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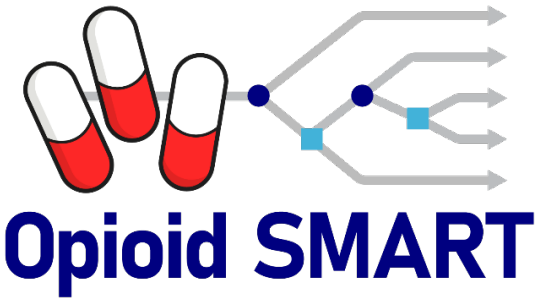

Opioid SMART WS1 and WS2

Study Title: Adapting and evaluating a complex adaptable intervention to reduce opioid prescribing in primary care (Opioid SMART)

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3. LIST OF ABBREVIATIONS

A&F	Audit and feedback
ASPIRE	Action to Support Practices Implement Research Evidence
BCT's	Behavioural change techniques
CI	Chief investigator
CNCP	Chronic non-cancer pain
CRN	Clinical Research Network
CROP	Campaign to Reduce Opioid Prescribing
CTIMP	Clinical Trials of Investigational Medicinal Products
CTRU	Clinical Trials Research Unit
DMEC	Data Monitoring Expert Committee
EHR	Electronic health records
FF	Feedback facilitation
FOG	Fellowship Oversight Committee
GCP	Good Clinical Practice
ICB	Integrated Care Board
IMD	Index of Multiple Deprivation
ITSC	Independent Trial Steering Committee
ITT	Intention to treat
LIHS	Leeds Institute of Health Sciences
MRC	Medical Research Council
NHS	National Health Service
NIHR	National Institute of Health Research
NPT	Normalisation Process Theory
NRES	National Research Ethics Service

PMT	Project management team
PPIE	Patient and public involvement and engagement
RCT	Randomised controlled trial
REC	Research ethics committee
SMART	Sequential multiple-assignment randomised trial
SOP	Standard operational procedure
UCD	User-centred design
WS	Work stream
WY	West Yorkshire
WYR&D	West Yorkshire Research and Development

4. PROJECT SUMMARY

Project Title	**Adapting and evaluating a complex adaptable intervention to reducing opioid prescribing in primary care (Opioid SMART)**
Project description	Opioid prescribing is an internationally recognised threat to population health and poses significant challenges for healthcare services. The UK is following the 'opioid crisis' trend in North America, with rapidly rising opioid-related mortality. Both patients and physicians are dissatisfied with opioid prescribing in chronic pain management. System-level interventions, such as audit and feedback (A&F), are effective at reducing opioid prescribing in primary care, with variable effects. The addition of co-interventions, such as feedback facilitation, may increase A&F effectiveness but with additional costs of delivery. An adaptable intervention uses individually-tailored decision rules to specify how, when and whether to increase the intensity of the intervention at critical decision points. AIM AND OBJECTIVES To develop and optimise an adaptable implementation strategy to reduce prescribing of opioids for chronic non-cancer pain (CNCP) in primary care using a clustered, sequential, multiple-assignment randomised trial (SMART). 1. To adapt and refine two interventions that reduce prescribing of opioids, A&F and feedback facilitation; (Work stream 1, WS1); 2. To evaluate the feasibility and acceptability of delivering the

	interventions in general practice; (Work stream 2, WS2); 3. To optimise and evaluate the adaptable intervention using a SMART design to determine whether feedback facilitation increases (cost-) effectiveness, when and for whom to intervene; (Work stream 3, WS3); 4. To evaluate intervention acceptability, adoption, appropriateness, feasibility, fidelity, penetration and sustainability. (Work stream 4, WS4). This protocol relates to work stream 1 and work stream 2 (WS1, WS2).
Project Design	User-centred design (WS1) Feasibility study (WS2)
Planned Sample Size	WS1: 25 stakeholders, including 5 PPIE representatives. WS2: 8 general practices
Planned project Period	Overall project: 03/2024-02/2029 (60 months) WS1: 10/2024-06/2025 (9 months) WS2: 10/2025-10/2026 (13 months)
Primary Outcome	WS1: Audit and feedback reports and feedback facilitation manual adapted and updated. WS2: Refined adaptive interventions with known feasibility and acceptability
Secondary Outcomes	WS1: Mapping of Behavioural Change Techniques (BCTs) across interventions
	WS2: Tools to support feedback facilitation
Interventions	A&F: Bimonthly centralised Electronic Health Record (EHR) data extraction (audit) and reports (feedback) delivered to practices by email and an online repository. Feedback facilitation: Initial half-day facilitation event delivered by trained facilitators with practice staff involving educational components, local barrier identification and action planning to improve clinical performance, followed by bimonthly follow-up calls with each feedback report for ongoing support.

5. BACKGROUND

5.1. Introduction

Primary care prescribing of opioids in England has more than doubled in the last decade, with larger increases for more potent opioids (1,2), reflecting international trends (3–6). Currently, over 1 in 20 adults are prescribed regular opioids for chronic non-cancer pain (CNCP) (7); an estimated 40% of these are overprescribed at an annual cost of £100M to the NHS. This estimate does not include costs associated with the management of adverse events (8), work absences, reduced social functioning (9) and societal costs of prescription opioid misuse, estimated to exceed £56M in the UK in 2015 (10). Overprescribing is strongly associated with deprivation, with the highest prescribing in the north of England (11,12). Over one third of patients eventually more than double their original opioid dose and around 10% are prescribed potentially hazardous high doses (3). Rather than reflecting previously untreated CNCP, these patterns suggest a wider change in the general approach to prescribing (13,14). Pain management guidelines suggest clinical benefit needs to be clearly demonstrated when considering long-term prescribing for CNCP (15). Furthermore, there is international agreement that high-dose opioids should be used with extreme caution for indications other than cancer-related pain (15). Over 90% of opioids are prescribed in primary care, with up to 10-fold variations in prescribing between practices, suggesting prescribing is driven by clinician habits rather than patient need (16).

- A provider-level intervention in the UK is needed to reduce overprescribing of opioids for CNCP, and fits national priorities, including:

- Department of Health and Social Care plan to reduce overprescribing and its associated health inequalities (17);

- Recommendations from the National Institute for Health and Care Excellence (18) and Faculty of Pain Medicine of the Royal College of Anaesthetists (19);

- The NHS long-term plan to undertake Structured Medication Reviews in patients taking potentially addictive pain management medication (20).

5.1.1 Interventions to reduce opioid prescribing in primary care

Whilst a growing body of work has investigated problematic opioid prescribing (16,21–24), less attention has been paid to evaluating proposed solutions. A Cochrane review found inadequate evidence for interventions targeting opioid use in individuals with CNCP (25). However, recent studies indicate the value of multifaceted provider- and system-level interventions (26–29) to change clinician prescribing behaviour, including audit and feedback (A&F), financial incentives, educational outreach, computerised prompts and patient education. A&F is a widely used foundational component of quality improvement (30).

5.1.2 Evidence for A&F

A&F improves patient care by comparing clinical performance against evidence-based standards and highlighting areas requiring action. A&F interventions are moderately, but variably effective (A&F median 4.3% absolute improvement; interquartile range 0.5-16%)

(31,32). A&F appears particularly effective at changing prescribing behaviour and is generally acceptable to primary care clinicians (31,33,34). The availability of electronic health records (EHR) makes practice-aggregated primary care prescribing data accessible at relatively low cost, meaning that A&F can be scaled up for population impacts.

A&F is effective at reducing opioid prescribing in primary care (35). The Chief Investigator designed and delivered an evidence- and theory-informed A&F Campaign to Reduce Opioid Prescribing (CROP) to 316 general practices. Practices received bimonthly comparative feedback with persuasive messaging prompting clinicians to "think twice" before initiating opioid prescribing for CNCP and actively review repeat prescribing. The A&F intervention cost around £50,000 (including staffing, data extraction and delivery) yet saved almost £1M in expected opioid prescriptions, with 15,000 fewer patients in West Yorkshire prescribed opioids over 2016-17. The biggest reduction occurred in the over-75s, at higher risk of falls and death. The feedback was well received and did not harm relationships with patients (36). However, practice achievements remained highly variable with 30% of practices increasing prescribing and only 10% reducing prescribing by over 1% during the intervention year.

5.1.3 Evidence for co-interventions to enhance feedback response

Theories suggest health professionals may not all have the knowledge, skills and resources to engage with and respond to feedback, creating variation in its effectiveness (37,38). Co-interventions to A&F (e.g., feedback facilitation, educational meetings) can increase feedback success by addressing these barriers to quality improvement. The Cochrane review on A&F found a lack of head-to-head comparisons supporting use of co-interventions (31,32). This work aims to address this knowledge gap.

Feedback facilitation (FF) seeks to strengthen responses to feedback by identifying causes and developing solutions for sub-optimal performance through application of implementation methods (e.g. analysis of barriers and enablers (39)) and strategies (goal setting, quality improvement and problem solving) (40) through social interaction (37,41). Primary care practices are 2.76 (95% CI 2.18-3.43) times more likely to adopt evidence-based care through feedback facilitation (relative to no intervention controls) (42). Higher intensity of facilitation (number of contact hours) is associated with larger intervention effects but has further cost and resource implications (42).

5.2 Adapting complex interventions to a new context

The ADAPT guidance (43) was developed through a systematic review, interviews and a consensus process and gives a step-by-step guide on adapting an existing complex intervention to a new context. Developing a new intervention for every new context wastes the knowledge and resources that were put into developing existing interventions. Adapting an intervention can be useful if there is a new setting or healthcare system or to improve the impact on population subgroups identified as not being reached or disadvantaged by the original intervention.

The ADAPT guidance describes four steps (43):

1. Look at the rationale for the intervention and review the intervention-context fit for the existing intervention.

a. Define the target population and the implementation problem.

b. Determine suitable interventions to be considered.

c. Review the intervention details and its previous evaluations in context.

d. Review effectiveness claims and risks of bias.

e. Map the intervention similarities and differences between new and old contexts, and importance of each in intervention functioning.

f. Work through any Intellectual Properties issues.

2. Work through adaptions.

    a. Assess barriers and facilitators in a new context and how the barriers might be overcome.

    b. Consider materials needed and any adaptions to existing materials, including logic models, protocols and delivery manuals.

    c. Pre-mortems of potential unintended consequences.

    d. Review costs of and resources for delivery which may be very different to the original context.

    e. Recruit team for delivery.

3. Pilot and evaluate adapted intervention as needed.

    a. Decide on what evaluations are needed by considering the uncertainties and new evidence needed regarding the initial intervention and the adapted intervention. This may also depend on the original evidence for the intervention and the number of adaptations needed. Evaluations may be pragmatic and range from non-randomised to full Randomised Controlled Trials (RCTs) and process evaluations. Consideration of information needed by policy makers and stakeholders and the resources needed for evaluations is also required.

    b. Pilots can help evaluate feasibility and further adaptations needed before implementation.

    c. Document any responsiveness in the adaptations, including how closely they align with the logic model to monitor for spontaneous adaptations that do not fit within the Mechanisms of action, guide ongoing delivery and plan for future adaptations.

    d. Conduct any (cost-)effectiveness and process evaluations as previously determined.

4. Deliver and continue the adapted intervention, scaling up as needed.

a. Develop relationships to ensure the adapted intervention is sustainable and ongoing needs are met.

b. Consider how the adaptive intervention can be monitored, and develop data monitoring systems, to allow comparisons across different contexts and identify populations not being reached and ensure ongoing consistency in delivery.

c. Report on the adapted intervention, e.g., using TIDIeR-PHP (44) or FRAME guidance (45) for adaptations. The guidance also includes specific questions including:

    i. Population health problem

    ii. Description of original intervention, effectiveness and context

    iii. New context, similarities and differences to original context

    iv. Rationale, type & processes of adaptions, including stakeholders

    v. Description of the adapted intervention in detail

    vi. How well the adapted intervention was delivered in the new context

    vii. Rationale for any evaluations

    viii. Role of original intervention developers in the adaptation process.

The guidance also notes that diverse stakeholders are needed throughout the adaptation process.

5.3 Assessing feasibility of delivery of the new adapted interventions

The updated MRC framework for complex interventions (46) suggests feasibility assessments should have defined progression criteria for the design of the effectiveness evaluation (e.g., recruitment, data collection, retention, outcomes and analysis), and for the complex intervention itself (e.g., content, delivery, acceptability, adherence, likelihood of cost-effectiveness and deliverability). If a programme theory suggests that the context of the intervention is important, or that implementation factors might influence effectiveness, acceptability or cost-effectiveness, then these should also be examined.

Guidance on feasibility studies in sequential multiple-assignment randomised trial (SMART) designs (47) identifies nine areas to consider in a SMART pilot that are relevant to this study:

1. Primary tailoring variable (Is the number of patients taking opioid medication for CNCP sensitive to change at 6-months to determine non-response of practices to A&F alone?);

2. Randomisation procedure (Is the randomisation process feasible to deliver in the time between data collection and its associated A&F report delivery?);

3. Other potential tailoring variables (What baseline characteristics of practices and time-varying measures (e.g., Index of Multiple Deprivation (IMD) scores, intervention adherence) should be collected that may be important on analysis?);

4. Identifying unanticipated tailoring variables (uncovering new and potentially important variables that might impact on practice engagement and achievement in reducing opioid prescribing);

5. Evaluation (SMART) assessments versus intervention assessments, ensuring a clear distinction between data collected as part of the intervention (e.g., rates of opioid prescribing to inform feedback reports) and data collected to evaluate effectiveness (e.g., fidelity to intervention);

6. Practice acceptability and fidelity to changes in intervention (What concerns do practices have regarding the intervention delivery and assessment of non-response?);

7. Practice concerns about changes in interventions (Are there any concerns regarding the addition of feedback facilitation to non-responders?);

8. Ethical and consent procedures (Is Integrated Care Board (ICB)-level consent and practice-level opt-out consent acceptable to practices?)

6. PROJECT AIMS AND OBJECTIVES

6.1. Aim

Overarching aim: To develop and optimise an adaptable implementation strategy to reduce prescribing of opioid painkillers for persistent pain in primary care using a clustered, SMART design. The overall goal is to reduce the NHS and societal costs of potentially harmful opioid prescribing.

This programme of work exemplifies adherence to the updated MRC framework for developing and evaluating complex interventions (46), so that the resulting adaptive implantation strategy is feasible, (cost-) effective, transferable, and scalable in real world contexts.

6.2. Objectives

This programme of work will be delivered through four work streams (WS):

WS1: User-centred design of an adaptable intervention package

- To update and refine two interventions known to be effective at changing prescriber behaviour in primary care, A&F and FF.

WS2: Feasibility study to evaluate the feasibility and acceptability of delivering the interventions in general practice

- Establish feasibility of delivering interventions designed in WS1;

- Establish intervention adherence;
- Establish availability and feasibility of collection of outcome, process and economic data;
- Explore practitioner acceptability of trial design and interventions;
- Establish levels of burden among:
    - Practices receiving the most intensive interventions;
    - Healthcare professionals changing practice.

WS3: SMART

- To optimise the adaptable intervention using a SMART design and evaluate:
    - Whether feedback facilitation is effective and cost-effective for practices who are non-respondents to feedback alone;
    - The optimal time to intervene with feedback facilitation for practices who are non-respondents to A&F alone;
    - Identify baseline tailoring variables moderate the effectiveness of feedback facilitation for non-responders.

WS4: Process evaluation

- To evaluate intervention acceptability, fidelity, penetration and sustainability through a mixed method, longitudinal approach to understand how and why implementation improves (or not) following the adaptive intervention, and key contextual influences.

This protocol relates to WS1 and WS2.

7. **INTERVENTIONS**

Two interventions, A&F and FF have previously been developed and found to be effective in changing prescribing behaviour in primary care (35,48).

7.1. **Audit and feedback**

The Chief Investigator designed and delivered an evidence- and theory-informed feedback campaign, the Campaign to Reduce Opioid Prescribing, to 316 general practices in West Yorkshire. Practices received bimonthly comparative feedback prompting clinicians to “think twice” before initiating opioids for chronic, non-cancer pain and actively review repeat prescribing. Email and six paper copies of the feedback reports were sent to the practice manager, asking them to share with prescribing clinicians. Reports gave the number of their patients aged over 18 prescribed opioids in the preceding eight weeks, excluding those with coded palliative care or drug dependence, compared to other practices within their Clinical Commissioning Group and West Yorkshire, as well as changes over time. Report content

and formats followed a design previously demonstrated to reduce high-risk prescribing in primary care that addressed identified Theoretical Domains Framework determinants of adherence to quality indicators (31). Feedback highlighted patient groups at higher risk of long term or stronger opioid prescribing (33). The reports incorporated evidence-informed behaviour change techniques, such as specific recommendations for action and action plans, designed to enhance effectiveness (49). Given competing priorities and demands that primary care physicians face in routine practice, the reports used non-judgmental and encouraging language. Practices received six bimonthly reports. Over 2016-17, the number of patients taking opioids, compared to controls, fell by 0.65/1000 adults/month (95% confidence interval -0.96, -0.34), equating to 15,000 fewer patients prescribed opioids (including reductions in new prescribing and stopping long-term prescribing) and £900,000 saved in predicted prescribing costs (35). The intervention cost less than £50,000 to deliver (£158 per practice). However, the associated costs to the practice implementing changes in prescribing is unknown. The feedback was well received and did not harm relationships with patients (36). Yet practice achievements were highly variable. The intervention has now been delivered across the North of England, an area with high socio-economic deprivation, reduced life expectancy and higher rates of chronic disease, with widening heath inequalities (50).

7.2. **Feedback facilitation**

The CROP feedback report was based on the feedback reports delivered as part of the Action to Support Practices Implement Research Evidence (ASPIRE) (48). The ASPIRE programme aimed to develop and evaluate an adaptable intervention package to target implementation of ‘high impact’ clinical practice recommendations in primary care. The facilitation intervention involved visits delivered by trained pharmacist facilitators to discuss practice performance and development of action plans. The facilitation (referred to as educational outreach in the programme) aimed to build on the feedback reports by facilitating individual and group reflection within the practice, discussing barriers to action, sharing models of good practice, enhancing motivation and action-planning. Pharmacists were recruited and trained in 2 days to deliver the facilitation sessions. The sessions were planned to fit within practice meetings and approximately 30-minutes in duration. They were offered to intervention practices taking part in the trial, but were not mandatory. All staff involved in patient and practice management were invited to attend. A key clinical champion to support practice engagement was identified. A follow-up session to review progress and refine action plans was offered, and two days of pharmacist support for patient identification and review.

8. **SETTING**

The study setting is all practices within NHS West Yorkshire Integrated Care Board (WY-ICB). This area receives Core20PLUS5 funding for serving the most deprived 20% of the population from the National Healthcare Inequalities Improvement Programme (51). Core20PLUS5 was established in 2021 by NHS England to reduce healthcare inequalities. All practices within this area received the CROP feedback intervention to reduce opioid prescribing in 2016-2017. Despite previous reductions in opioid prescribing in response to the CROP intervention, opioid prescribing remains higher than the national average (top quartile). Previous progress in reductions has stalled due to the impact of the COVID-19

pandemic on primary care consultations (telephone assessments rather than in-person and a reduction in consultation rates for non-COVID problems) and the wider health system (reductions in referrals, staff reallocation to COVID wards, lack of secondary care and MSK appointments and increasing waiting times for appointments and treatments). Reducing potentially harmful opioid prescribing remains a priority area for the ICB medicines optimisation leads.

WY-ICB covers a socioeconomically diverse population of 2.34 million residents that is broadly typical of national demographics, with the exception of higher deprivation levels (52). Currently over 270 general practices are organised within five sub-ICB locations. Within this study area, there are both more affluent and deprived areas. For example, in the Bradford and Craven sub-ICB, half of the practices are in the most-deprived decile (IMD), however the area also covers the more affluent areas of Ilkley and Addingham which are in the least deprived decile. This within-area variation will allow us to examine the impact of how tailoring variables moderate the effectiveness of A&F alone or combined with FF.

All practices within WY-ICB will receive the adaptable intervention of A&F with or without FF as part of a regional quality improvement initiative. Therefore, recruitment for WS1 (user-centred design) will be WY-ICB, whereas WS2 (feasibility study) will take place outside this area in NHS Humber and North Yorkshire and NHS South Yorkshire ICBs. These areas have also previously received the CROP intervention (2019-2020 and 2021-2022 respectively), remain high prescribers of opioid medications, and have similar demographics to West Yorkshire.

9. WS1: USER-CENTRED DESIGN OF AN ADAPTABLE INTERVENTION PACKAGE

9.1. Design

Stakeholder and Patient and Public Involvement and Engagement (PPIE) user-centred design (UCD), following ADAPT guidelines (43). UCD is a well-established method to optimise intervention usability and user experience (53) through repeated cycles of design and evaluation (54,55).

9.2. Recruitment and sample size

Twenty-five participants will take part in WS1, including five PPIE representatives. Healthcare professionals representing clinicians (GPs, advanced nurse practitioners, primary care pharmacists), PPIE representatives, practice managers, quality improvement and A&F experts and service commissioners will be invited to take part.

Recruitment by invitational email to known contacts will take place through different approaches depending upon the stakeholder role:

(i) To recruit general practice staff, invitations to take part in the study will be sent via email with a participant information sheet to all practices within WY-ICB via West Yorkshire Research and Development team (WYR&D) and through local Clinical Research Network (CRN) mailing lists;

(ii) PPIE representatives will be recruited from the Opioid SMART PPIE group;

(iii) A&F experts will be recruited via the Audit and Feedback 'Metalab';

(iv) Service commissioners will be identified from known contacts, using snowballing methods if needed.

We will ensure diversity of expertise in the recruitment process.

9.3. Eligibility criteria

9.3.1 Inclusion criteria

1. Consents to take part in 'World café' stakeholder workshops and/or individual testing rounds;

2. Prescribes opioid medication in primary care (clinicians), or involved in quality improvement in primary care, or commissions services, including medicines optimisation, for primary care, or expertise in delivering A&F and/or FF, or member of Opioid SMART PPIE group.

9.3.2 Exclusion criteria

1. Unable to speak or read English;

2. Unable to attend workshops or an in-person or online testing round

9.4. Consent

All participants will receive a participant information sheet and consent form prior to their first workshop or individual testing round. Consent will be obtained for data to be audio-recorded and field notes to be taken during stakeholder World café workshops and using think-aloud techniques and semi-structured interviews during individual testing rounds (56,57).

9.5. Methods

UCD workshops, followed by iterative rounds of design and evaluation, following ADAPT guidance.

9.5.1 Workshop 1 – Intervention-context fit (Project Management Team (PMT))

The first workshop will have four aims from ADAPT step 1:

(i) Review the CROP A&F and ASPIRE facilitation intervention details and its previous evaluations in the new context;

(ii) Review effectiveness claims for both interventions and any potential risks of bias;

(iii) Map the similarity and differences between the interventions' original use (within CROP and ASPIRE) and the new context (delivery within Opioid SMART) (43);

(iv) Identify any potential intellectual property issues that need to be addressed.

OUTPUT: A list of suggested adaptions to both interventions to take forward to workshop 2.

9.5.2 Workshop 2 – Working through adaptions (PMT)

The second workshop will have two aims. Firstly, to consider (i) how to embed behavioural change techniques (BCTs) addressing known determinants to opioid prescribing (58,59); (ii) modifications informed by process evaluations of the existing interventions, particularly those thought to have impacted on intervention effectiveness and suggestions for improvements (36,60,61); (iii) theory-informed hypotheses (62); and (iv) evidence from the updated A&F Cochrane review and a systematic review of FF (63) into the two interventions. Secondly, Normalisation Process Theory (NPT) will be used as a sensitivity tool to consider potential barriers and facilitators in the new context and suggested solutions to barriers will be developed, alongside any materials needed and costs and resources for delivery. NPT is a theory of implementation designed to assist interpretation of how people in healthcare teams individually or collectively embed (or not) new work practices (64). It includes four constructs: Coherence; Cognitive participation; Collective action; and Reflexive monitoring.

A pre-mortem will be held to identify any potential unintended consequences.

OUTPUT: Prototype interventions ready for iterative design and evaluation.

9.5.3 Rounds 3 to 7 - Iterative design and evaluation (Stakeholder panel).

This involves rounds of design and evaluation of the adaptable implementation package for potential fit within the organisational context of primary care and feasibility of operationalisation by the stakeholder panel. Each round will comprise designing the prototype adaptable intervention followed by formative evaluation with stakeholders (65,66). Each intervention will be revised as needed over an anticipated 3-5 rounds of testing, until the design is optimised (67).

The first two rounds will use a ‘World café’ format, with moderators at each table to guide the discussions (68). After an initial introduction, four rounds of discussions will take place, with each table focusing on different elements of the design. Participants will move around each table, with different groups forming for each round to ensure cross-pollination of ideas. The workshops will finish with a plenary of each table’s results, priority voting for amendments and wrapping up and closing of the events.

9.5.3.1 Workshop 3 - (15-20 Stakeholders):

The first stakeholder World café workshop will look at the audit and feedback reports. Stakeholders will consider: (i) the audit (measures of performance and data available), including inclusion and exclusion criteria for denominators, accuracy of population identified and relevance to improving prescribing of opioid medication for non-cancer pain; and (ii) the feedback (report presentation and content), including comparators, positive or negative framing, messages, educational content, improving reach within practices and display of information.

9.5.3.2 Workshop 4 - (15-20 Stakeholders):

The second stakeholder World café workshop will look at feedback facilitation. Stakeholders will consider: (i) content of initial facilitation meeting (identification of potential targets, components, barriers and facilitators; (ii) content of follow-up facilitation; and (iii) delivery of initial and follow-up facilitation (including duration, intensity, delivery method and improving reach and retention.

9.5.3.3 Individual testing rounds - (3-5 Stakeholders per round):

Further rounds (up to four) will take place with individual stakeholders to further refine and optimise the interventions as identified from the World café discussions. Paper-based prototypes from the previous round and the new prototypes will be shared to allow comparison of changes. Using a comparative previous prototype can encourage participants to feel more comfortable in reflecting on amendments and criticise design elements in the new prototype, as does the use of 'draft' versions of an intervention (69).

OUTPUT: Two interventions to take forward to feasibility testing (WS2):

1. *Audit and feedback:* Bimonthly centralised EHR data extraction (audit) and reports (feedback) delivered to practices by email and an online repository.

2. *Feedback facilitation:* Initial half day facilitation event delivered by trained facilitators with practice staff involving educational components, local barrier identification and action planning to improve clinical performance, followed by bimonthly follow-up calls with each feedback report for ongoing support.

9.5.4 Data collection and analysis

Think-aloud techniques will ask participants to talk through their thoughts and reactions as they review and make sense (understand) the interventions, including whether they feel prompted to act. Semi-structured interviews will prompt discussion of specific elements of content and presentation if not mentioned during the think-aloud and for impacts on motivation to act. For all individual testing rounds, participants will be asked to complete the System Usability Scale (70) to measure the subjective usability of both interventions. The System Usability Scale is a 10 item, validated questionnaire that uses a five-point Likert scale. It measures perception, is ideal for comparing old and new prototypes, and does not take long to complete (70).

Following each workshop and individual testing round, audio-recordings and field-notes will be transcribed and analysed thematically using a directed qualitative content analysis. Key themes will be summarised with implications for the design of the audit and feedback and facilitation interventions. The research team will consider how to make changes in response to the findings and develop further draft prototypes for the next round of testing (57). Following the final round of testing, where no new features are recommended for change, the final prototypes will be developed for feasibility testing (WS2).

10. WS2: FEASIBILITY STUDY WITH NESTED QUALITATIVE STUDY

10.1. Design

Mixed-methods feasibility study of interventions developed in WS1 with cluster randomisation at the practice-level. The Chief Investigator has already shown that it is feasible and acceptable to recruit practices and deliver A&F reports on opioid prescribing using routinely collected EHR data in the study area (35,36). Therefore, this study will assess the feasibility and acceptability of the feedback facilitation components in addition to A&F, and any adaptions made to the A&F in WS1 (for example, changes to audit searches).

10.2. Recruitment and sample size

10.2.1 Practice recruitment

Eight practices will be identified from Yorkshire and Humber who have previously received the CROP intervention and are not within West Yorkshire ICB. A 2x2 sampling frame of baseline opioid prescribing (above or below the mean number of patients taking opioid medication for non-cancer pain across the eight practices) and practice deprivation score (IMD, higher or lower than the sub-ICB average) will be used, to achieve a diverse group of practices with variation in hard-to-reach patient groups (36). Practices will be identified through existing contacts, WYR&D contacts and CRN mailing lists. An invitation to express interest in the study, along with an information sheet and contact numbers will be emailed to eligible practices.

10.2.1.1 Eligibility criteria

10.2.1.1.1 Inclusion criteria

a. Practice within Yorkshire and Humber that has previously received the CROP intervention and not located within WY-ICB;

b. Not currently in receipt of other interventions that aim to reduce prescribing of opioid medication;

c. Able to identify a lead clinician or quality improvement lead for the study;

d. Willing to take part in a FF event.

10.2.1.1.2 Exclusion criteria

a. Practice providing enhanced services for drug dependency;

b. Practice in lowest ICB decile for opioid prescribing.

10.2.1.2 Contractual agreement

Written contractual agreement to participate in the feasibility study will be obtained from practice managers or practice research leads using the Organisation Information Document (OID) for non-commercial research. Recruitment to the feasibility study will continue until eight practices have agreed to take part.

A formal power calculation is not appropriate for WS2 as effectiveness is not being evaluated.

10.2.2 **Healthcare staff recruitment**

Recruitment to the nested qualitative study interviews will involve the research team contacting practice staff members directly (for those they previously contacted during the study), and/ or the practice manager of recruited practices sending an email to relevant members of staff with a study information sheet, consent form and contact details for the research team. Snowball sampling will also be used, where practice staff can share the study with other relevant practice staff. A maximum of 25-30 staff will be recruited, approximately 3-5 per practice. Experience suggests this number generates rich qualitative data and saturation of themes in similar studies (36,71). It is unlikely that more than five staff per practice will be involved in quality improvement programmes.

10.2.2.1 Eligibility criteria

10.2.2.1.1 Inclusion criteria

a. Healthcare / practice staff with a prescribing or quality improvement role within the practice;

b. Employed or role within the practice during intervention delivery period.

10.2.2.1.2 Exclusion criteria

a. Unable to provide written consent;

b. Unable to meet in person, over telephone, or online for an interview.

10.2.2.2 Consent

Written consent to participate in the study interviews and for audio recording of the interview will be obtained from individual members of staff prior to the start of the interview.

10.3. **Randomisation**

Practices will be randomised (1:1) to receive bimonthly A&F and feedback facilitation, or bimonthly A&F intervention alone for six months. Stratified permuted block randomisation with fixed block sizes to maintain group sizes will be used, stratifying by baseline opioid prescribing (above or below the median number of patients taking opioid medication for non-cancer pain across the eight practices). Creation of the lists and the randomisation will be performed by the statistics team.

10.3.1 **Blinding**

Due to the nature of the intervention, practices, participants and the study team will not be blind to practice allocation.

10.4. **Endpoints**

This study will explore the feasibility and acceptability of delivering the interventions in general practice:

1. Establish feasibility of delivering interventions designed in WS1:
    - Time to process EHR data to identify responders and non-responders;
    - Time to delivery of facilitation event to practices including proportion of facilitation events delivered within 4 months of delivery of first feedback report;
    - Number of calls/ emails required to organise the facilitation event;
    - Duration of facilitation events and follow up facilitation calls;
    - Number of follow up facilitation calls delivered;
    - Number of calls/ emails required to organise follow up facilitation calls;
    - Time to delivery of follow up facilitation calls.
2. Establish intervention adherence
    - Number and roles of staff attending facilitation event;
    - Identification of priorities from data completed at facilitation event (Yes/No);
    - Identification of barriers (Yes/No);
    - Completion of an agreed action plan at facilitation event;
    - Evidence of discussions regarding progress made with action plan at follow-up facilitation calls;
    - Email delivery receipts for feedback reports;
    - Number and type of BCTs delivered at the facilitation event and during follow up facilitation calls;
    - Updated action plan sent back to practice staff following the follow up facilitation calls (Yes/No).
3. Establish availability and feasibility of collection of outcome, process and economic data
    - A&F data obtained for inclusion in feedback reports, including proportion of practices providing data at 6 months on proportion of patients prescribed opioids (per 1000 patients);

- Proportion of patients prescribed opioids after 6 months at each practice;
- Time taken to write each of the feedback reports (1 to 4)
- Time to obtain routinely collected data from EHRs;
- Number of accesses to feedback report online repository;
- Time taken by practices to run audit searches to collect outcome and process data (information regarding consultations delivered).
- Number of staff who agree to be interviewed and their roles;
- Number of patients having a medication review, length of review and method of consultation (face-to-face, telephone etc.) and role of healthcare professionals delivering long-term opioid medication reviews;
- Number of appointments for consultations regarding CNCP (where an opioid may reasonably be expected to be prescribed);
- Number of referrals to musculoskeletal, orthopaedics, physiotherapy, and pain teams following a consultation for CNCP;
- Number of attendances at emergency departments or admissions to hospital with an opioid-related condition for patients taking opioid medication;
- Number of patients who have experienced adverse events from opioids
- Number of patients on opioids with a past medical history of dependency
- Number of patients who have experienced an overdose on opioids
- Number of and description of patient complaints as a significant event
- Fidelity of facilitation delivery from audio and video recordings and facilitator field notes, including BCTs delivered as intended;
- Qualitative interviews.
- Protocol deviations / violations

4. Explore practitioner acceptability of trial design and interventions
    - Qualitative interviews

5. Establish levels of burden among practices receiving the most intensive interventions and healthcare professionals changing practice
    - Qualitative interviews

10.5. **Data collection**

Quantitative and qualitative data will be obtained at multiple time points during the feasibility study (table 1). An explanatory sequential approach will be undertaken, with initial quantitative data used to inform the qualitative data collection to develop explanations and expand upon findings (72). For example, if the quantitative data shows poor attendance at the facilitation event or follow up calls, the qualitative interviews will explore the barriers to, and potential facilitators to attending.

10.5.1 **Quantitative data**

Quantitative data will include routinely collected data, aggregated at a practice-level, from EHRs collected by the sub-ICB medicine optimisation lead and/or practice administrators. No individual patient level data will be obtained. Data items will relate to the audits from WS1 for inclusion in feedback reports and additional process and outcome data as specified above. Data will be securely stored in the University of Leeds OneDrive, with access restricted to the research team and Leeds Clinical Trials Research Unit (CTRU) staff working on the project. All patient data will be aggregated by practice and no individual-level data will be obtained.

We will collect descriptive summaries of the eight practices recruited to the feasibility trial. Where possible, we will collect this information from public domains (e.g., practice website; NHS GP patient survey; Fingertips). Where we cannot find data online, we will contact the practice directly for this information.

The baseline descriptive data we will collect includes the following:

- Practice Code
- Practice name
- Index of Multiple Deprivation (IMD) score (2019)
- Deprivation level
- Opioid prescribing baseline (Average opioid items/1,000 patients in 2024)
- Practice list size
- Average GP practice list size within the practice's Primary Care Network
- Sex of practice list (e.g., number of females patients at the practice)
- Life expectancy (Male)
- Life expectancy (Female)
- Ethnicity of the practice list
- Care Quality Commission (CQC) rating

- Quality and Outcomes Framework (QOF) score – percentage of total available points achieved
- Total number of appointments over the prior one month period
- Number of face-to-face appointments over the prior one month period
- Percentage of face-to-face appointments over the prior one month period
- Number of appointments per 1,000 patients over the prior one month period
- Number of same day appointments over the prior one month period
- Percentage of total appointments over the prior one month period that were same day appointments
- Number and proportion of practices with ‘Overall, how would you describe your experience of your GP practice?’ Reported as percentage of patients who rated 'Good'.
- ‘In the last 12 months, have you had enough support from local services or organisations to help you manage your conditions or illnesses?' Reported as percentage of patients who reported that they had received enough support.
- Percentage of patients with longstanding health conditions
- Percentage of patients who would recommend practice
- Number of GP partners (headcount)
- Number of GP partners (FTE)
- Number of salaried GPs
- Number of salaried GPs (FTE)
- Number of GPs (headcount)
- Number of GPs (FTE)
- Are they a ‘teaching practice’? (Yes / No)

10.5.2 **Qualitative data**

Qualitative data will be obtained through interviews with practice staff exploring intervention acceptability and feasibility (64) using the NPT as a guide for interview content.

NPT constructs will be used as sensitising devices to enquire about how general practices respond to and act upon the feedback and facilitation (64). Interviews will also ask about the acceptability and feasibility of delivery of the proposed SMART design (WS3) and any key

uncertainties identified during WS1 and WS2. Interviews will last 30-45 minutes and take place in person at the practice, or via online (Teams/Zoom) or telephone as requested by the participant. Audio-recordings from the interviews will be recorded and transcribed. Interviews will be transcribed by either Microsoft Teams or an external transcription company. Audio and video recordings from facilitation sessions and follow up calls will be transcribed by Microsoft Teams.

Table 1: Timepoints for intervention delivery and data collection

Month	Intervention delivery	Data collection
1	A&F report 1 Facilitation event	EHR audit data Facilitation recordings and field notes
2		Consultation data Other activity data (e.g., meetings discussing feedback)
3	A&F report 2 Facilitation follow-up call 1	EHR audit data Facilitation follow-up recordings Consultation data Other activity data
4		Consultation data Other activity data
5	A&F report 3 Facilitation follow-up call 2	EHR audit data Facilitation follow-up recordings Consultation data Other activity data
6		Consultation data Other activity data Interviews with practice staff
7	A&F report 4	EHR audit data Consultation data Other activity data Interviews with practice staff

10.6. **Data analysis**

10.6.1 **Quantitative data analysis**

Statistical analysis of the quantitative endpoints is the responsibility of the CTRU Statisticians. As this is a feasibility study, the analysis will focus on descriptive statistics and confidence interval (CI) estimation rather than formal hypothesis testing i.e., no formal evaluation of the interventions will be conducted as part of this feasibility study.

The analysis plan outlined in this section will be reviewed and a more final detailed statistical analysis plan will be written before any analysis is undertaken. The analysis plan will be written in accordance with current CTRU standard operating procedures (SOPs) and guidelines, and will be finalised and agreed by the appropriate members of the research team before any analyses are undertaken. Any changes to the finalised analysis plan, together with reasons for changes will be fully documented.

No formal analyses are planned until after the feasibility trial is closed to intervention delivery and follow-up. Final analysis will be carried out when all available outcome data has been received.

All analyses will be carried out on the intention-to-treat (ITT) population defined as all practices randomised, regardless of adherence to the protocol, withdrawal of consent or losses to follow-up. Practices will be included within the arm to which they were randomised.

All percentages, means, medians, interquartile ranges and ranges will be rounded to 1 decimal place (or 1 significant figure for numbers less than 1), whilst standard deviations and 95% confidence intervals will be rounded to 2 decimal places (or 2 significant figures for numbers less than 1). Unless otherwise stated, all percentages will be calculated using the total number of patients aged 18 and over registered with the practice, or relevant sub-group of, as the denominator. Where known, practices with missing data will still be presented.

All analyses and data summaries will be conducted on practice-level data. Quantitative data analysis will incorporate descriptive summaries of intervention fidelity of delivery and adherence (88); availability and feasibility of collection of process evaluation and economic evaluation data. Inferential analyses will be conducted on the proportion of patients prescribed opioids for CNCP after 6 months using logistic regression. The odds ratio and corresponding confidence interval of the prescription for opioids for A&F only compared to A&F and feedback facilitation will be reported (87).

10.6.2 **Qualitative data analysis**

Deductive coding of interview transcripts using Normalisation Process Theory (NPT) (64) as a framework analysis matrix (73). Analysis will follow seven steps: (i) transcription and anonymisation; (ii) familiarization with the interviews; (iii) coding; (iv) developing an initial framework; (v) applying the framework; (vi) charting data into the framework matrix; and (vii) interpretation. This process will continue until saturation (71). Analysis will be further refined by a constant comparison and contrastive approach to explore similarities and differences between practices, prescribing roles and interventions received.

10.6.3 **Triangulation of quantitative and qualitative results**

Results from both quantitative and qualitative analyses will be compared and further decisions made with the project and trial management teams on any further refinement to the SMART design and interventions.

OUTPUT: Refined adaptive interventions with known feasibility and acceptability.

10.7. Progression criteria

Green/continue:

≥ 70% of facilitation events delivered within 4 months of delivery of first feedback report;

≥ 80% of practices follow up for 6-month primary outcome of proportion of patients prescribed opioids (per 1000 patients);

Amber/Review:

50-70% of facilitation events delivered within 4 months of delivery of first feedback report;

60-80% follow up for 6-month primary outcome;

Red/Stop:

<50% of facilitation events delivered within 4 months of delivery of first feedback report;

<60% follow up for 6-month primary outcome.

If any criteria are graded as amber or red, a rescue plan will be developed outlining steps to be taken to improve recruitment and/or follow-up, and will be approved by the Fellowship Oversight Group (FOG) before proceeding.

10.8. Adverse events

Any adverse event identified by the practice or research team will be recorded and reviewed with the FOG. The qualitative interviews will ask specifically regarding any adverse impacts on the practice on taking part in the feasibility study.

10.9. Withdrawals

Practices will be able to withdraw from the feasibility trial. All data collected up to this point will be included in the analysis. Data for the primary outcome at 6 months will continue to be collected remotely by the sub-ICB medicines optimisation lead and included in the study analysis.

Healthcare professionals will be able to withdraw from the nested qualitative study up to 48 hours after the interview has taken place. Beyond this time, analysis will have commenced and it will not be possible to withdraw.

10.10. Equality, diversity and inclusion (EDI)

A diverse sample of practices will be recruited covering populations that are at higher risks of health inequalities, traditionally less involved in research and at higher risk of potentially harmful opioid prescribing. Recruitment of healthcare staff to interviews will aim to include a diverse range of healthcare roles and demographics. As the two interventions are at practice-level, we will not be excluding any patients aged 18 and over from the analysis, ensuring inclusion of underserved communities.

10.11. **Definition of end of Study**

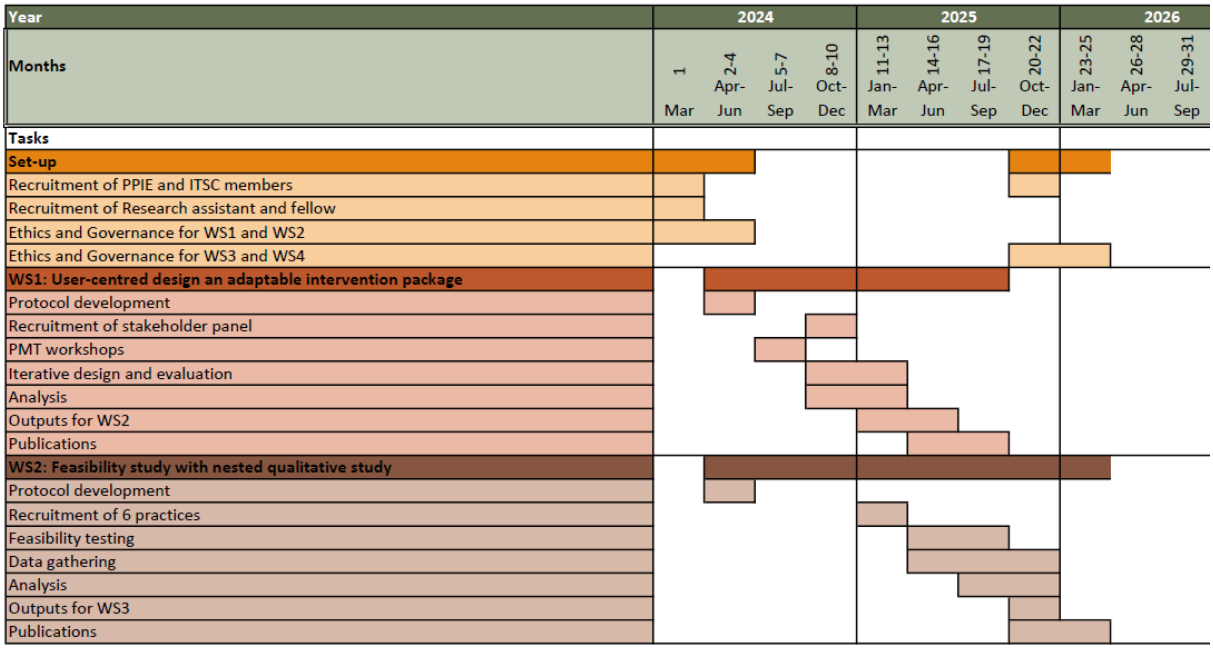
The end of the study is defined as once all data has been collected from the feasibility study and the analysis is complete. This is predicted to be by April 2026.

11. **PATIENT AND PUBLIC INVOLVEMENT AND ENGAGEMENT (PPIE)**

The Opioid SMART PPIE group consists of ten diverse members of the public who have personal experience of being prescribed opioid medication for CNCP or experience of PPIE in primary care implementation studies. They will meet 6-monthly for the duration of the study. There will be four PPIE meetings during WS1 and WS2. They will have the following objectives:

1. Introduction to Opioid SMART and recruitment to WS1 stakeholder panel:
    a. An overview of all work streams and timelines;
    b. Code of conduct for PPIE members;
    c. Recruitment to WS1.
2. Discussion of outputs from WS1 and input into WS2:
    a. Update on adaptations to interventions made during WS1;
    b. Input into recruitment for WS2 including ethical implications;
    c. Objectives and planned evaluations for WS2.
3. Discussion of initial outputs from WS2, updates to interventions, SMART planning.
    a. Initial findings from WS2 delivery of interventions;
    b. Further adaptations to interventions if needed;
    c. Plans for delivery of SMART (WS3).
4. Discussion of final outputs from WS2, SMART and process evaluation planning.
    a. Findings from completed analyses of WS2;
    b. Proposed changes to interventions for SMART (WS3);
    c. Plans for SMART and process evaluation (WS4) delivery.

12. TIMELINE



The end of trial is defined as the date of the last follow-up data receipt (i.e. when the data from A&F report 4 in month 6 has been transferred to OneDrive, or when qualitative interviews have been completed, whichever is later).

13. STUDY MONITORING

13.1. Fellowship Oversight Group (FOG)

The FOG will provide overall supervision of the study, project progress, methodology, and interpretation of findings. The group will aim to meet 3-monthly for the duration of the study.

14. QUALITY ASSURANCE AND ETHICAL CONSIDERATIONS

14.1. Quality assurance

The study will be conducted in accordance with current MRC Good Clinical Practice (GCP) guidelines and UK Policy Framework for Health and Social Care Research 2017.

14.2. Serious Breaches

Investigators are required to promptly notify the Sponsor of a serious breach (as defined in the latest version of the National Research Ethics Service (NRES) SOP). A 'serious breach' is defined as a breach of the protocol or of the conditions or principles of GCP (or equivalent standards for conduct of non-CTIMPs) which is likely to affect to a significant degree the safety or physical or mental integrity of the study subjects, or the scientific value of the research. All protocol deviations or breaches will be reported to the sponsor, to governance-ethics@leeds.ac.uk, within 1 working day.

14.3. **Ethical considerations**

The study will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 52nd World Medical Association General Assembly, Edinburgh, Scotland, and October 2000. The study documentation will be submitted to the identified Research Ethics Committee (REC). The study must be approved by that REC and receive approval from each participating practice prior to any data from these sites entering the study. The right of the practice to refuse participation without giving reasons must be respected. All patient data will be aggregated by practice and no individual-level data will be obtained. This study has been given a favourable opinion by the University of Leeds School of Medicine Research Ethics Committee (approved on 3rd September 2024, MREC 23-079). The study will also be submitted for approval to the Health Research Authority (HRA).

15. **CONFIDENTIALITY**

All information collected during the course of the study will be kept strictly confidential and held securely. The University of Leeds, as sponsor, will comply with all aspects of the 2018 Data Protection Act and operationally this will include

- Appropriate storage, restricted access and disposal arrangements for personal contact details.
- All transcripts will be anonymised and audio and video recordings deleted once transcription has been confirmed.

To ensure confidentiality of the data collected when published, fictitious site names and pseudonyms or study numbers not linked to sites or persons will be used. All identifiable data such as research site names will be removed.

16. **ARCHIVING**

At the end of the study, data will be securely archived at the University of Leeds for a minimum of 5 years. Data held by the University of Leeds will be archived in the Leeds Sponsor archive facility. Following authorisation from the Sponsor, arrangements for confidential destruction will then be made.

17. **STATEMENT OF INDEMNITY**

The proposed study is sponsored by the University of Leeds. The University of Leeds, as the employer of the Chief Investigator will be liable for negligent harm caused by the design of the study.

18. STUDY ORGANISATIONAL STRUCTURE

18.1. Responsibilities

18.1.1 Chief Investigator

As defined by the UK Policy Framework for Health and Social Care Research 2017, the Chief Investigator is responsible for the design, management and reporting of the study.

18.1.2 Co-Investigators

For the project, the Chief investigator will remain overall responsibility for the conduct of the study.

18.2. Operational structure

The **Project Management Team (PMT)** – The Chief Investigator and Research Fellows will provide overall supervision of the programme, in particular project progress, methodology, and interpretation of findings. The PMT will meet initially weekly and then fortnightly for the duration of the project.

The **Trial Management Group** (TMG) comprises of the Chief Investigator, research fellow and CTRU staff. The TMG will meet monthly during the study to oversee the study including the set-up of WS2, on-going management, promotion of the study and the results.

The Chief Investigator will be responsible for the day-to-day running of study.

19. POTENTIAL IMPACT

Increased effectiveness of practices to reduce opioid prescribing, with an estimated 30,000 fewer patients prescribed opioids. Demonstration of an innovative, systematic and hence reproducible approach to targeting high impact recommendations to improve patient care and outcomes at an acceptable cost.

20. DISSEMINATION

All work streams will be disseminated through publications and conferences. The findings from Opioid SMART will be used to prepare a protocol and funding application for a classic 2-arm RCT to definitively test the optimised adaptive intervention. For WS1 and WS2 we will use a recognised framework for knowledge exchange (74):

Push activities (one-way dissemination):

- Publications (2 planned) and conference presentations.
- A media plan for each research output.
- Plain language summaries of scientific outputs.

Pull activities (creating an appetite for study findings):

- Sending study updates to NHS England and National Clinical Director of Prescribing.

Linkage and exchange (building and sustaining relationships with key stakeholders):

- Maintaining and strengthening relationships with clinical organisations through conferences and meetings.

- Strengthening collaborations with international A&F 'Metalab' and the Health Quality Improvement Partnership (responsible for commissioning national clinical audits).

20.1. **PUBLICATION POLICY**

The success of the study depends upon the collaboration of all the study team and collaborators. For this reason, credit for the main results will be given to all those who have collaborated, through authorship and contributorship. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be based only on substantial contribution to:

- conception and design, or acquisition of data, or analysis and interpretation of data,

- drafting the article or revising it critically for important intellectual content, and final approval of the version to be published,

- and that all these conditions must be met (www.icmje.org).

In light of this, the Chief Investigator and relevant members of the study team will be named as authors in any publication.

The timing of any publication from the programme and this study will ensure scientific integrity is maintained. The publication policy for this study will follow the publication policy agreed by the study team.

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