# Safe and effective gradual reduction (tapering) of opioids in people with chronic non-cancer pain: systematic review of effects, barriers and facilitators and inequalities to inform service design in the NHS

Call: 18/145 HTA Pain Themed Call (Evidence Synthesis)

*Version control table*

| Version | Date submitted | Key revisions |
|---|---|---|
| 1.2 | July 2023 | Addition of current NIHR acknowledgement text |
| 1.1 | Sep 2020 | Addition of review summary table (III), emphasis on 'prescribed opioids' and 'non-caner pain added to objectives (III), update to project timetable (IV); addition of Juliet Housome to project team (IX); integration of search strategy (Appendix 1) |

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*Acknowledgment*

This study/project is funded by the NIHR Health Technology Assessment Programme (**NIHR128842**). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

## *I. Scientific abstract*


### Research questions

The key question for the NHS to be addressed is:

How can opioids be safely, satisfactorily and effectively reduced in people with chronic non-cancer pain?

In addition, our research will explore the barriers to and facilitators of effective reduction of opioids and inequalities people experience in accessing and benefiting from interventions to reduce opioid use.

### Background and rationale

Opioids have been used for pain management for centuries, but opioids have important limitations and can cause harm. Opioid dose needs to be increased to achieve pain relief, opioids can lead to dependency and some people may experience increased sensitivity to pain.

The long-term use of opioid therapy for the management of non-cancer pain has been questioned as current evidence does not support the effectiveness of this treatment and there is a dose-dependent risk for serious harms and costs.

People taking opioids may need support to reduce their use of opioids. Low quality evidence indicates that people can reduce their opioid use and experience reduced pain, but research has focused on limited effectiveness outcomes and not on factors that influence outcomes for, and the experiences of, different groups of people.

### Aims and objectives

The research aims to inform better practice, pathways and service design to support people with chronic pain to reduce their use of opioids and reduce inequalities.

We will undertake evidence synthesis, which includes a suite of systematic reviews of the quantitative and qualitative evidence, complemented with the use of an emerging method - qualitative comparative analysis (QCA). The reviews will synthesise evidence on effectiveness, safety (including adverse effects, AE) and acceptability of interventions to reduce opioid use; barriers to and facilitators of (B&F) effective intervention; inequalities in access to or benefiting from intervention. The QCA will identify components of interventions that are linked to safe reduction of opioids.

Will also consult with selected public and professional stakeholder groups in a focused manner to refine our findings and ensure relevance to patients and care in the NHS and to reducing inequalities.

### Methods

We have registered our evidence synthesis on PROSPERO (CRD42020171135).

We will use standard systematic review methods including meta-analysis (where appropriate) and GRADE/ CERQual for presenting evidence. Evidence will be selected and extracted by 2 researchers independently. We will work with public advisers throughout.

We will search CINAHL, Embase, MEDLINE, PsycINFO and Cochrane from inception and trial registries for controlled and uncontrolled studies of effectiveness as well as case reports for AE and qualitative studies for B&F reviews.

Outcomes will consider core sets and include pain severity, adverse effects, acceptability and patient satisfaction. B&F will include views and experience, accessibility. PROGRESS+ will be used to assess inequalities.

**Timelines**

Key phases of the project are:

| Months | |
|---|---|
| 1-2 | topic refinement and protocol |
| 2-12 | evidence identification and analysis |
| 11-14 | report development, including focused consultation |
| 13-14 | dissemination and engagement |

**Impact and dissemination**

We will engage widely with stakeholder groups, publish a number of reports, present at conferences, and support dissemination using digital media.

Our structured approaches will provide evidence in a way guideline developers and service providers can use to develop practical, effective actions in the NHS.

## *II. Background and Rationale*

**What is the problem being addressed?**

Opioids have been the mainstay of pain management for centuries. Although only a small dose may be required initially to manage someone's pain, the nervous system rapidly develops tolerance to the effects of opioids (Christie 2008), including the analgesic effect, which means that the opioid dose needs to be increased over time to achieve pain relief. Some people may experience hypersensitivity to pain as a result of opioid use.

The long-term use of opioid therapy for the management of non-cancer pain has been questioned as current evidence does not support the effectiveness of this treatment and there is a dose-dependent risk for serious harms (Chou 2015) and costs (NICE 2018).

Following reports of continuous increases in opioid prescribing in the USA (CDC 2017) and England (Curtis 2018), and rates of death associated with the use of prescription opioids (CDC 2011), there has been a call to reduce new prescriptions of opioids and aid patients to reduce high-dose prescribing.

Key questions for the NHS to be addressed are:

- How can prescribed opioids be safely, satisfactorily and effectively reduced?
- What are the barriers to and facilitators of effective reduction of prescribed opioids?
- What inequalities do people experience in benefiting from effective reduction of prescribed opioids?

- What considerations should be made in service delivery and practice to support effective reduction of prescribed opioids, reduce inequalities and reduce variation nationally?

Systematic reviews have focused on the effectiveness of interventions for the reduction of opioid use in non-cancer pain. These are limited by the low quality of the evidence available but indicate that gradual opioid reduction (tapering) can result in people reporting reduced rather than increased levels of pain (Eccleston 2017; Frank 2017; Fishbain 2018). Only limited attention was given in these systematic reviews to adverse events and no consideration was given to barriers and facilitators for effective intervention or important differences in effectiveness or patient experience for different groups of people.

Despite limited improvement in clinical outcomes and persistence of pain, most patients continue their long-term opioid prescriptions (Veiga 2018). An International Stakeholder Community of Pain Experts and Leaders has recently raised concern about 'forced', non-concordant opioid tapering as it can destabilise these patients (physically and emotionally), precipitating severe opioid withdrawal accompanied by worsening pain, profound loss of function and significant impact on quality of life (Darnall 2018).

**Why is this research important in terms of improving the health and/or wellbeing of the public and/or to patients and health and care services?**

The conflict between the physician's desire to relieve the patient's pain and fear of inducing addiction persists and can influence the selection of therapies including opioids.

The Centers for Disease Control and Prevention (CDC) have stated that the number of deaths in the USA from overdoses related to prescription opioids now exceed deaths from overdose involving heroin and cocaine combined (CDC 2011). In the USA, there has been more than a 19% reduction in annual prescribing rate from 2006 to 2017 suggesting a more cautious approach in the prescribing of opioids (CDC 2017). Nevertheless, in 2017 there were still almost 58 opioid prescriptions written for every 100 Americans (CDC 2018). Despite an increase in awareness of the risks associated with prescribing opioids for the long-term management of chronic non-cancer pain, the prescription of opioids in England has increased by 34% between 1998 and 2016 (Curtis 2018). Correction of the total morphine equivalency suggests that this increase was actually 127%, indicative of long-term use of opioids. Prescribing of opioids may have reduced in 2017 and 2018, but it is unclear if this trend will continue or what were the key facilitators of this reduction.

Despite limited improvement in clinical outcomes and continuous pain, most patients continue their long-term opioid prescriptions (Veiga 2018). More opioids are prescribed in the north than in the south of England and more opioids are prescribed in areas of greater social deprivation (Curtis 2018; Mordecai 2018). It is therefore paramount to consider and evaluate potential inequalities in access to interventions to reduce the use of opioids.

We propose to undertake evidence synthesis. This will comprise a comprehensive and carefully managed suite of systematic reviews of the quantitative and qualitative evidence complemented with an innovative application of qualitative comparative analysis (QCA).

This configuration of research approaches, across a mix of quantitative and qualitative synthesis complemented with efficient stakeholder engagement, has the potential to bridge

important limitations in evidence conducted to date and inform improved service delivery and practice and better, more equitable, outcomes for NHS users.

This combined approach makes extensive use of a range of evidence. The systematic reviews, QCA and stakeholder engagement will also support development of useful dissemination tools (initially in Word format) which presents a 'menu' of interventions to reduce opioid use with effect estimates, barriers and facilitators identified, intervention components supporting effective intervention and potential inequalities/ considerations to reduce inequalities. The timing of this research could also support development of components of the NICE guideline on dependence and managing withdrawal (NICE 2019) and facilitate immediate impact for the NHS.

**Review of existing evidence - How does the existing literature support this proposal?**

We reviewed existing evidence using a combination of a focused search of electronic databases, key citations and expertise within the investigative team (which includes an author of a recent BMJ 'Practice' overview of tapering opioids, Sandhu 2018). We conducted focused searches for related RCTs (last 2 years), non-RCTs, systematic reviews and qualitative studies (last 10 years) using the electronic databases MEDLINE, CINAHL, Joanna Briggs Institute (systematic reviews), PROSPERO, and The Cochrane Library (protocols).

Our searches support our proposal as we found no study duplicating our study, but an encouraging volume of evidence from qualitative research studies that could contribute to review components on acceptability and barriers and facilitators. We identified recent systematic reviews of intervention effects and primary studies (both RCT and non-RCT) that have been published since these reviews were completed. We comment on the recent systematic reviews and ongoing studies, below.

We are aware of 3 recent systematic reviews (1 Cochrane) that evaluated interventions to support opioid reduction in people with chronic non-cancer pain (Eccleston 2017, Frank 2017, Fishbain 2018). As discussed in Sandhu 2018 (co-authored by our Co-I, Eldabe) they are limited by the variation in intervention investigated, outcomes used and the low quality of studies. Studies had short follow-up and high drop-out rates, among other limitations. The reviews focused on intervention effectiveness and one was limited to RCTs. Consideration of adverse effects was also limited. Each of the reviews (Eccleston 2017, Frank 2017, Fishbain 2018) includes a different number of studies, adding to decision uncertainty for practice.

Other limitations in the systematic reviews are that they do not consider a comprehensive range of effectiveness outcomes, focusing on a narrow range of quantitative measures such as medication use. Core outcome sets for chronic pain studies were not implemented in the reviews (IMMPACT - Initiative on Methods, Measurement and Pain Assessment in Clinical Trials, Dworkin 2005). This risks ignoring outcomes important to patients and makes comparison difficult.

We conclude that although there are recent, well conducted systematic reviews none cover a suitably broad range of effectiveness outcomes or extend to consider factors influencing effective implementation or the importance of inequalities in access, effectiveness and opportunities for intervention adaptation.

Of 5 ongoing reviews of chronic pain and opioid use registered on PROSPERO, none combine effectiveness, adverse effects and quality of life assessment. Settings are limited to the emergency department setting in 2 ongoing reviews and 2 are prevalence studies. No relevant

protocols were identified on The Cochrane Library. None address inequalities or barriers and facilitators.

Our comprehensive suite of systematic reviews will therefore seek to address limitations of recent reviews (both published and ongoing) with a broad consideration of effectiveness outcomes (including core sets); inclusion of non-RCTs and adverse effects studies and update with emerging evidence from new studies.

We are aware of 2 ongoing trials I-WOTCH (ISRCTN49470934) and EMPOWER (NCT03445988) that are assessing self-management interventions for people with chronic non-malignant pain to reduce opioid use. Our systematic review will include the results of the I-WOTCH RCT, which is due to report in 2020 and we have negotiated access to the pre-publication manuscript. We will seek to negotiate early access to aggregate trial data for inclusion in our study. The anticipated completion date for the EMPOWER trial is November 2022. We commit to updating our effectiveness review when this RCT reports and secure funding outside this proposal for the update if necessary.

We will engage with guideline developers throughout (NICE 2018, NICE 2019) and have made direct contact with NICE guideline commissioning teams managing guidelines in development; 1 on chronic pain and another on dependency and withdrawal of drugs.

Our updated scoping search tested our proposed search strategy. This search (limited to 1 database) returned around 10 new studies potentially relevant for each of our proposed reviews, but not yet integrated into existing reviews that we identified. This indicates that there is sufficient evidence to inform our project aims, but that this evidence has yet to be comprehensively synthesised and presented for stakeholders.

## *III. Aims and Objectives*

### Study aim

The overarching aim of this study is to inform better practice, pathways and service design to support people with chronic pain to reduce their use of opioids and reduce inequalities.

### Objectives to support the study aim

Conduct evidence syntheses to:

1. Determine the effectiveness, safety profile and patient acceptability of interventions to reduce use of prescribed opioids for chronic non-cancer pain (REVIEW 1 effectiveness, REVIEW 2 adverse effects).
2. Identify barriers and facilitators (B&F) to safe and effective reduced use of prescribed opioids for chronic non-cancer pain from patient and professional and service perspectives (REVIEW 3).
3. Explore (through an emerging evidence synthesis method – qualitative comparative analysis, QCA) components of interventions or facilitators that are linked to safe and effective reduction in use of prescribed opioids for chronic non-cancer pain.
4. Assess inequalities in relation to access to, acceptability of and benefit from interventions to reduce use of prescribed opioids for chronic non-cancer pain (REVIEW 4, using evidence identified in reviews 1-3).

The table below summarises the scope of systematic reviews and analysis to be undertaken and key sources of evidence.

*Summary of evidence synthesis components*

| **Component** | **Focus/ approach** | **Evidence source** |
|---|---|---|
| Review 1 | Effectiveness | Bibliographic databases stated in IV.5 (core search) |
| Review 2 | Adverse effects | Core search with AE specific terms |
| Review 3 | B&F | Core search |
| Review 4 | Inequalities | Studies included in review 1, 2 and 3 |
| QCA | Analysis of intervention components and outcome | Studies included in review 1 and 2 |

The proposed suite combines configurative and integrative review approaches (Gough 2017). By conducting closely linked quantitative and qualitative synthesis a broader range of evidence is considered and can be 'triangulated' according to approaches described in Gough 2017. We will also include an adverse effects review component (following work from Golder 2016 and the PRISMA-Harms format, Zorzela 2016).

Our QCA will provide an explicit approach to exploring components of interventions that support safe and effective opioid reduction. Reviews using standard, quantitative analytical approaches use only aggregate data at follow-up and have made limited conclusions. Our QCA method uses 'more' of the evidence reported in studies by exploring intervention components across studies and identifying links to invention outcome (Thomas 2014, Kahwati 2016).

Furthermore, our cross-cutting consideration of inequalities has the potential to catalogue groups disadvantaged by higher burden of unwanted effects of opioid use and difficulties in accessing, persisting with or benefiting from opioid reduction. Integrating inequalities into the barriers and facilitators reviews will not only catalogue inequalities but could also identify barriers to or facilitators of more equitable inventions that should be considered in service design.

We will efficiently engage with selected patient and professional views with preliminary outputs from the suite of systematic reviews. Stakeholders will be asked to feedback on completeness of the effectiveness and B&F evidence from the systematic reviews. Additionally, stakeholders will be asked to indicate if the interventions identified in our effects review and if B&F identified in our B&F reviews are of importance in their local context. Inconsistency between factors identified in the B&F reviews and QCA and stakeholder views will be discussed in a revised report.

## *IV. Research Plan/ Methods*

### 1. Health technologies being assessed

Interventions or service delivery to support people with chronic pain to reduce their use of opioids and reduce inequalities. These include clinical strategies (pharmacological and non-pharmacological) for the safe tapering of opioids and support (such as information, mentoring) for people attempting to reduce their use of opioids.

### 2. Target population

Adults taking opioids who have chronic (non-cancer) pain.

### 3. Setting

Any health or care setting, including primary and secondary care, care homes and the community.

### 4. Methods for identification of studies

Methods of systematic review will be consistent with internationally recognised high-quality standards (such as CRD Report 4). We will register the reviews on PROSPERO and maintain an up-to-date record. The mixed method of review will be sequential, evaluative and explanatory as described in Gough 2017.

Literature searching will be based on a large single search of bibliographic databases (Embase, CINAHL, MEDLINE, PyscINFO and The Cochrane Library - using index terms, free text and CLUSTER approaches, Booth 2013) for published evidence on effectiveness and barriers and facilitators. Trial registries (ICTRP, clinicaltrials.gov, NIHR Be part of research) will be searched. A separate, explorative search will be undertaken for adverse effects. The results of this search may be combined with the effects and B&F search before we screen records.

UK-focused search across grey literature will be undertaken for views and experiences and B&F. This will be managed separately from database searches for published studies.

### 5. Search strategy

We will search CINAHL Embase, MEDLINE, PyscINFO and The Cochrane Library from inception onwards. We will develop an initial exploratory search in an iterative manner in MEDLINE from keywords identified by the review team and published topic-relevant systematic reviews. Keywords will include opioid terms AND tapering terms AND pain terms (see example search strategies below). We will use indexing terms (e.g. MeSH), free text and advanced search techniques (e.g. truncation, proximity operators). As with all systematic review searches, the initial search will evolve during discussions with the wider review team and stakeholders to ensure that the search terms (particularly the opioid terms) are relevant to our requirements (e.g. licenced, relevant to UK clinical practice).

Trial registries (ICTRP, clinicaltrials.gov, NIHR Be part of research) will be searched.

We will also undertake a separate search in order to identify papers related to the safety aspects. We will combine terms relating to opioids with an adverse effects search filter (see example search strategies). The filter is available for both Embase and MEDLINE and will be translated for the interfaces in other databases with careful consideration of indexing

practices. We will also use the latest software (once released) developed by OVID known as 'Safety Net' which uses natural language programming to uncover papers related to safety which are otherwise difficult to retrieve. This software is used after a conventional search has been carried out.

For all searches, we will use a sample of relevant records to conduct word and phrase frequency analysis in order to check the sensitivity of the searches and amend as required. An iterative approach to searching will be undertaken as our understanding of the literature increases. Once the searches are tested and validated in MEDLINE, we will translate them across other sources. We will exclude animal studies where possible and no date or study design limitations will be applied to the search strategies. Relevant studies identified by the searches will be filtered into the appropriate review workstream (effects, safety, barriers & facilitators, inequalities).

For the barriers and facilitators review we will also undertake a separate UK focused search of grey literature (such as NICE Evidence, HMIC, websites of selected organisations [British Pain Society's members' area] and higher education research repositories). We will also use an adapted version of the CLUSTER approach using citation searching, tracking lead authors, targeted Google Scholar searches and PubMed related articles, to identify sibling or related studies. Search results will be downloaded into EndNote and de-duplicated before being imported into the review management system for screening and selection.

## 5.1 Example search strategies

Our example search strategies demonstrate the search structure and use of advanced search techniques suitable for informing systematic reviews.

As with all searches, the search will evolve during discussions with the review team, project advisory group (PAG) and stakeholders to ensure that the search terms (particularly the opioid terms) are relevant to our requirements (for example relevant to UK clinical practice). We will test all searches to validate the search terms in MEDLINE before translating across other resources.

In our updated scoping exercise (from database inception to July 2019), the 'reducing opioids' search retrieved 3379 records in MEDLINE (English language and humans). Our rapid review of these results indicates at least 10 studies relevant to the effects review, 6 to B&F and 7 to inequalities. We anticipate more relevant studies to be identified across other databases and search methods.

*Adverse effects*

Our adverse effects (AE) of tapering opioids search will be begin with using the opioid tapering terms (see appendix 1) and AE terms (Golder 2019). The search will be reviewed and revised iteratively to develop a sensitive search strategy for adverse effects of drug reduction in general.

*CLUSTER search*

An adapted version of the CLUSTER (Citation tracking, tracking Lead authors, identifying Unpublished (grey literature) materials, Google Scholar searching, Theory tracking, ancestry searching for Early examples and follow up of Related projects) search approach will be undertaken to identify relevant sibling and related studies (Booth 2013).

## 6. Eligibility criteria

*Inclusion*

- Study design – RCTs, controlled observational studies and uncontrolled observational studies (effectiveness, AE/ safety, B&F reviews); case reports (AE/ safety review only); qualitative studies (B&F review only).
- Participants were adults (18 years or older) in any community or health or social care setting using prescription opioids for management of chronic non-cancer pain
- Intervention had an objective of opioid discontinuation or dose reduction

*Exclusion*

- Intervention not described
- Not chronic pain
- Not long-term opioid use (usually, less than 3 months)
- Not related to gradual opioid reduction (tapering)
- No original data reported (e.g editorial)
- No outcome data of interest

## 7. Outcomes for reviews

Outcomes of interest for the effects review will be based on an assessment of the previous systematic reviews on this topic (Eccleston 2017; Frank 2017; Fishbain 2018), with the addition of consideration of IMMPACT recommendations on core outcome measures for chronic pain clinical trials (Dworkin 2005).

*Primary Outcome Measures*

- Pain severity as measured in a patient self-reported scale e.g. NRS, VAS (REVIEW 1)
- Adverse effects - reported according to PRISMA Harms (REVIEW 2)
- Acceptability of the intervention and patient satisfaction (REVIEW 3)

*Secondary outcome measures*

- Physical functioning (e.g. ODI, BPI)
- Emotional functioning (e.g. HAD, BDI)
- Patient global impression of change (PGIC)
- Sleep quality (e.g. Pittsburgh Sleep Quality Index)
- Quality of life (e.g. EQ-5D, SF-36)
- Change in opioid dose (including cessation)
- Use of rescue treatments
- Opioid withdrawal-related symptoms (e.g. ShOWS) or dependence
- Mortality
- Dropout rates (and reasons)
- Social or economic activities (e.g. work)

*Barriers and facilitators*

Outcomes relevant to B&F (review 3) will include patient and carer or healthcare professionals' views and experience (e.g. preconceptions, satisfaction, concerns, anxiety, complaints);

stated B&F (e.g. access, concerns, support) and assessments of service accessibility such as audits or baseline assessments.

Additional outcomes may be considered, with agreement of the PAG (recorded in PAG minutes). Relevance to core outcome sets will be also be considered.

*Inequalities*

Participant characteristics related to PROGRESS+ equalities domains (O'Neill et al. 2014) will be recorded, where reported. Stated barriers will be mapped to PROGRESS+ domains.

## 8. Review strategy and strategy for reviewing literature

Standard systematic review methods will be used drawing on CRD Report 4 (NHS CRD 2001), Cochrane Handbook for Systematic Reviews of Interventions (version 6, Higgins 'in press') and Developing NICE guidelines: the manual (2014)

*Study selection*

Studies will be selected for inclusion through a 2-stage process using the predefined and explicit criteria.

The full literature search results will be screened independently by 2 reviewers to exclude records that do not meet the inclusion criteria and select records that may meet inclusion criteria for further review (stage 1).

Full records of selected records will be retrieved and independently assessed by 2 reviewers against the inclusion criteria (stage 2). Any disagreements on eligibility decisions will be resolved through consensus and, if necessary, by discussion with a third reviewer.

*Data extraction*

Data will be abstracted into pretested digital format. Data relating to both study design, outcomes/findings and quality will be extracted by 1 reviewer into an electronic database and checked for accuracy by a second reviewer.

Quality will be assessed by 2 reviewers independently and recorded on a database. Disagreement will be resolved through consensus and if necessary a third reviewer will be consulted.

*Quality assessment*

Studies will be quality assessed using an appropriate and validated quality assessment tool selected from those listed in NICE Guidelines Manual (NICE 2014) this includes the Cochrane Risk of Bias assessment for RCTs. We will develop GRADE (effectiveness evidence, Schünemann 2013) and GRADE CERQual (qualitative evidence, Glidewell 2018) profiles for prioritised outcomes.

*Data synthesis and reporting*

Information on quality will be tabulated and summarised within the text of the report. Each study will be graded (++, + or -) based on the extent to which the potential sources of bias have been minimised.

Attempts will be made to contact authors for missing data.

Review 1 and 2 – effects, AE

Statistics will be extracted as reported but where data allows, these will be standardised in evidence tables (noting all calculations). Dichotomous outcomes will be expressed as absolute risk reduction and number needed to treat where possible. Continuous outcomes will be expressed as mean differences. Statistical meta-analysis will be carefully considered with respect to heterogeneity of evidence. RevMan will be used for meta-analysis, to produce forest plots and explore heterogeneity. Forest plots may be used single studies. We will use funnel plots to explore possible publication bias.

We will state intended analysis in our final protocol.

Review 3 – B&F

Evidence will be presented in tables and synthesised narratively.

A thematic analysis is planned. A brief scoping search will be conducted to identify frameworks of potential relevance. The review may adopt or adapt existing frameworks or produce a *de novo* set of evidence frames.

The review process will include an evidence mapping phase to categorise evidence (and gaps) and configure the evidence by intervention type, patient group and barrier and facilitator categories. After mapping the evidence, key areas of interest will be identified and prioritised for analysis. Other areas will be researched in a later phase as resource allows.

The analysis will include the use of established frameworks for categorising intervention components (such as use of the TIDieR guideline headings to describe interventions, Hoffman 2014) as well as frameworks identified in our scoping activity.

Evidence tables consistent with those specified in the NICE guidelines development manual will be developed and barriers and facilitators described by intervention type or patient group/ setting.

QCA

A Qualitative comparative analysis (QCA, Ragin 1987) approach will be adopted to enable a rich exploration of the evidence from the effects (review 1) and adverse effects (review 2) systematic reviews. It has the potential to bridge qualitative and quantitative research methods, using qualitative approaches in a systematic and 'algorithmic way'.

QCA is a set theory methodology which aims to deal with complexity of interventions by adoption of a complexity-informed configurational approach. For interventions to support tapering opioids, complexity arises from the context of the healthcare system and its various actors and influences. According to this approach, complex interventions in context are configurations of factors/conditions that influence and shape each 'case'. A key concept in QCA is that of 'complex causality'. This concept implies that:

1. it is the *configuration* of conditions that leads to the presence of an outcome (conjunctural causation) and looking for independent effects of conditions is misleading;
2. different configurations of conditions might lead to the same outcome (equifinality); and
3. the occurrence and the non-occurrence of an outcome in social cases requires separate analysis and that the presence and absence of conditions might play crucially different roles in bringing about the outcome (asymmetric causation).

In QCA, interventions are a specific type of social cases and can be conceptualised as a dynamic and specific configuration of their constituents (conditions/ factors). The features of such a specific and dynamic configuration then determines the success or absence of success of the interventions. The 'complex causality' concept and the set of 3 underlying premises apply.

The QCA approach will 'dissect' opioid tapering interventions in order to reveal the configurations of conditions that appear to be associated with interventions that are successful or unsuccessful (or linked to adverse effects). These configurations can then be used to guide design and implementation of safe and successful tapering interventions.

Our approach will extract intervention components and outcomes into 'truth tables' for development into data sets for analysis in a current R 'QCA' package (for example v3.5, Dusa 2019), with reference to current versions of user guides for the 'QCA' package and by Thomann 2019.

Review 4 – inequalities

Impact on inequalities may be assessed in equity-focused studies (e.g. Gaither 2018) which explicitly set out to explore 1 or more inequalities domain or in non-equity focused studies (e.g. Weimer et al., 2016,) which although not specific to inequalities report or undertake analysis by 1 or more inequalities domain.

In non-equity focused quantitative studies, data may be analysed on one or more of the PROGRESS+ characteristics (e.g. Weimer 2016). In non-equity focused qualitative studies findings may demonstrate impact on disadvantaged populations (e.g. Frank 2016). We will use PROGRESS+ (O'Neill 2014) to extract data on health inequalities within the included studies. We will examine how health inequalities were assessed within the included studies, that is descriptive (reporting of baseline characteristics only) versus analytical (equity impact assessed via targeted, gap, gradient approaches).

Where possible, subgroup analysis on PROGRESS+ characteristics will be undertaken to assess the impact on health inequalities. Where evidence allows we will generate general themes in different uptake and effects (including AE) linked to inequalities.

Interpretation of review 1 with 'third order' themes from reviews 2-4 and QCA.

Our nested approach of using different reviews and evidence types will be used to develop 'third order' themes to contextualise findings from the effects and AE reviews.

Focused consultation

We will efficiently engage patient and professional views with preliminary outputs from the suite of systematic reviews. This consultation process will be an extension of the evidence synthesis (a form of field testing), rather than a separate research project about people with pain and experience of opioids.

We will invite selected professional groups (such as Royal Colleges of GPs; Anaesthetists (Faculty of Pain Medicine) and Nursing; British Pain Society; British Pharmaceutical Society and NICE guideline development group) to comment on our draft reports in relation to completeness of evidence and relevance to UK service delivery and practice.

Stakeholder views will be used to develop and will be discussed in a revised report.

We will aim to engage with 5 stakeholder groups representing a mix of patient and professional interests.

Public respondents will not be identifiable in any publication.

Presentation

Presentation will include evidence tables, GRADE profiles and evidence statements in line with current NICE methods and NIHR journal instructions for authors.

We will consider ways to present findings in an accessible format, such as presenting diverse quantitative data as harvest plots, review findings in logical models and piloting a menu of intervention effects and barriers and facilitators.

### *V. Dissemination, Outputs and anticipated Impact*

A comprehensive dissemination strategy will be used for the findings of our research.

This includes publication in open access, high impact journals, including NIHR journals; presentations to professionals, working with our expert PAG to champion the impact of the research; stakeholder engagement such as delivering question and answer sessions, including to patient and carer groups and service providers; media activity across news and community communication and a range of digital media (by establishing a web-based identity, using blogs, public-research engagement platforms (such as Kudos), audio visual presentations and use of social media to support and extend other dissemination. We have initially registered '@TaperSynthesis' as Twitter account and will create a similarly titled University IT system user account for the project to provide dedicated email and location for web content. The Core Management Group will agree a suitable title for the project to establish a clear and consistent identity. We will involve public advisers in all our dissemination activities.

Findings will be presented at key conferences such as the British Pain Society or British Pharmaceutical Society in 2020/21 (to disseminate findings) and the International Association for the Study of Pain (2020, to promote the project). Team members attending conferences will be provided with 'briefing sheets' to support key messages being communicated effectively and consistently.

Key impacts include an opportunity to integrate early reports from the I-WOTCH study into our analysis to produce an up-to-date evidence summary. Our use of structured approaches (giving evidence related to each project aim special attention) such as GRADE, QCA and PROGRESS+ aims to provide information in a way that guideline developers and service providers can use to develop practical, effective actions in the NHS.

Our Applicants are engaged with guideline developers at NICE and the British Pain Society.

### *VI. Project timetable*

This 14 month project will use a carefully managed set of reviews to explore effectiveness, AE, B&F and inequalities and a QCA of factors affecting outcomes to inform service design and delivery.

The schedule is based on careful day-by-day resource planning by the investigators, which was further rationalised to focus senior input. The scheduled is developed around a single

researcher leading the majority of reviewing with regular input from an expert team and immediate access to day-to-day support from the PI (Hill).

*Key phases of the 14 month project (months) are:*

- 1-2 topic refinement and protocol
- 2-12 evidence identification and analysis
- 11-14 report development, including consultation with selected stakeholders
- 13-14 dissemination and engagement

Evidence selection and analysis will be stepped, beginning with selection of evidence for the effects review. Evidence will then be selected for the other reviews. Analysis will begin first for the effects review, with analysis following for other reviews. In line with the mixed method sequence the preliminary analysis for the effects and AE reviews will be re-assessed with reference to findings from B&F, inequalities and QCA.

A draft logical model outlining the development of the work packages and their outputs is presented in appendix 2. This will be refined during our project.

### *VII. Project management*

The Co-Is will comprise the Core Management Group (CMG) which will meet in person/ online monthly. Smaller teams will be formed to complete work specific to work streams and will report to the CMG monthly. Hill (PI) will be a member of all work stream groups.

The project will recruit topic expertise, including public advisers, to form a Project Advisory Group (PAG) to inform research design and interpretation of evidence for practice.

We have obtained agreement from Bernhard Frank (Consultant in Pain Medicine, Walton Centre NHS Foundation Trust), Lauren Walker (NIHR Academic Clinical Lecturer in Clinical Pharmacology & Therapeutics, UoL) and the Pain Relief Foundation (to nominate patient advisers) to join the PAG. Additional methodological expertise will be included in PAG through the involvement of James Thomas (EPPI-Centre, University College London) and Ruth Garside (University of Exeter).

We will apply NIHR Research Governance Guidelines (NIHR 2019) where applicable for evidence synthesis (We will not recruit participants or require a data monitoring committee or ethics approvals, so some considerations are not relevant.). We will expand the PAG if necessary. Williams (Co-I) will Chair the PAG. The PAG will meet face-to-face or by remote conferencing system 2-3 times during the programme. At least once at protocol stage and to discuss our draft report. We will follow NIHR INVOLVE guidance throughout our project.

Work teams, CMG and PAG will be supported by an administrator.

### *VIII. Patient and Public Involvement*

To ensure our work is relevant to people with chronic pain and their families.

We will involve a small group of people with experience of use of opioids in developing the protocol, interpreting evidence, plain language summary and dissemination products. This group with be drawn from pain services in South Tees and Merseyside and members of the

Pain Relief Foundation. Furthermore, we will extend our engagement with patients and the public through a focused consultation on our initial findings and considerations for practice in order to gather views on the relevance and completeness of evidence and our initial interpretation of the evidence. In addition, 1 of our co-applicants is a person with chronic pain who gradually reduced their opioid use.

We will develop dissemination products with our public advisers for use patients and professional audiences.

582 *Project timetable*

| WBS: schedule*/ work packages | 2020 | | | | | 2021 | | | | | | | | | | | | 2022 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pre | Sep | Oct | Nov | Dec | Jan | Feb | Mar | Apr | May | Jun | Jul | Aug | Sep | Oct | Nov | Dec | Jan | Feb | Mar |
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
| | 0 | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | 56 | 60 | 64 | 68 | 72 | 76 |
| **PAG** | | | VC | | | | | | | VC | | | 2nd | | VC | | | | | |
| **PAP** | | | VC | | | VC | | | | Doc | | 2nd | VC | | Doc | | | | | |
| **Focused consultation** | | | | | | | | | | | | REP | | | | | | | | |
| 0. Scoping searches updated/ refined | 0 | | | | | | | | | | | | | | | | | | | |
| 0. RA recruit & induction | 0 | 1 | | | | | | | | | | | | | | | | | | |
| 1. **Scope/ protocol** | | 1 | | | | | | | | | | | | | | | | | | |
| 1. Protocol finalised | | 1 | | | | | | | | | | | | | | | | | | |
| 1. Qual. assurance | | | 2 | | | | | | | | | | | | | | | | | |
| 1. PROSPERO | 0 | 1 | | | | | | U | | | | U | | | U | + | + | + | + | + |
| **2. Search/ selection** | | | 2 | 3 | 4 | 5 | | | | | | | 12 | | | | | | | |
| 2. Search R1 R3 db | | | 2 | | | | | | | | | | U | | | | | | | |
| 2. Search R2 db | | | 2 | 3 | | | | | | | | | U | | | | | | | |
| 2. Search R3 grey | | | | 3 | | | | | | | | | U | | | | | | | |
| 2. R1,3 inc/excl ti.abs | | | | 3 | 4 | | | | | | | | | | | | | | | |
| 2. R1,3 full text | | | | | 4 | 5 | | | | | | | | | | | | | | |
| 2. R2 inc/excl ti.abs | | | | | 4 | | | | | | | | | | | | | | | |
| 2. R2 full text | | | | | 4 | 5 | | | | | | | | | | | | | | |
| **3. Extraction/ analysis** | | | | | | | 6 | 7 | 8 | 9 | | | | | | | | | | |
| 2. R1 analysis/QA | | | | | | | 6 | | | 9 | | | | | | | | | | |

| WBS: schedule*/ work packages | 2020 | | | | | 2021 | | | | | | | | | | | | 2022 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pre | Sep | Oct | Nov | Dec | Jan | Feb | Mar | Apr | May | Jun | Jul | Aug | Sep | Oct | Nov | Dec | Jan | Feb | Mar |
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
| | 0 | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | 56 | 60 | 64 | 68 | 72 | 76 |
| 2. R2 analysis/QA | | | | | | | | 7 | 8 | | | | | | | | | | | |
| 2. R3 analysis/QA | | | | | | | 6 | | | 9 | | | | | | | | | | |
| 2. R4 analysis | | | | | | | | 7 | 8 | | | | | | | | | | | |
| 2. QCA analysis | | | | | | | | | 8 | 9 | | | | | | | | | | |
| 2. Qual. assurance | | | | | | | | | 8 | 9 | | | | | | | | | | |
| **4. Report devel** | | | | | | | | | | | | | | | | | | | | |
| 3. Drafting sections | | | 2 | | | | 6 | 7 | | | 10 | 11 | | 13 | 14 | | | | | |
| 3. Draft reports | | | | | | | | | | | | 11 | | | | | | | | |
| 3. Focused consultation | | | | | | | | | | | | 11 | | | | | | | | |
| 3. Qual. assurance | | | | | | | | | | | | | 12 | | | | | | | |
| 3. Finalised reports | | | | | | | | | | | | | 12 | 13 | | | | | | |
| **5. Dissemination** | | | | | | | | | | | | | | | | | | | | |
| 5. Dissem. tools | | | | | | | | | | | | 11 | | 13 | 14 | + | + | + | + | + |
| 5. Peer reviewed pub | | | | | | | | | | | | | | | 14 | + | + | + | + | + |
| 5. Conf., engagement | | | | | | | | | | | IASP | | | | BPS | + | + | + | + | + |

Work Breakdown Structure WBS; Schedule in months and weeks (approx); Pre – pre project start date period; RA research associate; PAG project advisory group; PAP Patient advisory panel; db bibliographic databases; inc/ excl screening based on title and abstracts; U search updates; grey unpublished literature; P protocol; R review (1 effects, 2 adverse effects, 3 barriers & facilitators, 4 inequalities); REP report; VC remote meeting by video conference; Document review, + ongoing

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*NIHR reporting timetable*

| Anticipated date | Project progress to report |
|---|---|
| Nov 2020 | Finalised protocol, searches completed |
| Feb 2021 | Evidence selection reviews 1-3 |
| May 2021 | Ongoing analysis reviews 1-4 |
| Aug 2021 | Completed analysis reviews 1-4, QCA, initial results |
| Nov 2021 | Final report for NIHR<br>Refined analysis and manuscripts (based on stakeholder engagement and updated searches), updated dissemination plan |

Based on quarterly reporting

## *IX. Expertise in the team*

The project team comprises extensive operational and leadership experience in delivering high quality NIHR funded programmes. Team make-up has been carefully developed to access senior clinical involvement and methods expertise in an efficient manner.

The healthcare expertise includes patient and professional perspectives and experience of current UK practice in specialist pain services, general practice and pharmacy. Topic experts are also active in leading research in pain, improving use of medication and service development and delivery.

The combination of topic practice and research expertise with a set of specialist evidence synthesis methodologists is key to our proposed approach. It will deliver a broader assessment of tapering opioids effects and multiple factors influencing effective intervention – including equity; barriers and facilitators and exploration of components of interventions and context that contribute to intervention outcomes.

Our focused consultation activity adds value to develop an inclusive review which considers both patient-centred outcomes and experiences and provider insight and service impact and challenges.

Our careful structuring and sequencing of work packages around our core effectiveness review will support efficient use of the set of methods expertise, allowing experts to concentrate on particular reviews. University of Liverpool-based researchers (Hounsome, Maden) and PI (Hill) will be engaged in all work packages to coordinate activity. Core research team meetings, quality assurance processes and the PAG will further ensure quality.

Dr **Ruaraidh Hill** is Lecturer in Evidence Synthesis. He has extensive experience in technical and management roles within NICE and Cochrane. He has led all stages of evidence synthesis for NIHR HTAs and contributed to over 70 NICE clinical and public health guidance projects and lead update of the NICE guidelines manual.

Dr **Rui Duarte** is a Senior Research Fellow and HTA lead for LRiG. He has expertise in evidence synthesis and interventions for chronic pain.

Professor **Sam Eldabe** is a Consultant in Pain Medicine with a 2-3ry care perspective. He is Co-I for the NIHR HTA I-WOTCH trial (Improving the wellbeing of opioid-treated chronic pain). Sam has worked with a CCG to develop a community opioid withdrawal scheme.

**Juliet Hounsome** is a Research Fellow in clinical effectiveness assessment. She has 15 years' experience developing systematic reviews for NIHR and NICE HTA, including complex topics requiring large, extensive evidence synthesis. Juliet also has psychological research methods expertise which she has applied in areas such as public health and forensic/ clinical psychology.

Dr **Su Golder** is a qualified information specialist and Associate Professor with over 20 years' experience in systematic reviews. Research interests include information retrieval, methodology, difficult to locate data and adverse effects of healthcare. Su is a NIHR Post-Doctoral Research Fellow on AE data.

Dr **Esmaeil Khedmati Morasae** is a Research Fellow in Complex Systems and Policy with expertise in complex systems approach to population health issues. Experience includes health inequalities, complex interventions and complexity-informed methodologies like qualitative comparative analysis.

Dr **Michelle Maden** is a Post-doctoral Research Associate in Evidence Synthesis. She has over 15 years' experience of conducting complex searches for different types of evidence reviews. Michelle has developed an innovative theory-led approach to integrating considerations of health inequalities in evidence synthesis.

**Marty Richardson** is a biostatistician working across LRiG HTA projects (pairwise meta-analysis, meta-regression, NMA) and complex interventions with the Liverpool School of Tropical Medicine.

**Beth Shaw** is a lead in guideline development methods with over 10 years' experience as senior methods adviser at NICE. She is active in international methods groups and was a member of the GIN GRADE Working group.

**Carmen Smith** is a person with direct experience of chronic pain who will be fully engaged as Co-I. Carmen also has a role as facilitator in pain management and opioid reduction programmes.

Dr **Adam Todd** is a Reader in Pharmaceutical Public Health at Newcastle University. He is a qualified pharmacist and brings expertise in medication use and deprescribing. He also has a previously undertaken research exploring inequalities in pain and opioid utilisation across the UK.

Professor **Nefyn Williams** is Professor of Primary Care. He is an academic GP with an interest in musculoskeletal pain. His research includes the rehabilitation and treatment of painful conditions such as hip fracture, osteoarthritis and cancer. He is the CI on an NIHR HTA trial of rehabilitation following hip fracture.

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# APPENDIX 1

***Sample search strategy***

*Reducing (tapering) opioids*

Terms used for MEDLINE for effects and B&F will include (for example):

1 exp Analgesics, Opioid/

2 (opioid* or opiate*).mp.

3 (codeine or oxycodone or tramadol or hydromorphone or morphine or fentanyl or meperidine or pethidine or dextropropoxyphene or methadone or buprenorphine or pentazocine or hydrocodone or opium or butorphanol or tapentadol or papaveretum or meptazinol or dipipanone or dihydrocodeine or diamorphine).mp.

4 or/1-3

5 (taper* or wean* or (dose adj1 reduc*) or detox* or withdraw* or discontinu* or cease or cessation or terminat* or remove* or stop*).mp.

6 exp Pain/

7 pain*.mp.

8 (neuralgi* or myalgi* or neuropath* or arthriti* or osteoarthri* or arthralgi* or sciatica or headache* or migrain*).mp.

9 or/6-8

10 4 and 5 and 9

*Adverse effects*

Terms for MEDLINE will include (for example):

(ae OR co OR de).fs OR (safe OR safety OR side effect* OR undesirable effect* OR treatment emergent OR tolerability OR toxicity OR adrs OR (adverse adj2 (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes))).ti,ab

# APPENDIX 2

### *1.1 Preliminary logical model of safe tapering of opioids*

We present a simple logic model of patient pathway with limited moderators and modifiers where a person requests opioid tapering and safely reduces their opioid use. This is closely modelled on our experience of the I-WOTCH RCT and process evaluation of an opioid tapering support programme for people with chronic non-malignant pain.

The logic model will not restrict the review to only the interventions listed or to a set form of configuration of the evidence.

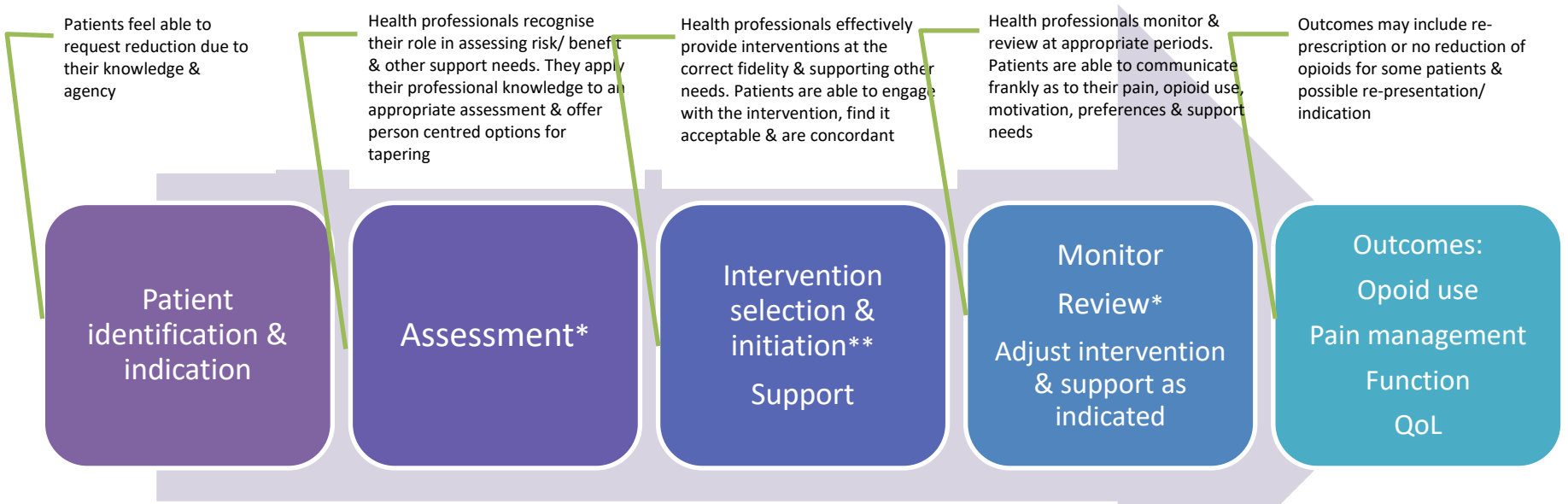
We propose to develop a refined logic model for safe tapering of opioids in the NHS from the evidence included the synthesis. This logical model may also use evidence from our expert engagement (particularly where there are gaps in evidence for important components of the model) and omit some evidence from the evidence reviews where context or interventions are not applicable to the NHS (such as where pharmaceuticals are not indicated for use in tapering in the UK or not available on NHS formularies).

Our preliminary logical model is subject to change. Currently, it outlines only key stages in safe tapering of prescribed opioids in people with chronic non-cancer pain. Modifiers include barriers, facilitators and inequalities.

Potentially relevant person- and setting-related components will be developed through the reviews. These include ‘pathways’ for care offered in general practice, the community and specialist services and by a range of care professionals and others (including patient experts). Key underlying theories relevant to interventions will also be presented and candidate moderating and mediating factors will be highlighted for potential interactions between logical model components. These will be tested, refined and built upon through the research and engagement with experts. The community and Clinical commissioning group (CCG) context will also be considered. Source, strength and quality of evidence will be indicated in the model using clear notation.

Short-term outcomes anticipated to result from the interventions include the patient-focused outcomes presented in IV. Research Plan/ Methods/section 6 of our protocol. Potential longer term outcomes of safe prescribing practise will be presented based on the evidence and expert input.

### *1.2 Tapering intervention pathway – annotated*




Interventions considered in the **effects** review may include support for knowledge & agency. The **B&F** review may identify modifiers of such interventions & underlying challenges to knowledge & agency. The **QCA** could explore the importance of (e.g) knowledge & agency in achieving good tapering outcomes

The **effects** review will describe assessments used in the interventions. The **B&F** review may identify modifiers of such levels of professional knowledge & professional development needs

The **effects** review will describe assessments used in the interventions. The **B&F** review may identify modifiers of such levels of professional knowledge & professional development needs

The **effects** review will describe review & adjustments (inc periods) & their effect on effectiveness. AE will be reviewed. The **B&F** review may identify modifiers. The **QCA** will explore the importance of intervention components (such as review period) in achieving good tapering outcomes

The **equalities** review will explore evidence for differential effectiveness by (e.g) PROGRESS+ characteristics. **Expert** panels will work with the reviewers to carefully consider applicability to & contextual considerations in the NHS (for example differing patient expectation & adjunctive use of non-opioids during tapering outside the UK & availability of CBT outside 2ndy care in the UK & CCG roles in limiting opioid use)

Example of '**positive**' patient pathway where a person requests opioid tapering and safely reduces their opioid use. *Person centred **assessment** of risk/ benefit of continued opioid use, risk/ benefit of tapering and nature of opioid use disorder (if present) and co-concomitant morbidities and psycho-social support needs. **Theories presented, below.

***Notes***

Simple logical model components are reproduced in larger font, below. A selection of theories relevant to the interventions are also presented.

***Annotations***

**Patient identification & indication**

Patients feel able to request reduction due to their knowledge & agency
Evidence inputs - Interventions considered in the **effects** review may include support for knowledge & agency. The **B&F** review may identify modifiers of such interventions & underlying challenges to knowledge & agency. The **QCA** could explore the importance of (e.g) knowledge & agency in achieving good tapering outcomes

**Assessment**

Health professionals recognise their role in assessing risk/ benefit & other support needs. They apply their professional knowledge to an appropriate assessment & offer person centred options for tapering
Evidence inputs - The **effects** review will describe assessments used in the interventions. The **B&F** review may identify modifiers of such levels of professional knowledge & professional development needs

**Intervention, selection & initiation. Support**

Health professionals effectively provide interventions at the correct fidelity & supporting other needs. Patients are able to engage with the intervention, find it acceptable & are concordant
Evidence inputs - The **effects** review will describe assessments used in the interventions. The **B&F** review may identify modifiers of such levels of professional knowledge & professional development needs

**Monitor, review, adjust**

Health professionals monitor & review at appropriate periods. Patients are able to communicate frankly as to their pain, opioid use, motivation, preferences & support needs
The **effects** review will describe review & adjustments (inc periods) & their effect on effectiveness. AE will be reviewed. The **B&F** review may identify modifiers. The **QCA** will explore the importance of intervention components (such as review period) in achieving good tapering outcomes

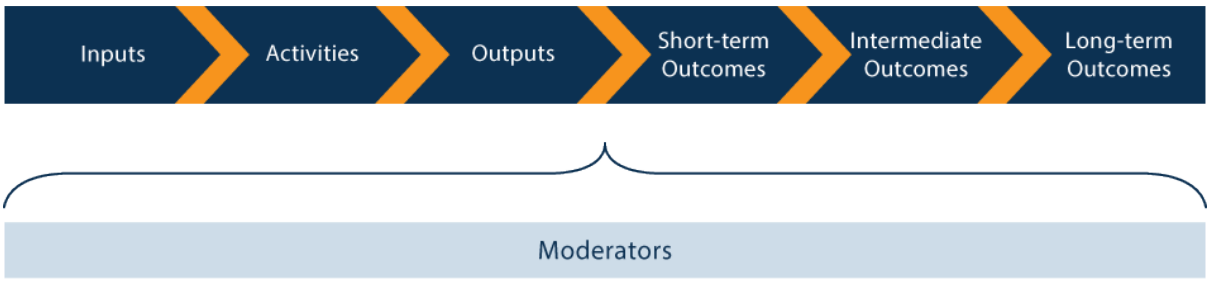
**Outcomes**

Outcomes may include re-prescription or no reduction of opioids for some patients & possible re-presentation/ indication
The **equalities** review will explore evidence for differential effectiveness by (e.g) PROGRESS+ characteristics. **Expert** panels will work with the reviewers to carefully consider applicability to & contextual considerations in the NHS (for example differing patient expectation & adjunctive use of non-opioids during tapering outside the UK & availability of CBT outside 2ndy care in the UK & CCG roles in limiting opioid use)

**Candidate theories for interventions**

- Capabilities-based theory
- COM-B (capability, opportunity, motivation-behaviour)
- IMB (information, motivation, behaviour)
- Motivational interviewing
- Normalisation process theory
- Patient centred communication
- Planned behaviour
- Relational Frame Theory (with respect to Acceptance and Commitment Therapy)
- Social cognitive
- Other theories as identified in the reviews or candidate programme theory developed from the evidence synthesis and expert input.

### *1.3 CDC logical model overview*




From: https://www.cdc.gov/eval/steps/step2/index.htm

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