Realist synthesis protocol for understanding which strategies are effective to prevent urinary tract infection in older people in care homes

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PROTOCOL

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Realist synthesis protocol for understanding which strategies are effective to prevent urinary tract infection in older people in care homes

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Abstract

Aim: To identify and characterize strategies, which contribute to the prevention of urinary tract infection (UTI) in older people living in care homes.

Design: The realist synthesis has four iterative stages to (1) develop initial programme theory; (2) search for evidence; (3) test and refine theory supported by relevant evidence and (4) formulate recommendations. Data from research articles and other sources will be used to explore the connection between interventions and the context in which they are applied in order to understand the mechanisms, which influence the outcomes to prevent UTI.

Methods: A scoping search of the literature and workshops with stakeholders will identify initial programme theories. These theories will be tested and refined through a systematic search for evidence relating to mechanisms that trigger prevention and recognition of UTI in older people in care homes. Interviews with key stakeholders will establish practical relevance of the theories and their potential for implementation.

Discussion: UTI is the most commonly diagnosed infection in care home residents. Evidence on the effectiveness of strategies to prevent UTI in long-term care facilities does not address the practicality of implementing these approaches in UK care homes. The realist synthesis is designed to examine this important gap in evidence.

Impact: Our evidence-informed programme theory will help inform programmes to improve practice to reduce the incidence of UTI in older people living in care homes and related research. Patient and public involvement will be crucial to ensuring that our findings reach carers and the public.

Patient and public contribution: Involvement of patient and public representatives is embedded throughout the study to ensure it is underpinned by multiple perspectives of importance to care home residents. Our co-investigator representing patient and public involvement is a lay member of the team and will chair the Project Advisory Group, which has two additional lay members. This will help to ensure that

our findings and resources reach carers and the public and represent their voice in our publications and presentations to professional and lay audiences.

KEYWORDS
care homes, caregivers, infection prevention, literature review, older people, realist synthesis, urinary tract infection

1 | INTRODUCTION

Urinary tract infection (UTI) is the most commonly diagnosed infection in older people, incidence being highest among those living in care homes. Conditions such as cognitive impairment and incontinence predispose older people to UTI and are more common among care home residents than older people living in their own home. Improving understanding of the strategies that could be effective in preventing UTI in care homes is a priority given the increased susceptibility of this population, the frequency with which UTI occur and the impact on the wider population in terms of acute care resources and increasing antimicrobial resistance. However, guidance on strategies that can be used to prevent UTI in care homes is limited, focuses mainly on preventing catheter-associated UTI even though most UTI in care home settings is not associated with an indwelling urinary catheter (IUC) and is based on non-UK care home settings where the context of care is different.

There is, therefore, a need to develop a consolidated body of evidence on what actions may be effective in preventing UTI in care home residents and reduce the use of antibiotics by improving how care is delivered. Recognizing UTI in older people can be challenging but is critical to implementation of prevention strategies. This requires a clear understanding of how care home staff can be supported to take appropriate action in response to the non-specific symptoms of UTI that care home residents commonly present with.

This review will address these gaps in evidence by developing evidence-informed programme theories about strategies that are effective in preventing and recognizing UTI and its recurrence in older people living in care homes. We have adopted a realist approach to the review to identify how and why strategies to prevent UTI may impact, and on whom. By engaging with stakeholders throughout the review process we will establish the practical relevance and potential for implementation of improvement programmes, taking account of the varying contexts in which care is delivered and the challenges presented by residents with complex health needs. We will formulate recommendations for preventing and recognizing UTI in care home settings, which can be integrated into policy and guidance to inform the delivery of improvement programmes, research and education programmes.

2 | BACKGROUND

Urinary tract infection is caused by the multiplication of microorganisms within the urinary tract, most commonly in the bladder but the urethra, ureters and kidneys can also be affected and infection can spread to the bloodstream. The disease can range from mild local infection to severe sepsis, which has a mortality of up to 40% (Caljouw et al., 2011; Gharbi et al., 2019). The risk of UTI increases with age in both men and women and is greatest among those living in long-term care facilities with approximately 50 infections per 100 person-years at risk (Caljouw et al., 2011). Several factors predispose older people to UTI including genitourinary tract disorders, increased susceptibility to asymptomatic bacteriuria (bacteria in the urine), cognitive impairment and incontinence (Biggel et al., 2019). Older people living in care homes are more likely to have these comorbidities and have higher rates of resistant bacteria compared to older people living in their own homes (Marwick et al., 2013).

More than 50% of antibiotic prescriptions in long-term care settings are for UTI (Biggel et al., 2019). Resistance to antibiotics normally used to treat UTI is common in the United Kingdom, with 40% of uropathogens now resistant to trimethoprim (Public Health England, 2017). Older people who experience repeated episodes of UTI, and therefore, frequent exposure to antibiotics are at greater risk of acquiring bloodstream infections caused by resistant pathogens (Abernethy et al., 2017). Inadequate antimicrobial therapy significantly increases the risk of infection spreading to the bloodstream.

UTI is one of the most common reasons for hospitalization from care homes, accounting for one-third of admissions. In those admitted with bloodstream infections, half occur as a result of a urinary source (Genao & Buhr, 2012). Although most UTIs in care home settings are not associated with an invasive device, the presence of an IUC provides a route for bacteria colonizing the perineum to gain access to the bladder and increases the risk of UTI by 3%–8% per day (Maki & Tambyah, 2001). A prevalence survey of 425 care homes in the United Kingdom found 6.9% of the 12,827 resident population had an IUC (McNulty et al., 2014). This study also provided evidence of variation in practice both in relation to discharge from hospital with an IUC and its removal once in the care home, suggesting there is room for a more pro-active approach to reducing IUC use.

Guidance about strategies for UTI prevention in care homes in England is lacking and focused mainly on IUC (National Institute for Health and Care Excellence (NICE), 2012). Moreover, it does not account for varied situations or contexts in which care is delivered, the challenges presented by residents with complex health needs, or the demands of care delivery by unregistered staff with limited supervision (Dudman et al., 2018). A recent systematic review of interventions to reduce UTI in nursing home residents (Meddings et al., 2017) identified 19 studies, all but one from outside of the

United Kingdom. Most were small scale, non-randomized before and after studies. The majority were focused on prevention of infection related to IUC, with six studies focusing on improving continence care and bladder training.

There have been a number of quality improvement initiatives in the United Kingdom, published mainly in grey literature, which have focused on preventing UTI by improving hydration of elderly care home residents. Wilson et al. (2019) used improvement methods in two residential care homes to develop and test practical care interventions aimed at extending drinking opportunities and choice. This study highlighted some of the important practical and organizational barriers in this care setting that affected the environment of care and the sustainability of interventions. These included the approach to communication between care staff, the organization of care, the priority given to various care activities and monitoring and responding to indicators of resident safety.

Recurrent UTI is defined as more than 2 episodes in 6 months or 3 in 12 months and is recognized as a problem that is amenable to treatment (National Institute for Health and Care Excellence (NICE), 2018). Treatment options include low-dose antibiotic prophylaxis and non-antimicrobial interventions such as D-Mannose, or vaginal oestrogen in post-menopausal women. However, there is no evidence that residents of care homes who have recurrent UTI are identified, assessed or offered preventative treatment and so the potential of these approaches needs to be explored.

Mechanisms that support early recognition of UTI by care home staff, nurse practitioners and general practitioners (GPs) are critical to driving improvements in UTI prevention as they enable informed assessment of individual residents and monitoring of the effectiveness of prevention strategies. However, identifying UTI in care home residents is challenging and overdiagnosis is a known problem, leading to inappropriate antibiotic treatment for residents with non-specific symptoms or asymptomatic bacteriuria. Public Health England (2020) has recently recommended specific criteria to support more accurate diagnosis of UTI in older adults. The guidance is designed to be read and applied by primary care prescribers in general practice to determine the most appropriate course of treatment. It comprises complex algorithms and decision trees based on the classic signs and symptoms of UTI but does not account for atypical symptom presentations that are more common in older people, such as a change in behaviour or mental state. In addition, most of the signs and symptoms are not easily recognized in people with living with dementia, who constitute a significant proportion of residents in care homes for older people. As the recognition of UTI is driven by the observations made by care home staff, there is a need to understand how systems can be implemented to support these staff to recognize UTI more accurately and communicate their observations to healthcare professionals in primary care so that the most appropriate decisions are made about antibiotic treatment (Jones et al., 2021).

Using patient information to support early recognition of UTI is one approach that has recently been evaluated and has highlighted the importance of linking simple information on recognizing UTI with prevention strategies, such as hydration and continence management (Jones et al., 2021). A number of intervention studies, both in the United Kingdom and overseas, have focused on assisting care home staff to recognize UTI and to communicate their observations about changes in a resident's condition to the GP. These studies reveal the complexities inherent in improving practice given the various ways in which a resident with UTI may present, the knowledge and support needs of care home staff, the need to convey information using a common language and to involve the resident and family carers in decision-making, managing their expectations regarding treatment.

Given the increased susceptibility of this population, the frequency with which UTI occur and the impact on the wider population in terms of acute care resources and increasing antimicrobial resistance, improving understanding of how approaches to prevent and recognize UTI may work is a priority. This requires coherent, evidenced based programmes to support the prevention and recognition of UTI that are both relevant and practical to implement in care homes in the United Kingdom. The purpose of the Strategies for Older People living in care homes to prevent UTI ('StOP UTI') study is to undertake a realist synthesis of evidence to determine which strategies work and generate evidence-informed programme theories, which explain the mechanisms through which they work (or why they fail). It will also assess the approach to recognizing UTIs as this is essential to driving and evaluating prevention initiatives.

This theory-driven understanding of what needs to be in place for the successful implementation of UTI prevention programmes will identify the 'active components' of complex interventions, thus helping to guide the development and successful delivery of programmes to prevent older people in care homes in the United Kingdom from acquiring UTI. The primary research question is underpinned by a secondary (applied) research question, from which the research aim and objectives are derived (Figure 1). The outcomes of interest are a reduction in number of UTIs (including recurrent UTI), reduction in UTI-associated bloodstream infections, reduction in antimicrobial use and reduction in hospital admissions.

3 | METHODS

3.1 | Rationale for using realist synthesis

A realist synthesis (or realist review) will be undertaken, employing a systematic approach to the searching of evidence, with an explanatory focus and seeks to understand what works and how complex programmes work in particular contexts and settings (Pawson et al., 2005). The review will examine the relationship within and between interventions to recognize and prevent UTI in older people and the context of care homes in which they are applied. This will enable explanations about their mechanisms of action and what outcomes they produce to be described (Rycroft-Malone et al., 2012).

As an approach to research evaluation, realist synthesis provides a means to understand the triggers for particular behaviours, the effects of such behaviours and what contextual factors influence them

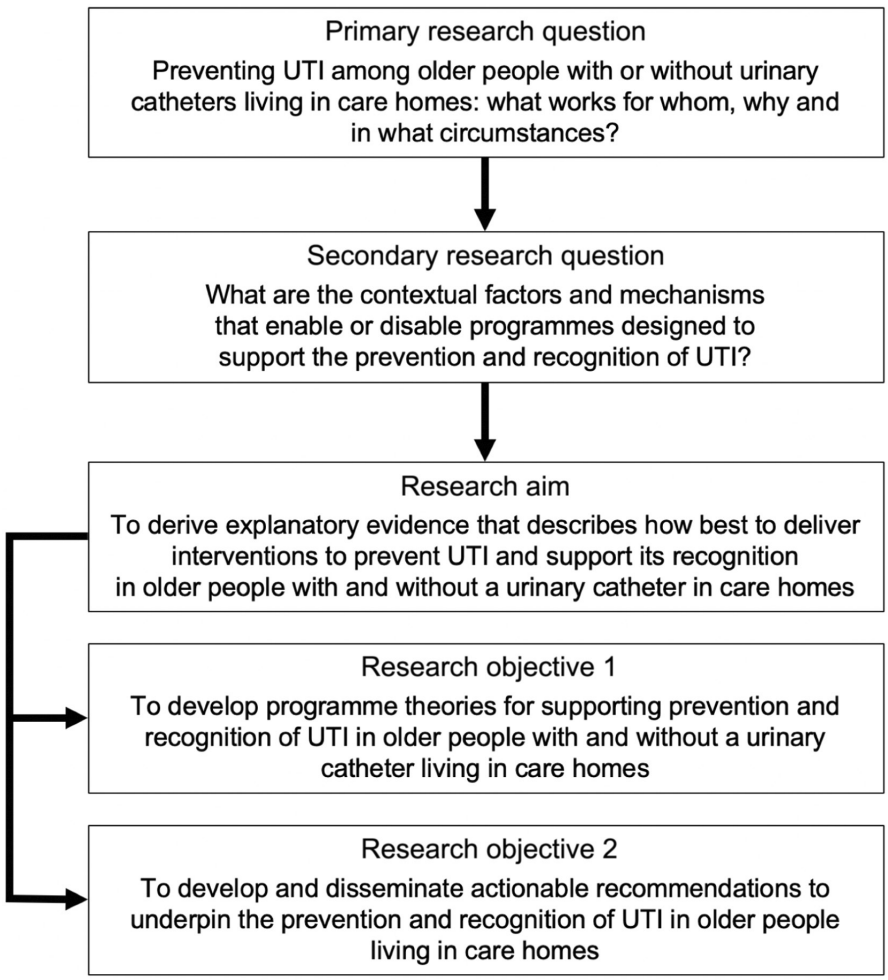

FIGURE 1 Research questions, aim and objectives.

(Booth, 2015). In a realist approach, a programme theory (or theories) is the underlying assumption(s) about how an intervention may work and the impacts it is expected to have (Pawson et al., 2005). Programme theory focuses on how participants respond to a change or intervention to bring about a set of intended outcomes. It, therefore, represents the underpinning mechanism of action, rather than the intervention (Pawson et al., 2005) and realist synthesis results in the development of context, mechanism, outcome configurations (CMOc) that explain how a theory might or might not work.

Context-Mechanism-Outcome configurations are often referred to as mid-range theories because they are expressed at the level of abstraction that permit empirical testing (Wong et al., 2013). They are essential to understanding how interventions to prevent UTI can and should be delivered in the care home context, providing a clear account of the mechanisms of action. Mechanisms of action explain the way in which the resource element of an intervention might work. In adopting a realist approach, mechanisms represent a combination of the resources offered by an intervention, for example a risk assessment tool, and the reasoning or behaviour that is required to implement them, for example how this changes the reasoning of stakeholders to bring about the desired outcome (Pawson et al., 2005). CMOc, therefore, provide explanations of what works, for whom and in which contexts and circumstances (Figure 2).

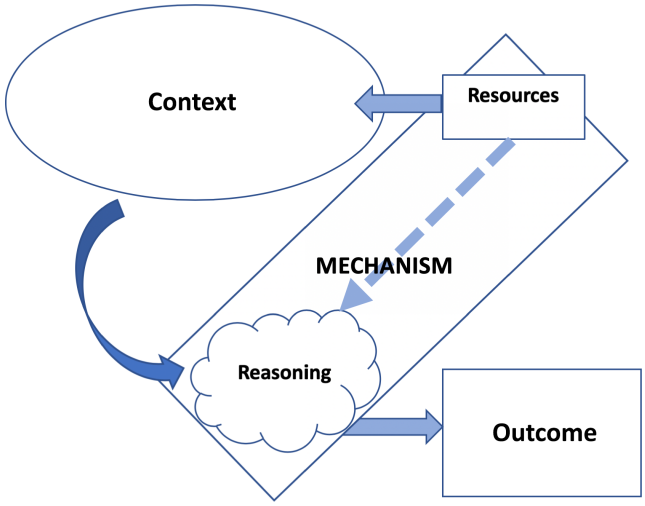

FIGURE 2 A CMOc Framework (adapted from Dalkin et al., 2015).

The analytical task will be to construct causal explanations of phenomena of interest to prevent UTIs and how they operate to impact on delivering effective care for older people living in care homes. These causal explanations are expressed as the interdependency

between CMOc. This will address an important gap in evidence by providing a theory-informed understanding of what needs to be in place to support the recognition and prevention of UTI and its recurrence in older people living in care homes in the United Kingdom.

3.2 | Study design

Unlike undertaking a systematic review where the search strategy is exhaustive, the approach in a realist synthesis is both iterative and purposive and may require multiple search strategies throughout the review process (Emmel et al., 2018). This realist synthesis will draw on evidence from health and social care, including primary research and improvement project reports in grey literature. Purposive searching will also include wider literature that provides opportunities for transferable learning, such as evidence on how patterns of care, organization culture and leadership in care homes support outcomes of implementation. The synthesis will examine the relationship between phenomena of interest and the context in which they are applied to provide explanations about the causal mechanisms and the outcomes they produce.

The review and synthesis of evidence will be conducted in four stages over 18 months (Figure 3):

1. defining the scope of the review and generating initial programme theories;
2. retrieving and reviewing the evidence,
3. extracting and synthesizing the evidence and
4. developing the narrative (Rycroft-Malone et al., 2012).

Whilst these stages are described sequentially, in practice there is considerable iteration between them with stakeholder engagement, including involvement of experts by experience and their families/carers, embedded throughout. The review will be reported according to RAMESES guidelines for realist syntheses (Wong et al., 2013).

Stakeholders will be involved throughout the process to inform the development of initial and refined programme theories (CMOc) and to establish their practical relevance and potential in the real-world setting of care homes. A stakeholder analysis exercise will be undertaken at the start of the review to identify a range of people who need to be involved in the various aspects of the review process. Lists of potential stakeholders will be drawn up to consider their potential input for the review and at what stage. Stakeholder group membership is intended to include users of care home services, their care partners and families; providers of services, service commissioners, aged care policy makers and other relevant organizations (e.g. inspectorate bodies). We will use a purposive approach to identifying stakeholders based on the stakeholder analysis.

This level of stakeholder engagement aims to promote joint decision-making at key stages of the review and will ensure that the synthesis is underpinned by multiple perspectives and focuses upon what is important to care home residents and those who provide care. The narrative we develop around each programme theory will describe the relationships between mechanisms and the contexts in which they occur. In Stage 1, our stakeholder workshops will guide initial theory development. In Stage 3, the teacher-learner interviews will inform theory refinement. Our stakeholder conference in Stage 4 will enable us to work co-creatively to tailor our outputs towards care home residents, managers and staff, clinicians, educators and researchers and support dissemination of findings that can be used to improve existing practices and inform development of future interventions.

3.3 | Stage 1: Programme theory development

In realist synthesis theories are ideas about how particular interventions may or may not work in practice. Stage 1 will formulate initial programme theories, driven by consultation with stakeholders, which will be refined and tested throughout the review. A process of concept mining (Dalkin et al., 2015; Williams et al., 2016) will be used to map evidence about approaches to recognizing and preventing UTI in older people living in care homes, how they might work and any reported enablers or barriers to their successful implementation. This will involve searching different bodies of evidence and consulting with stakeholders to develop the scope of the study and identify information, key terms and concepts that could help with theory building.

3.3.1 | Scoping of the literature

The initial scoping search will be used to build an understanding of the topic area and identify provisional programme theories. Beginning with this framework and through discussions with stakeholders and our Project Advisory Group (PAG) we will seek to maximize opportunities for identification of this literature. We will start by conducting a review of evidence that directly addresses the recognition and prevention of UTI in older people in long-term care facilities. This will include the following bibliographic databases: OVID Medline, OVID Embase, CINAHL Plus, Cochrane Library, Web of Science Core Collection, Sociological Abstracts via Proquest, Bibliomap and NIHR Journals Library. Supplementary searches, for example, using key index studies (highly cited) to find 'sibling' studies/papers (contemporaneous papers/studies that share a context), will also be undertaken at this stage, using Google Scholar and 'Publish or Perish' software.

We consider it important to include evidence from health systems in other countries, including similarly resourced systems where there are services for long-term care, to identify potential strategies that may be realistic in the UK context. We have limited our search to English language papers published within the last 10 years, taking account of both the relevance and volume of literature retrieved in order to achieve a manageable approach without excluding important key studies. Non-English language articles are excluded due of lack of translation resources. Search

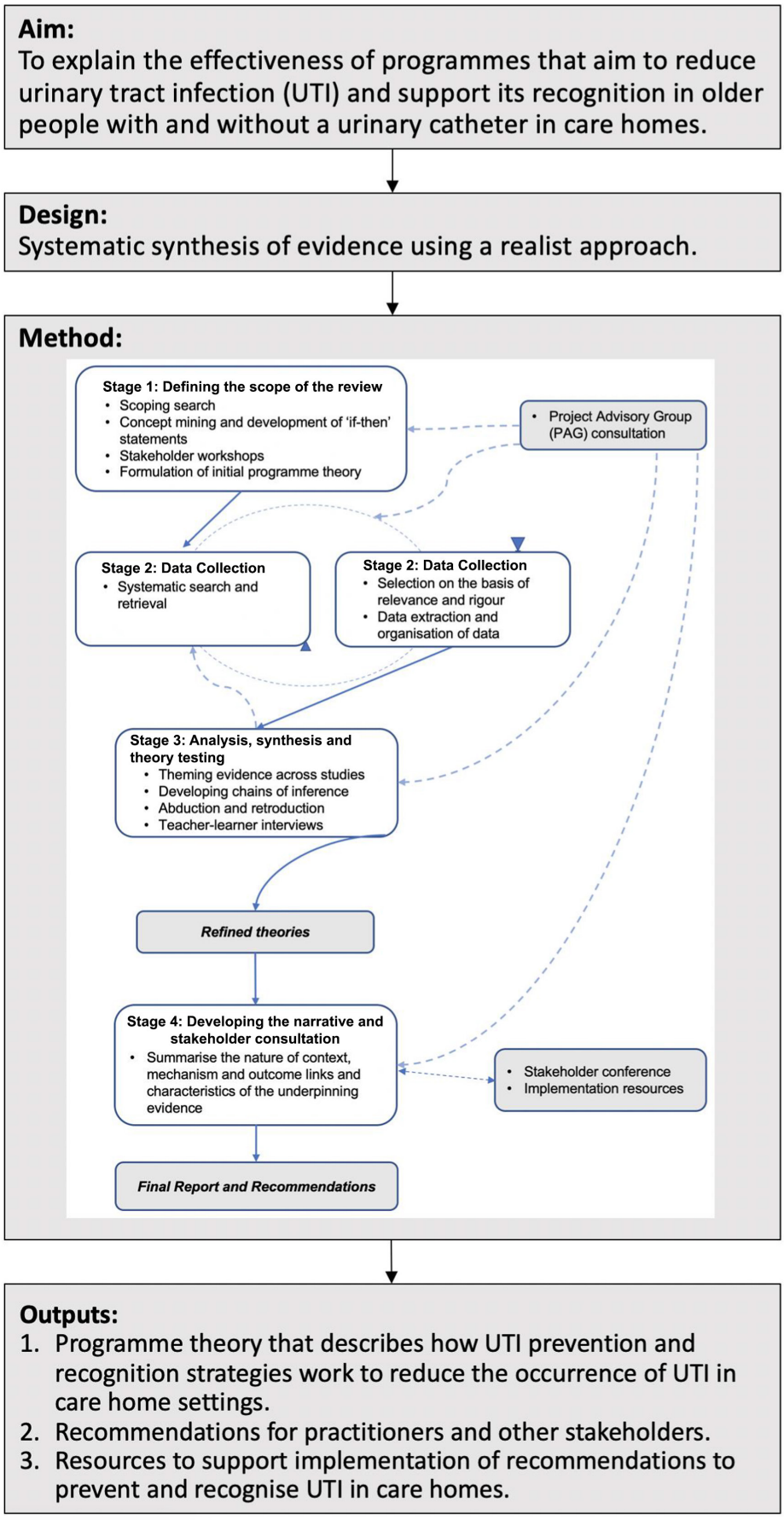

FIGURE 3 Study protocol.

terms include UTIs, catheter-associated UTIs, nursing homes, residential facilities and long-term care. These terms will be tailored to the mesh headings used within each database. This generic topic-based multipurpose search will be followed by more targeted searches in Stage 2 exclusively to inform the realist synthesis (Booth et al., 2020).

3.3.2 | Stakeholder involvement

A theory-building workshop will be used to explore what is necessary for UTI to be effectively recognized and prevented and identify the common approaches used and how they are understood to work in care home settings. Stakeholders will be invited to contribute on why they think certain approaches work, in what circumstances and why. Three key groups have been identified, although other expert groups may be co-opted as part of the scoping process:

- Providers of care: Care home managers and support workers.
- Recipients of care: Care home residents and their representatives.
- Professional practitioners: Clinicians and specialists with a role in care homes.

Using the evidence from the concept mining process and the output from the workshops a set of preliminary hypotheses in the form of 'if-then' statements will be developed as tentative programme theories. This will provide an initial explanation of how different types of interventions for recognizing and preventing UTI in care home settings might work given the impact of ageing on its prevention and recognition (Genao & Buhr, 2012) and the complexities inherent in how care is organized and knowledge mobilized in long-term care settings (Cammer et al., 2013).

3.4 | Stage 2: Evidence retrieval

The purpose of this stage is to determine whether the initial programme theories are supported by evidence within the literature and to ensure that all the relevant literature has been identified. Guided by the initial programme theories we will search purposively for sources of programme theory and for empirical studies to test and refine theory (Booth et al., 2020; Rycroft-Malone et al., 2012). As described above, unlike undertaking a systematic review where the search strategy is exhaustive, the search strategy in a realist synthesis is both iterative and purposive and may require multiple search strategies throughout the review process (Figure 2; Emmel et al., 2018). The searching evolves to uncover theories, which were not apparent at the beginning of the concept mining process but that emerge as new lines of inquiry are studied. In realist methodology, the programme theory is the unit of analysis rather than the intervention (Pawson et al., 2005). This means we will be able to draw on related wider literature, which may provide opportunities for transferable learning.

3.4.1 | Search strategy

We will build on the scoping search by more targeted searches for published and grey literature, and also policy and narrative literature, using the same bibliographic databases and approaches, along with OpenGrey, NHS Evidence, Social Care Online and websites of relevant organizations. We will search for literature specific to the care of older people in care homes in areas such as interventions for people with dementia in care homes, and evidence on how patterns of care, culture, organization management and leadership in care homes support outcomes of implementation. This will also include interventions that focus on the reliable recognition of UTI, minimizing UTI risk and recurrence in older people with and without a urinary catheter (Biggel et al., 2019; Mody et al., 2017), managing incontinence and incomplete bladder emptying (Biggel et al., 2019), general hygiene to reduce infection (Biggel et al., 2019), improving hydration (Wilson et al., 2019) and UTI prophylaxis (NICE, 2018).

We aim to identify 'conceptually rich' or 'contextually thick' evidence and will therefore, use citation searching and author searching to identify clusters of related papers (Booth, 2015). It is likely that some relevant evidence may exist in unpublished form, and therefore, we will seek to maximize opportunities for identification of this literature through consultation with our PAG, stakeholders and communication with relevant policy, professional and third sector organizations.

3.4.2 | Review inclusion criteria and quality appraisal

The test of inclusion for a realist review is based on relevance and rigour (Pawson et al., 2005). Relevance of evidence is determined by the extent to which it can contribute to theory building and/or testing. Rigour is defined as the credibility and trustworthiness of the methods used to generate that particular piece of data.

3.4.3 | Selection and assessment of data

The titles and abstracts of identified articles will be screened and cross-checked by at least two members of the team. All potentially relevant papers will be retrieved in full text for a more detailed assessment of relevance and rigour, with the same level of checking applied. Discrepancies in opinions about the relevance of articles will be resolved through discussion among the project team and decisions documented.

3.4.4 | Data extraction

The data extraction process will be undertaken by one reviewer, with at least a 30% proportion of those identified for inclusion being peer-reviewed and checked by a second reviewer. Evidence

will be extracted to record two aspects of the review process. A conventional summary table will include the study characteristics, including methods, setting and outcomes. This will be adapted for non-research-based literature. A bespoke data extraction form based on the initial programme theories will be used to structure the extraction of relevant information, insights and the charting of data so that the theory areas are populated with evidence on what appears to work, for whom, how and in what contexts (Williams et al., 2016). It will be used in conjunction with a conventional data extraction form, used for systematic reviews, to record information about study characteristics and findings of relevance to the review questions and provide consistency. The evidence tables will then be reviewed by the project team to check against propositions developed in the initial programme theories and note any new evidence to support or refute them. This combined approach will provide evidence of relevance and rigour.

3.5 | Stage 3: Testing and refining programme theories

Stage 3 will involve theming of the evidence within and across the evidence tables and the formulation of chains of inference from the identified themes to develop Context-Mechanism-Outcome configurations (Pawson et al., 2005; Rycroft-Malone et al., 2012). CMOc are essential to understanding how interventions to prevent UTI can and should be delivered in the care home context, providing a clear account of the mechanisms of action. They will provide explanations of what works, for whom and in which contexts and circumstances.

3.5.1 | Synthesis

'If – then' statements will be refined into CMOc and linked to the underpinning source(s) of evidence. Findings from different studies will be compared and contrasted, seeking both confirmatory and contradictory findings as part of the synthesis and theory refinement process. For each hypothesis, a record of this process will be systematically documented to capture data across studies that contributes to the context, impact/effectiveness and interpretation of the evidence (Williams et al., 2016).

As realist synthesis is theory-driven, we will use abductive reasoning, to seek the most likely explanation from an observation or set of observations and make inferences on plausible explanations for the hypotheses, and retroduction to identify what lies behind a phenomenon and reviewing across the evidence tables to identify emerging patterns (Pawson et al., 2005).

3.5.2 | Theory testing and refining

We will conduct up to 10 'teacher-learner' interviews to elicit stakeholder (teacher) views on the plausibility of the programme theories and establish the credibility and transferability of the underpinning CMOc (Pawson et al., 2005). A purposive sample of key stakeholders, such as managers, clinicians, support workers, lay representatives of older people and service commissioners or funders will be identified to participate in semi-structured audio-recorded online interviews. The interviews will be guided by the content of the CMOc to elicit participants' perspectives on whether or not they resonate with their experience. They will be transcribed verbatim and the findings used to further refine the CMOc.

3.6 | Stage 4: Actionable recommendations

In Stage 4 we will develop a narrative around the final programme theory, summarizing the nature of CMOc links and the characteristics of the underpinning evidence (Rycroft-Malone et al., 2012). In consultation with our Project Advisory Group we will produce a theory-driven account of what needs to be in place for implementation of programmes to support the prevention and recognition of UTI in care homes. This will describe the relationships between interventions and the contexts in which they occurred and will be used to underpin recommendations for preventing and recognizing UTI in a care home setting.

We will develop material that describes the CMOc in a way that is relevant to the care home setting, together with a range of implementation support tools and promotional material, including training/information videos and case studies. This material will be informed by our PPI representatives, Project Advisory Group and other stakeholders we involve in the realist synthesis. This includes views captured in a stakeholder conference, to ensure the resources will be relevant and practical for care home staff and other stakeholders to use.

4 | DISCUSSION

Care homes are complex environments and many residents have frailty or comorbidities that increase their susceptibility to UTI. Strategies to prevent UTI, including those demonstrated to be effective in long-term care facilities in settings outside of the United Kingdom, may be able to improve care in the context of UK care homes. As UK care homes vary widely in relation to size, funding models and types of healthcare support, there is limited understanding of how, and to what extent, UTI prevention can be optimally implemented. This realist synthesis will describe some of the causal mechanisms that may explain how interventions to prevent UTI may bring about improvements in care homes.

5 | ETHICS AND DISSEMINATION

The 'StOP UTI' study was identified as a service evaluation/service development following submission to the UK Health Research

Authority and subsequent review by the Faculty Ethics Committee at the lead author's institution.

We aim to publish this realist synthesis in a peer-reviewed journal with international readership. We will disseminate the outputs from this research to a wide range of stakeholders from long-term care settings. Patient and public involvement will be crucial to ensuring that our findings reach carers and the public. National organizations, such as NHS England and Social Care Institute of Excellence and third sector organizations, such as Age UK and Care UK, will be approached for wider dissemination.

AUTHOR CONTRIBUTIONS

JP, JW and HL conceived the study. JP, JW, AT, JRM, LW and HL participated in its design. JP and JW drafted the manuscript. All authors commented on and revised the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

No conflict of interest has been declared by the authors.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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