriate, adjust numbers required.

Amended Plan:

We intend to randomise around 350-370 people in the Midlands (175-185 to the intervention) and around 180-200 people in North East England (90-100 to the intervention). We will provide around 20 groups in the Midlands, and around 16 groups in North East England.

Having monitored response rates for our early groups across both regions, we will cluster groups of geographically proximate practices with between 50,000 – 100,000 to launch recruitment for a group.

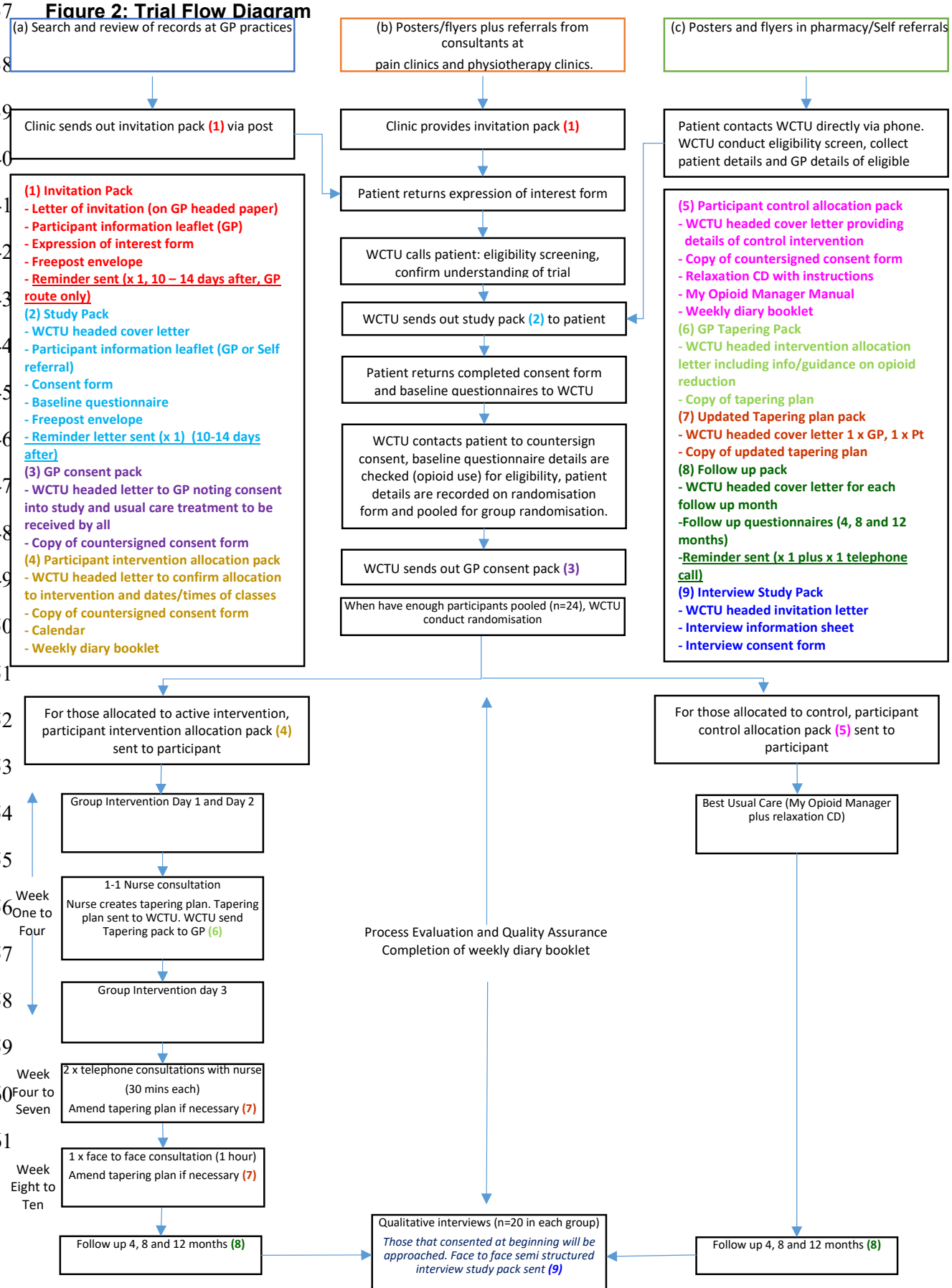
2.6.3 Post-randomisation withdrawals and exclusions

Researchers in collaboration with the CIs will monitor the participants and highlight any concerns to the PIs. Participants may be withdrawn from the trial at the discretion of the investigator and/or Trial Steering Committee due to safety concerns.

In accordance with the Declaration of Helsinki, each participant is free to withdraw from the research study at any time (including follow-up) without providing a reason and without prejudice, if they so wish. Participants are informed of this in the participant information sheet.

Unless a participant explicitly withdraws their consent, they should be followed-up wherever possible and data collected as per the protocol until the end of the trial. Anonymised data recorded up to the point of withdrawal will be included in the analysis. Should a participant decide to withdraw after the intervention commences, or should the investigator(s) decide to withdraw the participant, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete and final evaluation at the time of the participant's withdrawal will be recorded in the Case Report Form (CRF). If the reason for withdrawal is a Serious Adverse Event (SAE), monitoring of the participant will continue until the outcome is evident. The specific event must be recorded in the CRF.

Figure 2: Trial Flow Diagram



2.7 Trial treatments / intervention

2.7.1 Main trial intervention

I-WOTCH is an 8-10 week programme with a mixture of group sessions led by two facilitators (a trained I-WOTCH nurse and either a lay person with chronic pain and experience of opioid withdrawal/tapering, or an allied health professional) and one-to one sessions (face to face and telephone with the I-WOTCH trained nurse). Key components of the intervention are highlighted in Table 2.

The group element of the intervention will run on three weekdays early in the intervention period. We will try, where possible, to run the sessions during school terms to accommodate those with children. The start time of the group sessions will be 10:00am and the finish time will be 3:00pm. The group days will be held in easily accessible venues in the community which have disabled parking and/or near to public transport to allow participants easy access. The venues will be booked in advance, and refreshments (tea and coffee) will be provided for the three days. In light of feedback from our PPI group we have changed the three days from being three consecutive days to being two consecutive days followed by a further day of group work after participants have agreed a withdrawal treatment plan. This will be followed by two telephone consultations with the nurse and a then final face-face-consultation in weeks eight to ten (Table 3).

The group intervention will be delivered using a range of methods including: group discussions, brainstorming, sharing narratives and experiences, problem solving, watching educational DVDs and role play. There will be scheduled activities to explore challenges and barriers of opioid withdrawal and formulating plans to overcome these barriers. We will also incorporate cognitive restructuring techniques, mind focus and mindfulness. Details of the topics and content of the intervention are provided in Table 4.

Table 2: Key components of the I-WOTCH Group Sessions

Key components of group sessions	
General pain management topics include:	**Opioid specific topics include:**
Acute versus Chronic pain	The rationale of prescribing in chronic pain
Coping and pacing skills	Opioid induced tolerance and need for dose escalation
Posture and movement advice	Evidence of usefulness of opioids short and long term
Communication Skills	Side effects of opioids short term and long term
Relaxation techniques	Case studies of successful discontinued opioid therapy
Mindfulness	Opioid withdrawal symptoms
	Advantages of slow supervised taper
	Symptom management during tapering
	Pain control after opioids

Where possible, each group will have an average of 12 participants (with a maximum of 16 participants). The study was statistically powered for 12 participants in a group.

At time of the eligibility call, attendance at Days 1 & 2 is deemed mandatory to be able to be considered for randomisation. All participants must attend Day 1 of the group course at a minimum. If a participant is unable to attend day 1, where possible , they will be given the opportunity to attend an alternative intervention course, otherwise they will be sent copies of all the written material that is provided to course attendees.

One-to-one Consultations

The initial one-to-one consultations will give participants an opportunity to discuss in detail their opioid reduction regimes and where participants will be able to jointly agree their opioid reduction plan. These initial sessions are scheduled to take place after the initial two days and prior to the follow-up group day. Nurses will have the opportunity to gather goals, and use motivational interviewing to help participants engage in the behaviour change. Study nurses will provide a detailed advice sheet for participants to give to their GPs. This will provide information for the GP to taper opioids and minimise withdrawal effects, thus supporting coordinated care. All tapering plans will be checked by a clinical member of the I-WOTCH team on receipt.

During the training, nurses will be taught communication skills to facilitate discussion with the participants on opioid reduction and motivational interviewing. Participants will also cover communication skills during the I-WOTCH group sessions (how to communicate effectively with their healthcare professionals).

Table 3: Course structure

Week	Course
One - Four	I-WOTCH Day one 10.00am – 3.00pm I-WOTCH Day two 10.00am – 3.00pm One to one consultation with specialist nurse. Jointly agreed withdrawal treatment plan (e.g. Thursday/Friday) I-WOTCH Day three 10.00am-3.00pm
Four– seven	Up to two telephone consultations
Eight to ten	One to one consultation with specialist nurse.

Table 4: Detailed course content	
Day 1 Living with and dealing with pain	**Outline of content**
Introduction	Aims of the course Group members introduce themselves to each other. Agree group 'rules of engagement'
Information	Information / Education about persistent pain and opioid and other drug use. Introduce our reference patient to discuss and learn from throughout the course.
Putting pain and drugs in context	Acceptance Mind mood pain and opioids Pros and cons of using opioids and other drugs The pain cycle (including use of drugs) Breaking out of the pain and drug cycle
Relaxation	Relaxation and Mindfulness
	Reflections, summary of day
Day Two: Doing something about life with pain	
Reflections	Reflection of Day 1
Making changes	Problem solving, goal setting and action planning Barriers to change unhelpful thinking Pacing
Non drug pain management techniques	Reframing negatives to positives Attention control and distraction Identifying things that make pain more manageable Posture and movement advice Mindfulness
Drug pain management techniques	Withdrawal Drug reduction strategies

	Case studies of successful opioid withdrawal
	Reflections and summary of day
Withdrawal Plan	
One to one withdrawal treatment plans	Participant and nurse jointly devise and agree a withdrawal strategy. The recommended tapering regime will be sent to the GP. The GP will then be able to implement the change in prescription when the participant next see's the GP. Should the GP have any questions about the recommended tapering regime they will be able to contact a clinical member of the study team including the Co CI Prof Eldabe. All relevant contact details will be provided to the GP.
Day three: Communication and relationships	
Reflections	Reflection of day 1 and day 2
Communication skills	Communicating with healthcare professionals Communication and listening skills
Dealing with unwanted emotions	Managing anger, frustration and irritability Recognising depression
Practice	Practicing non drug pain management techniques
Contingency planning	Set back strategies
	Reflections and summary of course
Follow up	
Two one-to-one telephone consultations	Reinforce messages and management of symptoms other than pain Monitor progress against agreed withdrawal plan
One face-to-face consultation	Reinforce messages and management of symptoms other than pain

712

713 Opioid tapering

714 *Drug Choice:*

715 Participants will be tapered as, a first choice, on their drug of presentation. In case of participants
716 presenting on long-acting preparations such as fentanyl transdermal patches these can be tapered
717 in decrement of 12 mcg/hr patches and an oral formulation of alternative opioid with equianalgesic
718 potency introduced when the lowest increment of the patch is reached.(14)

719 *Speed of Tapering:*

We propose to use 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.(14) 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 to suit prescribing.

Equianalgesic dosing:

For the calculation of equianalgesic doses we will use the data provided by the Faculty of Pain Medicine(https://www.rcoa.ac.uk/faculty-of-pain-medicine/opioids-aware/structured-approach-to-prescribing/dose-equivalents-and-changing-opioids). For drugs not included in the table for example for methadone, we will use other published data.(43, 44) We will use the same general approach to estimating opioid equivalent doses for our final analyses. All study nurses will be provided with a printed and electronic version of these data. We will provide training in equianalgesic dose calculation as well as an electronic means of calculating and communicating the tapering plan to participants and general practitioners. Nurses will be provided with an android App developed by Warwick University IT department. The App will facilitate the calculations of tapering regimes, as well as equianalgesic doses of systemic opioids when switching from patch preparations. Where appropriate we will use 'weak' opioids (codeine/dihydrocodeine) as part of the tapering regime. For the purposes of managing changes in medication during the taper, individual variability will need to be taken into account.

Frequency of usage:

People utilising opioids, as rescue analgesia at a frequency of less than one dose per day will not require a formal tapering regime but will still be supported to completely withdraw from opioids.

Planning of, and support for, tapering regime

At the initial face-to-face meeting with the intervention nurse a withdrawal plan will be agreed. This will be based on the regime outlined here but will take participant preference and wishes into account. This will allow for some flexibility in approach according to individual circumstances. There will be up to two subsequent telephone consultations and one face-to-face consultation over the specified duration of the tapering plan where progress against individual withdrawal plans will be assessed and encouragement to continue will be given.

The facilitators will be trained to deliver the intervention following the latest version of the two intervention manuals – the Facilitator Manual (for use by the research nurses, lay facilitators and allied health professionals) and the Nurse Tapering Manual (research nurses only).

2.7.2 Control intervention

This is a pragmatic trial. In a real life situation health care providers, and patients, may attempt to identify low cost, 'off the peg' interventions and activities in the hope that they might be of assistance. Our previous experience of trials of complex behavioural interventions in populations experiencing chronic pain, an intractable condition which patients (and their health care professional) commonly find demoralising, is that it is difficult to recruit participants to studies where the control arm receive treatment as usual. Instead we offer all participants (intervention and control) what might be described as 'potential best usual care'.(12, 45) This represents the type of usual care package that might be available at very low cost to commissioners, or individual health care practitioners, interested in addressing this problem outside of the trial situation. This approach

will allow us to standardise care in the control arm as far as possible and avoid risk of further demoralisation amongst those randomised to the control arm.(46)

There are two participant-facing components to this;

- 'My Opioid Manager'

An anglicised version of My Opioid Manager (http://www.opioidmanager.com/uploads/3/4/3/2/3432072/myom_book_final.pdf) will be provided as a hard copy to all participants and also make an electronic version available that can be accessed through a secure website requiring individual login. 'My Opioid Manager' is also available as a free iBook for iPad and an as interactive App freely available in iTunes (for iPhone and iPad) and Google Play (for Android smartphones). We will advise participants of their availability but we will not be producing anglicised versions of these for this study.

- Relaxation package

We have included a relaxation CD as part of the control intervention. We will update the material used for the COPERS study and make this available as a CD.

Additionally we will ensure that all general practices recruiting participants for the study are aware of best practice in the use of opioids for chronic non-malignant pain. This will further serve to standardise the control intervention and reduce the possibility of any practice specific factors affecting outcomes. We will provide written information on the study to all GPs working on best current advice on the use of opioids for chronic non-malignant pain and advice on the use alpha2 adrenergic blockers to reduce symptoms of opioid withdrawal. We have considered providing practice based educational sessions but in view of the large number of practices involved this will not be practical. We will, however, offer to provide sessions on appropriate use of opioids for chronic non-malignant pain and information about the I-WOTCH trial at local GP educational events in localities in which we are running the trial.

2.7.3 Compliance

During the main phase of the trial, we will record the number of sessions each individual attended, including the follow up calls completed.

We will periodically observe the consent process and baseline and follow-up assessments. The research fellow/senior research fellow based at Warwick will have responsibility for quality control of the interventions. The research fellow/senior research fellow will periodically make quality control visits to observe the group sessions. Quality assurance checks will be undertaken by the WCTU to ensure the integrity of randomisation, study entry procedures and data collection.

2.7.4 Internal pilot of intervention

We will recruit 45-50 people, from 8-10 general practices in Coventry and Warwickshire to a randomised internal pilot. This equates to two practice clusters. This site is close to the main study team allowing close monitoring and evaluation. It is also the middle of our three localities for current opioid prescribing, giving the best benchmark for recruitment across the full trial. Our intent, if appropriate, is to include data from pilot participants in the final analysis to maximise the efficiency of the overall trial design.(80) All data collection and outcomes will be collected according to main trial protocol. This will allow us to populate two intervention groups of 12 people and recruit a further 24 control participants. Data from this pilot will provide crucial data on recruitment and participants' baseline characteristics allowing us to make any required adjustments to sample

size (see below), recruitment processes, and recruitment sampling frame. A successful pilot study is a key milestone we need to achieve before starting the main trial. The key success parameters for this pilot study will be

- June 2017 we would have randomised 45-50 participants

- September 2017, three months after completion of recruitment, to have delivered the I-WOTCH intervention package to two groups within the RCT with 70% of those randomised to intervention receiving the essentials of the I-WOTCH intervention; defined as attending at least half of the group sessions, and attending the first one to one session to agree an opioid reduction plan

We will arrange a TSC meeting towards the end of the pilot phase to consider if we have sufficient evidence to justify proceeding to a main study.

We will run a formative process evaluation of the pilot phase to assess the acceptability of randomisation, acceptability of the control condition, feasibility of group delivery, outcome assessment burden, and any problems encountered during the intervention. We will seek to do brief interviews people who appeared eligible but who did not join the study. This work will inform any changes to our processes that may be needed before proceeding to the main study. This will use the same theoretical framework and approach described below for the main process evaluation. We will test the acceptability of randomisation, acceptability of the control condition, feasibility, outcome assessment burden and any problems encountered during the intervention.

2.8 Process Evaluation

The process evaluation will explore any barriers and enablers to the intervention becoming part of everyday life, from both the perspective of those delivering and receiving the intervention. Key areas to be addressed in the process evaluation will include context, fidelity (the extent to which the intervention was delivered as conceived), dose delivered (the number of components of the intervention offered to participants) and dose received (the extent to which participants used or completed the tasks).(47) Some participants will be asked to complete feedback forms to provide comments on their time in the intervention.

<u>Quantitative data</u>

We will collect detailed data on the uptake of the I-WOTCH programme. This will include numbers attending each component of three course days; understanding which sessions within a course participants choose to attend gives finer resolution than simply whether they attended for at least part of a day. We will also collect data on the take-up of the one-to-one sessions with nurses and follow-up telephone calls.

<u>Observational data</u>

We will digitally audio-record all intervention delivery group sessions, to minimise the risk of those delivering the intervention changing their behaviour when being recorded. From this we will analyse a purposively selected subset of 10% of recordings different group session, covering all geographical areas, and across all time periods of the intervention.

This is being undertaken:

i) To assess fidelity

ii) To understand what areas generated discussed by participants and understand the issues discussed.

Fidelity will be assessed, looking at whether all components are delivered as expected. We are aware that the effectiveness of complex interventions may be dependent on the 'skills' of those

delivering them.(48) 'Skills' include separate but related constructs of adherence and competence and these will be assessed with the aid of a checklist whilst being open to any additional dimensions that emerge as important.

We will also record the individual nurse consultations and any follow –up telephone consultations. All these will be recorded on an encrypted digital recorder, then a 10% sub sample analysed, selected purposively to reflect diverse range of gender, age, geographical location and baseline opioid use.

Interviews with study participants

We will undertake semi-structured interviews with a purposive sample, approximately 20 in each group of intervention and control participants.(49) Selection will be informed by age, gender, geographical location, baseline & follow-up opioid use, and programme uptake (from those that have consented to take part in the interviews). We will continue interviews until no new information emerges from the interviews. In order to prevent our interview study introducing bias into the primary trial analysis these will take place at the end of the follow-up period.

The topics covered in the interview will include participant responses to the intervention (or control), how they felt they were able to use it, how easy or difficult it was to use, were some components more challenging to use than others, specific barriers or enablers, and exploring the "dose" received via prompts on the components of the intervention that were utilised, dropped or never used and their overall experience of using this intervention. For those in the active intervention, their experience of being in a group will also be explored. We anticipate these interviews will last about one hour and will be digitally recorded.

Interviews with staff delivering the intervention

At the end of the study a purposive sample of the staff delivering the intervention (n=20) will be interviewed about their experiences of teaching the intervention, including barriers and enablers. To look at what worked, what was more challenging and their overall experiences of the programme. We anticipate these interviews will last up to an hour and will, be digitally recorded.

Reducing bias

We will ensure that those delivering the intervention will be sufficiently separate from the evaluation team.

Analysis

Digitally recorded interviews and group sessions will be anonymised and transcribed verbatim. We will use NVivo 10 to organise the data. Transcripts from interviews will be coded and analysed using framework analysis.(50) Recordings of group intervention delivery sessions will be coded using a checklist to assist with the process of understanding "dose received" and fidelity, but also be open to any additional elements included that were not as originally conceived. The analysis of any discussion that takes place during the group sessions will be analysed using the same approach as in the interviews. Intervention fidelity will be assessed using the principles outlined by Mars et al.(51)

Integrating quantitative and qualitative findings

Data from quantitative and qualitative findings will be integrated as outlined by O'Cathain et al.(52) We will use both 'following a thread' which involves selecting a question or component from one aspect of the findings and following across, and "mixed methods matrix" where, for example, responses on quantitative scales can be compared to interview transcript, and data on each case can be concisely stated and recorded on a matrix.(52)

2.9 Blinding

2.9.1 Methods for ensuring blinding

Blinding will be impossible for participants and facilitators. However, where possible we will ensure that the intervention delivery team is separate from the data collection team.

Routine data sources such as GP prescribing data are not prone to bias. Our primary clinical outcome is a participant completed outcome. Participants will, inevitably be aware of their treatment allocation. We will develop and sign off a detailed pre-specified statistical analysis plan before any outcome data are accessed for analysis.

2.10 Concomitant illness

At the start of the study, potential participants will be screened during their eligibility assessment for any concomitant illnesses. If the illness influences the potential participant's eligibility to continue in the trial (e.g. serious mental health problems that preclude participation in a group intervention) the investigator will be informed and they will be excluded.

2.11 End of trial

For this study, the end of research is defined as the date when the last participant completes their 12 month follow-up after randomisation.

Although the study is low risk, the Sponsor and CIs reserve the right to terminate the research on safety grounds at any time. Before terminating the research, the sponsor and investigators will ensure that a review of the overall benefit-risk analysis confirms the balance to be no longer acceptable. Should termination be necessary both parties will arrange the relevant procedures which include informing the Research Ethics Committee. On termination of the research, the sponsor and CI's will assure that adequate consideration is given to the protection of enrolled participants' interests.

The trial will be stopped prematurely if:

- Mandated by the Ethics Committee
- Following recommendations from the Data Monitoring Committee (DMC)
- Funding for the trial ceases

The Research Ethics Committee will be notified in writing when the trial has been concluded or terminated early.

3. METHODS AND ASSESSMENTS

3.1 Schedule of enrolment, delivery of intervention and data collection

Table 5: Contact points: enrolment, intervention and data collection

	Initial Contact (1)	Contact (2)	Contact (3)	Contact (4)	Contact (5)	Contact (6)
Contact	**Contact/ screening**	**Enrolment (Baseline)**	**Intervention**	**4 month follow up**	**8 month follow up**	**12 month follow up**
Clinician's decision to inform potential participant of study or potential participant collects invitation pack from clinic/practice reception or patient directly contacts study team	✓					
Potential participant is sent invitation pack and returns completed expression of interest form	✓					
Eligibility screening (inclusion/exclusion criteria)	✓					
Potential participant receives study pack		✓				
Potential participant completes and returns consent form		✓				
Participant completes and returns questionnaire		✓		✓	✓	✓
Eligibility is confirmed		✓				
Informed consent		✓				
Intervention delivery			✓			
Adverse events		✓		✓	✓	✓

Table 5: Contact points: enrolment, intervention and data collection						
	Initial Contact (1)	**Contact (2)**	**Contact (3)**	**Contact (4)**	**Contact (5)**	**Contact (6)**
Contact	**Contact/ screening**	**Enrolment (Baseline)**	**Intervention**	**4 month follow up**	**8 month follow up**	**12 month follow up**
Completion of weekly diary booklet (EQ5D and ShOWS) from randomisation to 4 months		✓	✓	✓		

4. ADVERSE EVENT MANAGEMENT

Our experience across multiple studies of group interventions is that adverse events directly attributable to the intervention are rare. This includes events during the session, e.g. severe psychological disturbance, or a fall during travel to and from the venue. We will manage any suspected adverse events during group or one to one sessions in line with Warwick CTU's standard operating procedures.

4.1 Definitions

4.1.1 Adverse Events (AE)

An Adverse Event (AE) is defined as any untoward medical occurrence in a participant and which does not necessarily have a causal relationship with this treatment/intervention. An adverse event can be any unfavourable and unintended sign, symptom, or disease that occurs during the time a participant is involved in the research (i.e. 12 month research period) *whether or not* it is considered to be related to the intervention.

The following are *expected* adverse events and as such will not be reported on an AE form. They will however be captured on the weekly diaries and 4, 8 and 12 month follow up questionnaires:

- Experiencing mild or moderate levels of emotional distress as a result of discussing experiences of living with opioid use to other people during the delivery of the intervention.
- Those related to opioid tapering: Anxiety, rapid heart rate, palpitations, higher blood pressure, restlessness, sweating, tremors, nausea, abdominal cramps, diarrhoea, poor appetite, dizziness, hot flushes, shivering, myalgia or arthralgia, rhinorrhoea, sneezing, lacrimation, insomnia, yawning, temporary worsening of chronic pain.

4.1.2 Serious Adverse Events (SAEs)

A Serious Adverse Event is an AE that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical condition.

For any SAEs which occur during the research study we will follow the appropriate WCTU SOPs.

4.2 Reporting related and unexpected SAEs

Participants will be asked if they have experienced any SAE/AE(s) while tapering opioid use at the nurse consultations, and if so, the symptoms which they have experienced. The research nurses in each region must report any SAEs to the trial coordinating centre within 24 hours of them becoming aware of the event.

Weekly diaries and four, eight and 12 month questionnaires will be checked on receipt for any S/AEs, and if appropriate, the participant will be asked for further details.

SAEs will be reported using the SAE form. The participants GP will not be informed of any S/AE's unless there are safety concerns and there is chance of significant harm to the participant or others. The SAE form will be completed and faxed to the dedicated fax at Warwick CTU: 02476 150549. The trial coordinator will liaise with the investigator to compile all the necessary information. The trial coordinating centre is responsible for reporting any related and unexpected serious adverse events to the sponsor and REC within required timelines. All SAEs will be recorded for inclusion in annual reports to the REC.

The causality of SAEs (i.e. relationship to trial treatment) will be assessed by the investigator(s) on the SAE form (Table 6).

Table 6: Description of SAEs Relationship to trial

Relationship to trial treatment	**Description**
Unrelated	There is no evidence of any causal relationship
Unlikely to be related	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication or device). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible relationship	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication or device). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical

	condition, other concomitant treatments).
Probable relationship	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

The TMG will review all SAE data which accumulates over the course of the trial. All serious AEs will be followed for a final outcome until the end of the follow up period (12 months). An outcome of "unknown" will not considered to be an acceptable final outcome. An outcome of "not yet resolved" will be considered an acceptable final outcome for non-serious AEs at the end of a participant's involvement in a research study, and for SAEs at database lock.

5. DATA MANAGEMENT

Submitted data will be reviewed for completeness and entered onto a secure, backed-up bespoke database held at WCTU which will be accessible only to authorised members of the team. Due care will be taken to ensure data safety and integrity, and compliance with the Data Protection Act 2018. Participants will be identified using a unique research number, allocated at entry into the study, and their initials in order to maintain anonymity. The unique research number will be recorded in the participant's CRF. Handling of personal data by the research team will be clearly documented in the participant information sheet and consent obtained.

Personal identifying information will be held at securely WCTU, when received in response to the invitation. This will include a copy of the participant consent form. Personal contact details of trial participants will be needed to organise the baseline and follow-up meetings and send information about dates, venues and timings for the intervention. This information will be filed separately from all other trial information.

In the unlikely event a disclosure is made which jeopardises the safety of the participant or another person, this will be reported to the CI's who will decide on the appropriate action. In such circumstances the participant should be informed that information will be shared with another party and the nature of the information to be shared, unless the CI's considers it unsafe to do so.

5.1 Data collection and management

All data for an individual participant will be collected by individuals from the I-WOTCH research team, delegated members of the Clinical Research Network and/or NHS Trust where appropriate, and recorded in the CRF. Original copies will be sent to WCTU, with copies of CRFs held by the research nurses in relation to the intervention. Participant identification in the CRF will be through their initials and unique research number allocated at the point of entering into the study. Data will be collected from the time the potential participant is considered for entry into the research through to completion of the intervention and follow-up period. Data will be subject to a full set of validation checks and additional data checking procedures to assure quality of data entry.

Follow-up study questionnaires will be sent at four, eight, and 12 months. The eight month questionnaire will be sent with an I-WOTCH study pen and a tea-bag, and the 12 month questionnaire will be posted to participants with a £10 high street voucher as a token of our appreciation. An I-WOTCH study pen and teabag will be enclosed with the 12 month reminder postal questionnaire as an incentive to complete. A third and final reminder will be posted out to

participants at the eight and 12 month timepoints, this questionnaire will be the key clinical outcomes only. If there are missing data (for our key clinical outcomes), this will be followed up with the participant who completed the form, as soon as possible. We will phone the participant and enter the correct information onto the form, this will be initialled and dated.

Particular procedures will be followed to resolve missing/unreturned questionnaires as detailed in the study Data Management Plan.

All (paper) data will be held securely by a member of the research team at WCTU for the baseline questionnaires, intervention evaluation sheets, postal questionnaires at four, eight and 12 months.

5.2 Database

The database will be developed by the Programming Team at WCTU and all specifications (i.e. database variables, validation checks, screens) will be agreed between the programmer and appropriate trial staff including the trial statistician.

5.3 Data storage

All essential documentation and trial records will be stored by WCTU in conformance with the applicable regulatory requirements and access to stored information will be restricted to authorised personnel.

5.4 Data access and quality assurance

We will develop questionnaires to record relevant information. Case Record Forms (CRFs) will be designed by Research Fellows and the Trial Coordinator, in conjunction with our TMG, building on the expertise of the applicants. All electronic participant-identifiable information will be held on a secure, password-protected database accessible only to essential personnel. Paper forms with participant-identifiable information will be held in secure, locked filing cabinets within a restricted area of WCTU. Participants will be identified by a code number only. Direct access to source data/documents will be required for trial-related monitoring. For quality assurance, the data and results will be statistically checked. A full data management plan will be produced by the Trial Coordinator and statistician to outline the data monitoring checks required.

5.5 Archiving

Trial documentation and data will be archived for at least ten years after completion of the trial.

STATISTICAL ANALYSIS

5.6 Power and sample size

Initial plan:

For the purposes of our sample size calculation we have used our primary clinical outcome measure, the PROMIS-PI-SF-8A (26) Using the PROMIS primary outcome, participants in the control arm are likely to obtain a mean score of 50, SD 10.(53) To show a 3.5 points difference on PROMIS-PI-SF-8A at 5% significance with 90% power, using a simple sample size calculation requires data from 346 participants. There may, however be clustering effects by group 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, in fact trivial or negligible.(13, 41, 42) However, 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 need to recruit 468 participants. Experience in similar studies is that towards the end of recruitment that to ensure the final intervention group is adequately populated there can be a need to over-recruit slightly more people than originally projected.

This sample size will provide similar statistical power to show a standardised mean difference 0.35 in the morphine equivalents of opioid used in the month prior to the end of the study.

In the COPERS study we recruited from 25 general practices with a total list size of 223,425 with an average list size of 8,937. We approached 5,878 (2.6%) people and recruited 531 (9%) to the study; 23% of these were using strong opioids. If these recruitment rates were replicated in the I-WOTCH study this would equate to 0.5 participants/1,000 registered patients. This means to recruit 468 participants we will require a population base of 936,000 (105 practices). Recruitment should be better in North East England because of higher opioid usage. We will therefore seek to recruit from around 100 general practices approximately 33 from each of three geographical locations with 850,000-900,000 patients; supplemented by recruitment from community pain services, community musculoskeletal services and local pharmacies.

Amended plan:

Responses to invitations to the study were lower than anticipated in comparison to the COPERS recruitment rates that our original estimates were based on, so the population base of the study was increased to mitigate this and ensure that our original sample size target of 468 could be met. This was done by approaching additional GP practices for the groups already planned, as well as scheduling additional groups across both regions. Recruitment processes have already started in each of these sites. This means we are in a position to recruit substantially more than 468 participants. One limitation of the original study design was that we specified a single primary outcome; pain interference as measured by the PROMIS-PI-SF-8A. However the target of our intervention is reducing opioid usage. This may be equally important as reducing pan interference .At this time we cannot predict whether the intervention will impact these outcomes in the same manner. For example, if we successfully reduce opioid usage by a meaningful amount but there is no effect on pain interference, the I-WOTCH intervention might still be considered worthwhile. We now have an opportunity to extend our recruitment to allow us to have two adequately powered primary outcomes.

The original sample size of 468 participants provides 90% power to show a 3.5 point difference on the PROMIS-PI-SF-8A (primary outcome) at 5% significance assuming a mean score of 50 and standard deviation of 10 in the control arm. This sample size also accounted for a relatively modest ICC of 0.01 assuming 10 participants per group as well as 20% loss to follow-up. The actual group size is smaller than anticipated meaning the need for sample size inflation for any clustering effects is reduced. A 3.5 point difference on PROMIS-PI-8A equates to detecting a standardised mean difference of 0.35. Assuming the effect size is of a similar magnitude for opioid use and adjusting the significance level to 2.5% (i.e. testing the two primary outcomes at the 2.5% level), the total sample size required is 542 participants (271 per group).

5.7 Statistical analysis of efficacy and harms

Data will be summarised and reported in accordance with CONSORT guidelines for randomised controlled trials, and we will use intention-to-treat analyses.(54) Hierarchical linear regression models will be used to estimate the treatment effects (with 95% confidence intervals), and will be

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 will include estimation of and adjustment for nurse effects. If there is negligible nurse effect, then the usual linear regression will be used for the analysis. Any categorical data will be assessed in a similar way, using logistic regression models. Pre-specified sub-group analyses will examine the interaction of treatment assignment with symptoms of anxiety/depression and baseline opioid use. Analysis will be conducted using formal tests of interaction.(55) This trial is not powered to identify interactions. Thus, whilst pre-specified, these analyses should be considered as no more than exploratory. We will explore 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.

5.8 Health Economic Evaluation

We will develop an initial cost effectiveness model using existing data from COPERS and the I-WOTCH pilot study, and integrate these with published data. Value of information methods will be used to characterise uncertainty in the model's input parameters, quantify their impact on the cost effectiveness of I-WOTCH and to identify those parameters for which additional data collection is warranted. These results will be used to inform the design of the main clinical trial. The second phase of the economic evaluation will be in the form of a *within-trial* cost-consequences analysis, to quantify healthcare resource use, costs and health related quality of life (HRQoL) observed during the main trial period for each treatment group. Since the costs and health benefits associated with each treatment strategy are likely to extend beyond the trial duration, the third phase will carry out a *model-based* economic evaluation (updating the initial value of information analysis) to estimate the long term cost-effectiveness of I-WOTCH versus best usual care. This *comprehensive iterative approach* has been tested and successfully been implemented by one of the applicants in the context of a number of previous NIHR and MRC funded studies.(56, 57)

Primary data from the pilot study on changes in HRQoL - measured with the EQ-5D and PROMIS-PI-SF-8A (26, 34) together with patient reported healthcare resource use will be used to inform the parameters of a cost effectiveness model. Relevant health states and clinical events relating to non-malignant chronic pain to be modelled will be determined through a search of the literature and consultation with clinical experts. These will be used to develop a de-novo state transition (Markov) decision analytic cost effectiveness model.

The uncertainty associated with all model parameters will be characterised using probability distributions. Bayesian value of information analysis will be conducted to:

i) estimate the level of decision uncertainty associated with I-WOTCH's cost-effectiveness given the existing evidence base; and
ii) determine whether the cost of the main trial is likely to be offset by its contribution to reduce the current level of uncertainty associated with I-WOTCH's cost-effectiveness.

Similarly, the value of information associated with single model parameters will be estimated. This process will identify those parameters on which it would be most valuable to reduce current levels of uncertainty through primary research. Bayesian expected value of sampling information will be used to determine the main trial sample size that will maximise the value of information associated with the main trial.

Within trial cost consequences analysis

Health benefits will be measured in terms of changes in HRQoL as measured by the PROMIS-PI-SF-8A and the EQ-5D instruments. The latter is the health benefit measure recommended by NICE for use in economic evaluation studies. Healthcare resource use will be estimated based on data from I-WOTCH pilot and main trial, and collected using a combination of participant self-reported informationand GP records. Healthcare resource use will be costed using national average figures (e.g. BNF for drugs, PSSRU unit costs and NHS reference costs for other healthcare resources). Descriptive statistics (e.g. mean, standard deviation, interquartile range) for health care resource use, total costs and HRQoL (PROMIS-PI-SF-8A and EQ5D) will be reported at 4, 8 and 12 months follow up. The impact of participant's baseline characteristics (e.g. type of non-malignant pain, number of years on opioid treatment) on healthcare resource use, costs and HRQoL will be assessed using regression models (e.g. two-part or GLM models for costs; Beta-based regression and adjusted limited-dependent variable mixture models.(58, 59) Given the trial follow up is 12 months, costs and health benefits for the I-WOTCH and best usual care groups will be left undiscounted.

Model-based long term cost-effectiveness analysis

The long term consequences of opioids dependence in patients with chronic non-malignant pain will be modelled in terms of its impact on activities of daily living, and other clinically relevant events (e.g. sleep apnoea, falls and fractures), updating the state-transition (Markov) model initially developed for the value of information analysis which used the data from the I-WOTCH pilot, main trial and the published literature. Data from the main I-WOTCH trial will be used to update the model parameters as follows. Transitions between health states as well as the occurrence of clinical events of interest will be governed by a series of risk equations estimated from the main trial data, and linked to a series of cost and HRQoL regression equations. These will be reformulated (to reflect the longitudinal nature of the outcomes of interest), and re-estimated to derive input parameters for the Markov model (e.g. the cost and EQ-5D associated with the membership of a given health state; the impact of an opioid induced adverse event on the mean cost and EQ-5D). The results will be presented in terms of incremental mean costs and incremental mean QALYs; an incremental cost effectiveness ratio will be estimated if appropriate. Probability distributions will be used to characterise sampling uncertainty for each model input parameter (e.g. Beta for probabilities, Gamma for costs). Probabilistic sensitivity analysis (PSA), will be used to propagate parameters uncertainty through the model and to quantify their effect on the costs and HRQoL outcomes. Decision uncertainty will be represented using a cost-effectiveness acceptability curve. This curve depicts the probability associated with recommending I-WOTCH as a cost-effective therapy, for different QALYs threshold values. The results of the PSA will be also used to update the Bayesian value of information analysis conducted following the I-WOTCH pilot, in order to identify which parameters are associated with the greatest source of uncertainty, and quantify the health economic value of further research in this area. The perspective for both analyses will be that of the NHS and Social Services for England and Wales. Life expectancy, costs and HRQoL will be discounted at 3.5% following NICE guidelines.

6. TRIAL ORGANISATION AND OVERSIGHT

6.1 Sponsor and governance arrangements

The University of Warwick will act as Sponsor for the study. University policies and SOPs will be adhered to.

6.2 Regulatory authorities/ethical approval

All required ethical approval(s) for the trial will be sought using the Integrated Research Application System.

Before enrolling patients into the trial, each trial site must ensure that the local conduct of the trial has the approval of the relevant NHS Trust Research & Development (R&D) department. Sites will not be permitted to enrol patients into the trial until written confirmation of R&D approval is received by Warwick Clinical Trials Unit/research team name.

Any substantial protocol amendments will be notified to all relevant parties for approval.

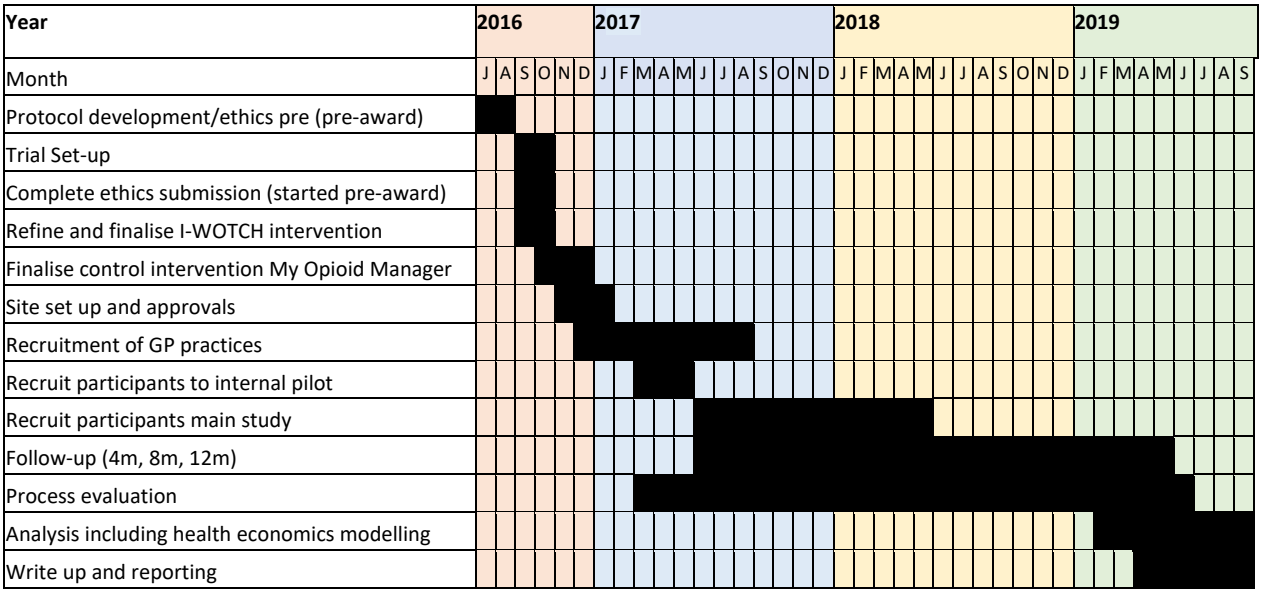
6.3 Trial Registration

This trial will be registered with an International Standard Randomised Controlled Trial Number (ISRCTN) Register.

6.4 Indemnity

NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS bodies carry this risk themselves or spread it through the Clinical Negligence Scheme for Trusts, which provides unlimited cover for this risk. The University of Warwick provides indemnity for any harm caused to participants by the design of the research protocol. Confirmation of Public Liability insurance will be required for all non NHS venues used for the delivery of the intervention.

6.5 Trial timetable



6.6 Administration

The trial co-ordination will be based at WCTU, University of Warwick.

6.7 Trial Management Group (TMG)

The Trial Management Group, consisting of the project staff and co-investigators involved in the day-to-day running of the trial, will meet regularly throughout the project. Significant issues arising from management meetings will be referred to the Trial Steering Committee or Investigators, as appropriate.

6.8 Trial Steering Committee (TSC)

The trial will be guided by a group of respected and experienced personnel and trialists as well as at least one 'lay' representative. The TSC will have an independent Chairperson. Face to face meetings will be held at regular intervals determined by need but not less than once a year. Routine business is conducted by email, post or teleconferencing.

The Steering Committee, in the development of this protocol and throughout the trial will take responsibility 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 DMC
- Informing and advising on all aspects of the trial

6.9 Data Monitoring Committee (DMC)

The DMC will consist of independent experts with relevant clinical research, and statistical experience. The DMC will have its first meeting jointly with the TSC and then agree its own meeting scheduele. Confidential reports containing recruitment, protocol compliance, safety data and interim assessments of outcomes will be reviewed by the DMC. The DMC will advise the TSC as to whether there is evidence or reason why the trial should be amended or terminated.

DMC meetings will also be attended by the Chief Investigator and Trial Co-ordinator (for non-confidential parts of the meeting) and the trial statistician.

6.10 Essential Documentation

A Trial Master File will be set up according to WCTU SOP and held securely at the coordinating centre.

The coordinating centre will provide Investigator Site Files to all recruiting centres involved in the trial.

7. MONITORING AND QUALITY ASSURANCE OF TRIAL PROCEDURES

We will perform a risk assessment and produce a monitoring plan in line with the level of risk identified.

8. PATIENT AND PUBLIC INVOLVMENT (PPI)

We have had substantial patient and public involvement in the design of this trial. At the outline stage of this application we ran two meetings at the North East and North Cumbria clinical research network (PPI) event in February 2015 with nine lay volunteers all with experience of opioid use that offered valuable information on their experiences of opioids in chronic pain, motivation to stop/reduce opioids and perceived challenges to reducing or withdrawing completely. For the main application we built on the PPI involvement by further engaging with the North East and North Cumbria clinical research network (PPI). A meeting on the 26th August 2015 with ten lay volunteers (with varied experiences of opioid withdrawal) gave further input into the feasibility of the intervention with particular emphasis on the development of the I-WOTCH Intervention. We have already had interest from lay participants to convene a reference group (6-8 participants) for the life time of the project to offer valuable input at each stage of the trial.

In addition to the above, we have also had significant input from our lay co-applicants who are involved in research and formal members of the TMG. They have been involved in the development of this study, and have commented on draft proposal documents.

9. DISSEMINATION AND PUBLICATION

The results of the trial will be reported first to trial collaborators. The main report will be drafted by the trial co-ordinating team, and the final version will be agreed by the Trial Steering Committee before submission for publication, on behalf of the collaboration.

The success of the trial depends on the collaboration of doctors, nurses and researchers from across the UK. Equal credit will be given to those who have wholeheartedly collaborated in the trial.

The trial will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org).

Scientific presentation and publications

The findings from this trial will inform clinical practice on the identification and management of patients with non-malignant chronic pain to reduce and withdraw from their opioid use. In addition to the main HTA report publication, we aim to present findings to the professional community at scientific meetings such as the British Pain Society and relevant International Conferences (e.g. World Pain Congress). We will also present findings at meetings of professional bodies such as The Royal College of General Practitioners, British Psychological Society and The Royal College of Nursing. We will publish the results in high quality peer-reviewed journals and have requested funding for open access publishing. As this will be the first intervention to address pain management and opioid reduction, we will develop an intervention paper, which will describe the development, content and intensity of the programme including the group and one-to-one element. The underpinning theory of behaviour change drawing on cross disciplines of addiction will also be described which detail strategies used to encourage adherence and commitment to withdrawal of opioids over time. Trial data will be clearly reported to allow inclusion in future Cochrane and other systematic reviews.

Research impact: Participating centres /healthcare professionals

The study team will work with the lead NHS site, UHCW, to ensure effective dissemination of our findings to healthcare professionals. For the healthcare professionals involved in the study we will disseminate results of the study through the study website. We will also host an introduction to the

intervention and trial results for commissioners and clinicians at the University of Warwick to feedback trial results and inform of the intervention. This process has been used in previous clinical trials and has proved a very popular format, allowing two-way communication between clinicians and researchers. These meetings ensure that clinical teams are informed of trial results and thanked for their valuable contribution. Importantly, it also allows for implementation of clinical changes based on trial findings prior to formal peer review publication.

Research impact: participants, patients and general public

For the patient participants and group facilitators, we will develop a study newsletter and also post a lay summary of the findings on a study specific website; with contact information should they wish to discuss the findings. Our PPI representatives will be involved with 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.

To the wider public we will also disseminate results through local and national media and via the dedicated study website. We will involve the Communications experts at UHCW and our respective higher education institutions and the NIHR Collaborations for Leadership in Applied Health Research and Care (CLAHRC) in the West Midlands and North Thames in our dissemination strategy. They are experienced in disseminating results through Twitter, Facebook and other electronic media and in gaining press coverage.

Research impact: NHS and development of training to support roll-out of the intervention

The anticipated impact of this research is the reduction of opioid use following the I-WOTCH intervention.

To facilitate the implementation of the intervention within the NHS the study findings and intervention will be made available to NHS healthcare professionals, managers, policy makers and commissioners. In addition to the HTA monograph, a summary of the study findings will be available via the WCTU website so that health care professionals can provide evidence to NHS managers and commissioners of the clinical and cost-effectiveness of the intervention.

We will adapt the comprehensive facilitator's manual and training programme used in COPERS in line with the I-WOTCH Intervention. The manual will become a reference point for the lay facilitators and nurses throughout the intervention. The main adaptions will be inserting text into the manual on the specific topics: The text will reflect back ground literature, importance of introducing this as part of the Opioid reduction topics along with examples and case scenarios on how to incorporate and give examples of delivery of the topic within the group and possible interactions with the patients.

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STATISTICAL ANALYSIS PLAN

Version: 1.0

Contents

SECTION 1: ADMINISTRATIVE INFORMATION

10. SECTION 1: ADMINISTRATIVE INFORMATION

Title: *Improving the Wellbeing of people with Opioid Treated CHronic pain (i-WOTCH)*

Trial registration number: *49470934*

SAP Version: *Version 1.0 (29 January 2019)*

Protocol Version: *Version 1.6*

SAP revisions: *None*

Roles and responsibility:

- Dr Dipesh Mistry, Warwick Clinical Trials Unit (WCTU) –Statistician (Author of SAP)
- Dr Ranjit Lall, Warwick Clinical Trials Unit (WCTU) – Statistician (Co-applicant)
- Dr Harbinder Sandhu, Warwick Clinical Trials Unit (WCTU) – Co-Chief Investigator
- Professor Sam Eldabe, The James Cook University Hospital – Co-Chief Investigator

Signatures of:

	Name	**Date**	**Signature**
Authors of SAP	James Griffin/ Dr Dipesh Mistry		
Senior statistician	Dr Ranjit Lall		
Co-Chief Investigator	Dr Harbinder Sandhu		
Co-Chief Investigator	Professor Sam Eldabe		

SECTION 2: INTRODUCTION

11. SECTION 2: INTRODUCTION

Background and rationale

Nearly eight million people in the UK have long-term painful disorders such as low back pain, neck pain, arthritis, fibromyalgia, neuralgia (nerve pain), and pain after surgery. This pain has a major impact on daily living and wellbeing of those affected. Such pain is more common with increasing age and in more disadvantaged groups in society. Typically those affected are offered pain killing drugs as their main treatment choice. A substantial minority of those affected are using long-term strong opioid drugs. These include tablets such as tramadol or oxycodone and long-acting patches such as fentanyl or buprenorphine. Morphine is sometimes prescribed.

Although opioids can be very effective in the short term they have little effect on long-term pain. In the long term they may lose their pain relieving effects completely; or even cause a paradoxical increase in pain.

There are concerns about the adverse health impact of strong opioids. Around half of people taking opioids have undesirable side effects; including nausea, vomiting, constipation, sleep disturbance, unusual drowsiness, & reduced mental capacity. In the older population, side effects mean opioid drugs increase both number of broken bones and number of deaths.

Over recent years there have been substantial increase in the amount of these drugs prescribed in the UK. There is a need for a proven intervention, targeting opioid use that helps people with long standing pain to get on with their lives without opioid drugs.

A complete summary of the background to the trial can be found in the i-WOTCH protocol.

Objectives

In the i-WOTCH study we will test the hypothesis that a group multicomponent self-management intervention combined with individual support will improve activities of daily living, for people using strong opioids for chronic non-malignant pain.

SECTION 3: STUDY METHODS

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Trial design

The overarching aim is to conduct a definitive randomised controlled trial to test the effectiveness and cost effectiveness of a multicomponent self-management intervention targeting withdrawal of strong opioids in comparison to best usual care (i.e. the control intervention) for people living with chronic pain. The interventions will be run in three locations (North East England, North East London, and West Midlands). We will adapt our existing search algorithms to identify people living with chronic non-malignant pain who have been prescribed strong opioids on more than one occasion in the previous year from GP records. Participants will be recruited from around 100 general practices, community pain/musculoskeletal services and pharmacies across the three locations.

Randomisation

The randomisation allocation ratio is 1:1 and will be stratified by geographical locality, baseline pain severity (low intensity/high intensity) and baseline opioid use (0-29, 30-59, 60-89, 90-119, 120-149 and 150+). These data will be collected via self-reported postal questionnaires while obtaining consent. Random allocations will be made using a minimisation algorithm developed by the programming team at the WCTU. The algorithm will allocate participants to minimise imbalances across the factors detailed above.

To ensure we populate the groups we will cluster groups of 4-5 geographically proximate practices with 40,000 – 50,000 patients to launch recruitment at around the same time. We will then randomise participants when we have sufficient participants to populate a group in batches of around 24 participants. This will help reduce any delay between randomisation and start of the intervention.

Original Sample size

The original sample size calculation used the PROMIS-PI-SF-8A as the primary clinical outcome measure. Using the PROMIS primary outcome, participants in the control arm are likely to obtain a mean score of 50, SD 10. [1] To show a 3.5 points difference on PROMIS-PI-

SF-8A at 5% significance with 90% power, using a simple sample size calculation requires data from 346 participants. There may, however be clustering effects by group 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, in fact trivial or negligible. However, 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 need to recruit 468 participants. Experience in similar studies is that towards the end of recruitment that to ensure the final intervention group is adequately populated there can be a need to over-recruit slightly more people than originally projected.

This sample size will provide similar statistical power to show a standardised mean difference 0.35 in the morphine equivalents of opioid used in the month prior to the end of the study.

In the COPERS study we recruited from 25 general practices with a total list size of 223,425 with an average list size of 8,937. We approached 5,878 (2.6%) people and recruited 531 (9%) to the study; 23% of these were using strong opioids. If these recruitment rates were replicated in the I-WOTCH study this would equate to 0.5 participants/1,000 registered patients. This means to recruit 468 participants we will require a population base of 936,000 (105 practices).

Revised sample size

At the 19/06/18 HTA monitoring meeting the HTA encouraged the IWOTCH trial team to ensure reported recruitment (in May and June 2018) did not slow down during the summer period. The trial team went to great efforts to ensure groups were scheduled and that timelines working up to these groups were adhered to, to mitigate any potential drop in recruitment over a traditionally slow recruitment period. Due to these efforts, it was anticipated that the sample size target of 468 would be achieved by the end of October 2018 and that we may overshoot this target. By the time the target is achieved, there is likely to be a reasonable number who have already consented to join the study. We feel

some level of commitment to these patients and thus considered over recruiting even though this was beyond the target agreed by the research ethics committee.

At the application stages of this study, we wanted to specify two primary outcomes; the PROMIS-PI-SF-8A as a measure of pain interference and opioid use without a correction for multiple comparisons. At that time we chose not to increase the sample size to allow for multiple comparisons because of uncertainty regards actual recruitment. In particular we did not know what proportion of those we identified might want to join the study and in light of this uncertainty we specified just one primary outcome. However we now know that the conversion rate is good.

The target of our intervention is reducing opioid use with the PROMIS-PI-SF-8A as a patient centred outcome as our primary outcome. With the original sample size for a single primary outcome, we cannot predict whether the intervention will impact these outcomes in the same manner. For example, if we successfully reduce opioid usage by a meaningful amount but there is no effect on pain interference, the I-WOTCH intervention might still be considered worthwhile. Therefore by over recruiting, there is an opportunity that allows us to have two adequately powered primary outcomes.

The original sample size of 468 participants provides 90% power to show a 3.5 point difference on the PROMIS-PI-SF-8A (primary outcome) at 5% significance assuming a mean score of 50 and standard deviation of 10 in the control arm. This sample size also accounted for a relatively modest ICC of 0.01 assuming 10 participants per group as well as 20% loss to follow-up. The actual group size is smaller than anticipated meaning the need for sample size inflation for any clustering effects is reduced. A 3.5 point difference on PROMIS-PI-8A equates to detecting a standardised mean difference of 0.35. Assuming the effect size is of a similar magnitude for opioid use and adjusting the significance level to 2.5% (i.e. testing the two primary outcomes at the 2.5% level), the total sample size required is 542 participants (271 per group). We anticipate to randomise 539 to 603 participants by the end of December 2018.

Framework

A superiority hypothesis testing framework will be used to compare the intervention arm to the usual care arm.

Statistical interim analyses and stopping guidance

There are no planned interim analyses or stopping guidelines for this study.

Timing of final analysis

Once all of the data has been collected from participants, entered onto the database and fully validated the database will then be locked. The final analyses on all outcomes will then be conducted stratified by each of the follow-up time points.

Timing of outcome assessments

Primary and secondary outcomes will be collected at baseline, 4, 8 and 12 months follow-up. The outcomes at the 12-month time point will be assessed for the primary analysis.

SECTION 4: STATISTICAL PRINCIPLES

13. SECTION 4: STATISTICAL PRINCIPLES

Confidence intervals and P values

The two primary outcomes will use two-sided tests at the 2.5% significance level. All other statistical tests will be two-sided at the 5% significance level. The estimate, 95% confidence interval (95% CI) and P value will be reported for each test undertaken.

Adherence and protocol deviations

We will look at two levels of adherence in this study; minimal adherence and full adherence. Minimal adherence with the intervention is defined as the participant attending day 1 of the intervention plus the first one-to-one session. Full adherence is defined as the participant attending all three days, the first one-to-one session and one or more phone calls.

Analysis populations

All analyses will be based on 'Intention-to-treat' (ITT). The participants will be analysed according to the treatment they were randomised to, irrespective of the treatment they actually received. All participants will be included in the analysis, regardless of whether they adhered to the protocol. The main summary tables and analyses will be based on the intention-to-treat population.

SECTION 5: TRIAL POPULATION

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Screening data

A detailed summary of the screening data will be presented as frequencies and percentages to describe the representativeness of the trial sample. The screening summary will start at the GP practice population search level (i.e. how many practices were approached, the number records searched, the number of mail outs etc.) right the way through to final consent and randomisation.

Eligibility

Patients are eligible to be included in the trial if they meet the following criteria:

Inclusion criteria

- Provision of written informed consent
- Aged 18 years old or above
- Using opioids for chronic non-malignant pain
- Report using strong opioids for at least three months and on most days in the preceding month
- Fluent in written and spoken English
- Willingness for General Practitioner to be informed of participation

Exclusion criteria

- 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
- Using opioids for malignant pain
- Unable to attend group sessions
- Previous entry or randomisation in the present trial.
- Participation in a clinical trial of an investigational medicinal product in the last 90 days.

The eligibility will be summarised using frequencies and percentages to describe how many people were:

- Eligible and randomised
- Eligible and not randomised
- Ineligible and randomised (in error)
- Ineligible and not randomised; summarising the main reasons for exclusion

Recruitment

The CONSORT diagram will illustrate the flow of participants throughout the trial. This will include:

- Number screened
- Of those screened, how many ineligible or declined
- Number randomised
- How many withdrew, died and were lost to follow-up at each follow-up time-point
- How many included in the final analyses at the primary endpoint listing reasons why participants were excluded

Withdrawal/follow-up

All withdrawals will be summarised by group using frequencies and percentages.

Level of withdrawal - will be summarised by treatment group i.e. withdrew from intervention alone but remained on follow-up, withdrew completely, withdrew from receiving text messages and withdrew from taking part in the interview study.

Timing of withdrawal – withdrawal timings in this trial will be summarised by treatment group as follows:

- Withdrawals after randomisation but before first group session (intervention arm only);
- Withdrawals during group sessions (intervention arm only);
- Withdrawals from follow-up - (i) withdrawal prior to 4 month follow-up (ii) withdrawal after 4 month follow-up but before 8 month follow-up (iii) withdrawal after 8 month follow-up but before 12 month follow-up

Withdrawal reason – participants have the option to provide a reason for withdrawal if they withdraw. Withdrawal reasons will be summarised.

Follow-up rates - follow-up rates are based on CRF completion at follow-up time points.

$$\% \text{ Follow-up rate (at time T)} = \frac{\text{Number of participants assessed at time T}}{\text{Total no.that should have been assessed at time T}} \times 100$$

Follow-up rates will be computed at the 4, 8 and 12 month follow-up time-points.

Baseline patient characteristics

The demographic characteristics and pre-randomisation clinical outcome measures of all randomised participants will be summarised by treatment allocation. The table below lists the demographic and clinical measures that will be collected.

Type of Data	Outcome measures
Demographic:	- Age - Gender - Ethnic group - Age at leaving full time education - Education - Occupation - Current work status
Clinical measures:	
Activities of daily living*	Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Interference Short Form (8A)(PROMIS-PI-SF-8A) [2]
Opioid use*	Opioid consumption over the last 4 weeks
Opioid prescriptions	Prescribed opioid medication from GP records expressed as average daily morphine equivalent
Pain severity	PROMIS-3A Scale v1.0 - Pain Intensity Short-Form 3A [3, 4]
Symptoms	Severity of Opioid Withdrawal (Symptoms): Short Opiate Withdrawal Scale (ShOWS)[5]
Health Related Quality of Life	- SF-12 V2 [6] - EQ-5D-5L [7]
Sleep quality	Pittsburgh Sleep Quality Index [8]

Emotional well-being	Hospital Anxiety and Depression Scale (HADS) [9]
Self-Efficacy	Pain Self Efficacy Questionnaire [10]

*Primary outcome measure

For continuous data, the number of participants (n), mean, standard deviation (sd), median and interquartile range (IQR) will be used to summarise the outcome measures by treatment allocation. The number (%) of participants will be used to summarise categorical outcome measures.

SECTION 6: ANALYSIS

15. SECTION 6: ANALYSIS

Outcome definitions

The table below lists and describes the primary and secondary outcomes. This includes details of specification of outcomes, timings and the derivation of the outcome (if required).

Outcome	Time point	Derivation of outcome
Primary outcome		
PROMIS-8A* [2]	1, 2, 3, 4	The PROMIS-8A (pain interference) is an eight- item, generic, self-report measure which assesses the consequence of pain on relevant aspects of an individual's life and key activities of daily living: engagement with social, cognitive, emotional, physical, and recreational activities. The PROMIS-8A scores will be converted from raw data collected on paper questionnaires to a total raw score between 8 and 40 (with higher scores indicating worse outcome i.e. more pain interference). To calculate standardised scores with a mean of 50 and standard deviation of 10 we will use the recommended conversion tables from PROMIS. These converted T-scores (ranging from 40.7-77) will then be the primary unit of measurement for analysing the primary outcome.
Opioid use*	1, 2, 3, 4	We will collect opioid consumption over the last 4 weeks by questionnaire. The dosage of opioids will be expressed as average daily morphine equivalent.
Secondary outcomes		
Opioid prescriptions	1, 2, 3, 4	Prescribed opioid medication from GP records expressed as average daily morphine equivalent
PROMIS-3A [3, 4]	1, 2, 3, 4	The PROMIS-3A (pain intensity) is a three-item measure where each item is scored from 1 to 5. The PROMIS-3A scores will be converted from raw data collected on paper questionnaires to a total raw score between 3 and 15 (with higher scores indicating worse outcome i.e. more pain intensity). To calculate standardised scores with a mean of 50 and standard deviation of 10 we will use the recommended conversion tables from PROMIS. These converted T-scores will then be the unit of measurement for

		analysing the outcome
ShOWS [5]	1, 2, 3, 4, 5	The ShOWS consists of 10 questions each with a score range of 0 (None) to 3 (Severe). The responses to the 10 items are then added to give a global score ranging from 0-30 where a higher score indicates more severe symptoms.
SF-12 V2 [6]	1, 2, 3, 4	SF-12 score computed using the algorithm/software provided by the authors. The algorithm produces mental and physical component scores ranging from 0-100 where a higher score reflects better physical and mental functioning.
EQ-5D-5L [7]	1, 2, 3, 4, 5	A recent statement by NICE highlighted serious concerns regarding the EQ-5D-5L tariffs published by Devlin et al [7]. For that reason, the 'eq5dmap' command in STATA will be used to map from the EQ-5D-5L to EQ-5D-3L using previously used and more reliable tariff values. The EQ-5D score ranges from <0-1 where a higher score reflects better quality of life.
Pittsburgh Sleep Quality Index (PSQI) [8]	1, 2, 3, 4	The PSQI contains 19 self-rated questions and 5 questions rated by the bed partner or roommate (if available). Only the self-rated questions are included in the scoring. The 19 self-rated items are combined to form seven "component" scores, each of which has a range of 0-3 points. In all cases, a score of 0 indicates no difficulty and 3 indicates severe difficulty. The seven component scores are then added to obtain a global score, with a range of 0-21 points, 0 indicating no difficulty and 21 indicating severe difficulty.
Hospital Anxiety and Depression Scale (HADS)	1, 2, 3, 4	The HADS consists of 14 questions each with 4 responses with an assigned score. Seven questions measure anxiety and the other seven measure depression. The scores are simply summated to give an anxiety and depression score both ranging from 0-21 where a higher score reflects more severe anxiety and depression.
Pain Self-Efficacy Questionnaire (PSEQ)	1, 2, 3, 4	PSEQ consists of 10 questions, each with 6 responses (Not at all confident to Completely confident) which are scored from 0-6 respectively. The PSEQ is computed by simply summing the scores across the 10 questions. The score ranges from 0-60 where higher scores reflect stronger self-efficacy beliefs.
Safety reporting		
Adverse Events and Serious	Throughout the trial	

Adverse Events		

1 Baseline
2 4 month after randomisation
3 8 months after randomisation
4 12 months after randomisation
5 Weekly from allocation to 4 months
*Primary outcome measure

Analysis methods

Participant characteristics and outcomes will be summarised as mean and standard deviation (sd) for continuous data or frequency and percentage for categorical data, summarised by treatment arm. The median and interquartile range (IQR) will be presented if data are non-normal.

The primary analysis approach will be intention to treat. Mixed effects regression models will be used to estimate the treatment effects for both primary and secondary outcomes. The covariates that will be included as fixed effects in the models are age (years), gender (male/female), geographical locality, baseline pain intensity (low/high) and the baseline value of the dependent variable. A random effect for the intervention group will also be included in the model to account for the natural clustering through the group element of the i-WOTCH intervention. We anticipate the group effects and corresponding ICCs to be relatively small. Nonetheless the models will account for potential heterogeneity in outcome due to the group effect. The adjusted treatment effect estimates (mean difference) will be presented along with their associated 95% confidence interval (CI). The primary analyses will assess the overall difference in the primary outcomes between the self-management (intervention) group and the usual care group at the 12 month time point. Model assumptions will be assessed as appropriate.

In reality pain interference and opioid use may be similar importance when interpreting these results. If we achieve a positive result on both outcomes, or have no effect on either outcome, interpretation is straightforward. However, if we achieve a substantial reduction in opioid use and there is no effect on pain interference then we would still regard the intervention as being successful. To reduce use of opioid pain killers without any detrimental effect on pain interferes with people's lives would be a great success. The long

term gains from reduced opioid use, beyond the lifetime of the trial, are likely to be highly important. In the event we have no effect on opioid use but we still succeed in reducing pain interference the intervention will still be worthwhile.

If possible, we will undertake a complier averaged causal effect (CACE) analysis for the primary outcomes for the two pre-defined levels of adherence to assess whether the level of compliance influences the intervention effect. Pre-specified subgroup analyses will also be conducted for the primary outcome using formal statistical tests for interaction to examine whether baseline anxiety, depression and opioid use are moderators of treatment effect.[11] The median value will be used as the cut-point to define these subgroups.[12]

Missing data

The level of missingness in the primary outcomes will be assessed and if required, multiple imputation techniques will be used to impute data and estimate the treatment effect as a sensitivity analysis.

Additional analyses

A number of participants will be included in the process evaluation interviews conducted from pre-randomisation to follow-up. It is possible that discussing their expectations and experiences before and during the study may influence the treatment effectiveness. A sensitivity analysis will therefore be performed that excludes these participants from the main analysis.

An additional sensitivity analyses will be performed to estimate the treatment effect size having adjusted for any imbalance in the death rates across the treatment arms.

Participants in this trial are recruited from primary care and pain clinics. Typically those participants recruited from pain clinics will be on more opioids and will have worse pain. For this reason, we will compare the baseline characteristics for participants recruited from primary care to those recruited from pain clinics. An additional analyses will also be undertaken to adjust for this to see if it affects the treatment effect estimate for the primary outcomes.

In order to inform future studies, we will report the effectiveness of the intervention based on the primary outcomes for people with different pain disorders, namely back pain, chronic wide spread pain and multi-site pain.

Harms

The frequency and percentage (%) of serious adverse events (SAE) and adverse events (AE) in the trial will be compared between the two treatments using the chi-squared test provided the expected values in the cross-tabulation are greater than five, otherwise Fisher's exact test will be used. Odds ratios and 95% confidence intervals will be reported. Adjusted analyses will not be performed for any harm data. The event type, severity assessment, expectedness and relatedness to intervention will also be summarised by treatment arm.

Statistical software

Statistical analyses will be conducted using the statistical software package STATA 15.0.

SECTION 7: TEMPLATE TABLES

16. SECTION 7: TEMPLATE TABLES

The template tables have been presented in a separate document that consists of the following sections:

SECTION 1 - Screening through to randomisation

SECTION 2 - Participant baseline and demographic data

SECTION 3 - Participant follow-up

SECTION 4 - Intervention data

SECTION 5 - Study outcome data

SECTION 6 - Adverse events and serious adverse events

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