Community-based complex interventions to sustain independence in older people, stratified by frailty: a systematic review and network meta-analysis

Study protocol

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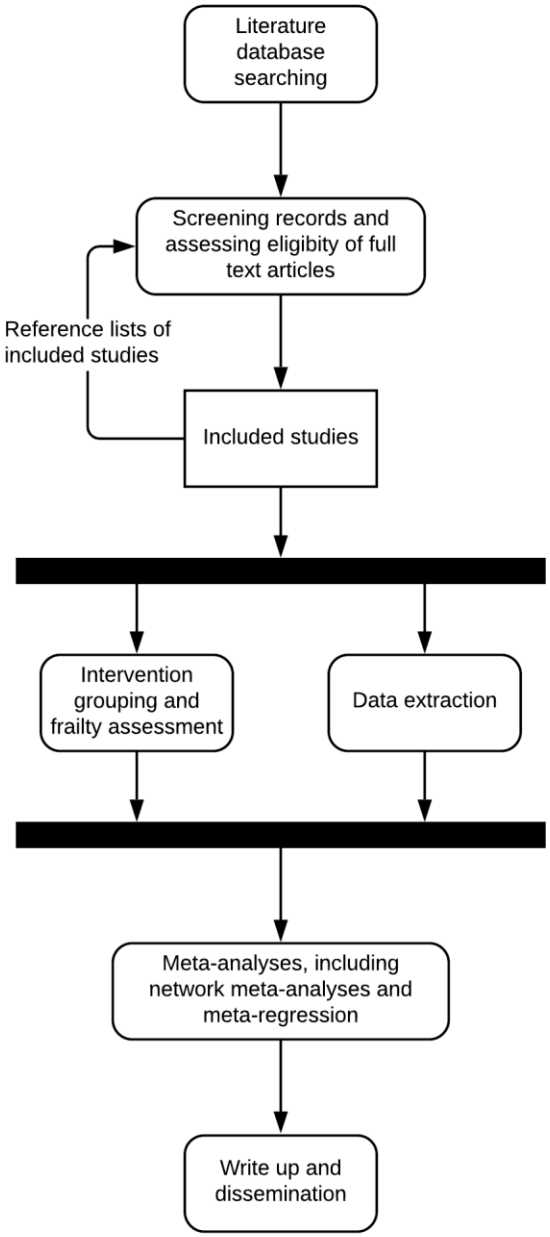
STUDY FLOW CHART



STUDY SUMMARY

Research questions

i) Do community-based complex interventions to sustain independence in older people increase living at home, independence and health-related quality of life?
ii) Do community-based complex interventions to sustain independence in older people reduce home care requirement, depression, loneliness, falls, hospitalisation, care home admission, costs and mortality?
iii) How should interventions be grouped for network meta-analysis (NMA)?
iv) What is the optimal configuration of community-based complex interventions to sustain independence in older people?
v) Do intervention effects differ by frailty level (not frail; pre-frailty; frailty)?

Background

The 2019 NHS Long Term Plan emphasises development of community services to help people age well and maintain independence, including people living with frailty. However, there is insufficient guidance for policymakers, commissioners and providers about which services should be implemented.

Aim

To synthesise evidence on the effectiveness of community-based complex interventions to sustain independence for older people, including the effect of frailty and pre-frailty, and group interventions to identify the best configurations.

Methods

Review design

Systematic review with NMA, following Cochrane methods, GRADE and PRISMA NMA guidance.

Eligibility criteria

Randomised controlled trials (RCTs) and cluster RCTs of community-based complex interventions to sustain independence for older people living at home (mean age 65+), compared with usual care or another complex intervention.

Study selection/data collection

Two independent researchers will assess title/abstract, study eligibility, and extract data, resolving disagreements by consensus.

Data items

Main outcomes

- Living at home
- Activities of daily living
- Home-care services usage
- Hospitalisation

- Care home admission
- Costs
- Cost-effectiveness

Additional outcomes

- Health status/health-related quality of life
- Depression
- Loneliness
- Falls
- Mortality

Risk of bias

Two independent reviewers will assess risk of bias (RoB) using Cochrane's RoB 2 tool, including additional criteria for cluster RCTs.

Summary measures

For continuous outcomes, we will calculate intervention effect as mean difference. For binary outcomes, we will calculate risk ratios/odds ratios. For survival (time-to-event) outcomes, hazard (rate) ratios will be extracted.

Analysis

Random-effects meta-analyses, to allow for potential between-study heterogeneity in each intervention effect. An NMA will then be conducted using a multivariate random-effects meta-analysis framework.

Assessment of inconsistency

Consistency will be examined for each treatment comparison where there is direct and indirect evidence, and across the whole network using 'design-by-treatment interaction' models.

Risk of bias across studies

Funnel plots will be presented to examine potential publication bias.

Additional analyses

Meta-analysis results will be presented by different levels of frailty (not frail; pre-frailty; frailty), and by extending the standard and NMA to a meta-regression.

Timelines for delivery

-6-3m: Run searches; screen records; obtain papers; assess eligibility.

3-20m: Summarise studies; extract data; intervention grouping & frailty assessment.

20-24m: Prepare data for analysis. Synthesise data in meta-analysis/NMA.

21-26m: Write-up/dissemination.

Impact and dissemination

Potential for major impact, supporting delivery of the NHS Long Term Plan, with dissemination to policymakers, commissioners, health/social care professionals, older people and researchers.

1. BACKGROUND AND RATIONALE

UK population projections indicate that older people are the fastest growing demographic, with the percentage of people aged 65 and over expected to grow from 18% currently to 21% in 2027 and 24% by 2037 [1]. Older people are core users of health and care services, so the ageing population demographic has profound implications for service planning and delivery. The importance of the ageing population demographic in health systems is reflected in national policy. The 2019 NHS Long Term Plan identifies that our growing and ageing population is a key driver of NHS service demand [2]. The Plan emphasises development of community services to help people age well, including people living with frailty as a key societal group. However, there is currently insufficient guidance for policymakers, commissioners and providers about which community services should be implemented.

Frailty is an especially problematic expression of population ageing, with increased risk of losing independence, hospitalisation, care home admission and mortality [3]. Around 10% of people aged 65 and over have frailty, rising to around 50% of people aged over 85 [1].

We are proposing a systematic review with network meta-analysis (NMA) of community-based complex interventions for older people. We plan additional meta-regression to assess impact of frailty and pre-frailty, an intermediate state between robust health and frailty. We plan the evidence synthesis as an update of a landmark 2008 systematic review and meta-analysis that summarised evidence from 89 trials including 97,984 people [4]. The review reported that, in general, complex interventions provided in the community are effective for older people but lacked detail about what types of complex care improve outcomes, and does not include studies published over the last decade, which are potentially influential.

The clear focus on ageing well and frailty in the Long Term Plan means that there will be immediate and sustained interest in identifying and commissioning evidence-based services. The results of our proposed systematic review and NMA will therefore remain highly relevant and important to the needs of the NHS and social care in the future, if commissioned.

Evidence explaining why this research is needed now

NHS expenditure increases considerably with advancing age, with a threefold increase for people aged over 70 [5]. Social care expenditure for older people is expected to rise to £12.7 billion by 2022 [6]. Costs increase for older people who are relatively fit, with an average £1,237 of annual health and social care spending, to £6,955 for people living with advancing frailty [7]. Total annual NHS and social care spending on frailty is estimated at £15 billion [7].

There is a critical evidence gap regarding which community-based interventions are clinically and cost-effective, and therefore appropriate, for older people, including those living with frailty and pre-frailty. This evidence gap means that there is considerable uncertainty regarding how interventions should best be configured and commissioned to enable delivery of the NHS Long Term Plan. Aligned with national health and care policy, the NIHR has prioritised older people living with frailty in the current themed call.

Previous systematic reviews and meta-analyses have reported evidence for clinical and cost-effectiveness of community-based complex interventions for reducing hospital admission, nursing home admission, falls and functional decline [4,8,9]. However, previous reviews have not used NMA to summarise whether different types of interventions have differential effects on outcomes, limiting usefulness for policymakers, health and social care commissioners and providers. For example, the landmark 2008 review on community-based complex interventions gives insufficient guidance for those planning and delivering services, specifically how interventions might best be configured to improve outcomes [4]. This review also used a disability-based, non-validated definition of frailty to categorise trials, and frailty was considered only in relation to one intervention (Comprehensive Geriatric Assessment). Standard meta-analysis techniques were used to synthesise the evidence. Recognising that

research evidence, understanding of frailty, and meta-analysis methods have advanced considerably in the last decade the review requires a contemporary update to inform commissioning and delivery of evidence-based services.

Our proposal has considerable potential to generate new knowledge through a contemporary, robust synthesis of the available evidence on community-based complex interventions for older people, categorised by level of frailty (not frail, pre-frailty, frailty). The use of NMA and meta-regression will generate new knowledge on how services should be best configured and commissioned.

2. AIM, RESEARCH QUESTIONS, OBJECTIVES

Aim

To synthesise evidence on the effectiveness of community-based complex interventions to sustain independence for older people, including the effect of frailty and pre-frailty, and group interventions to identify the best configurations.

Research questions

i) Do community-based complex interventions to sustain independence in older people increase living at home, independence and health-related quality of life?
ii) Do community-based complex interventions to sustain independence in older people reduce home care requirement, depression, loneliness, falls, hospitalisation, care home admission, costs and mortality?
iii) How should interventions be grouped for network meta-analysis (NMA)?
iv) What is the optimal configuration of community-based complex interventions to sustain independence in older people?
v) Do intervention effects differ by frailty level (not frail; pre-frailty; frailty)?

Objectives

i) To identify randomised controlled trials (RCTs) and cluster randomised controlled trials (cRCTs) of community-based complex interventions to sustain independence in older people.
ii) To synthesise evidence of their effectiveness for key outcomes in a meta-analysis of study-level data.
iii) To identify key intervention components and study-level frailty to inform groupings for NMA and meta-regression.
iv) To compare effectiveness of different intervention configurations using NMA.
v) To investigate the impact of frailty and pre-frailty using meta-regression.

3. RESEARCH PLAN

Design

Systematic review with NMA of trials evaluating community-based complex interventions to sustain independence in older people (mean age 65 years and over), compared with usual care or another complex intervention meeting our criteria, with follow-up for at least 24 weeks. The review will follow Cochrane methods [10], evaluate quality of evidence following CINeMA [43] and GRADE NMA guidance [11] and be reported using PRISMA NMA guidelines [12].

Health technologies being assessed

This review will assess community-based complex interventions for older people that are targeted at the individual and focused on sustaining their independence.

Complex interventions have been defined as interventions with several interacting components (intervention practices, structural elements and contextual factors) [13]. They typically attempt to introduce new, or modify existing, patterns of collective action in healthcare or formal organisational settings, with an intention to lead to changed outcomes [14]. We will use this definition of complex interventions to inform our eligibility criteria.

Eligibility criteria

Types of studies

Randomised controlled trials (RCTs) and cluster randomised controlled trials (cRCTs).

Where only one unit of randomisation (an individual or cluster) is allocated to an arm of a trial, we will exclude the trial as the treatment effect is completely confounded with the unit. We accept minimisation as a method of sequence generation, in keeping with the Cochrane risk of bias guidance.

Types of participant

We will include studies involving older people living at home (mean age of study participants 65 years or older).

We will exclude trials in residential/nursing homes as these are the subject of other large-scale reviews, including a Cochrane Review of physical rehabilitation in care homes led by joint lead applicant Crocker [15]. If settings are mixed, we will only include studies if data can be extracted specifically for participants living at home.

Types of intervention

Aligned with our focus on community-based complex interventions, trials will be considered eligible if:

- the intervention is both initiated and mainly provided in the community;
- the intervention includes two or more interacting components (intervention practices, structural elements and contextual factors);
- the intervention is targeted at the individual person, with provision of appropriate specialist care;
- a focus of the intervention is sustaining (maintaining or improving) the person's independence.

Although a broad range of interventions will potentially be eligible, we anticipate rehabilitation interventions will be of key importance. These are typically complex system processes where the physical and social environment are integral to independence outcomes. These interventions can be delivered, for example:

- individually or in group settings;
- proactively, targeting people at risk of losing independence;
- to improve function in those who have lost independence.

Interventions can involve therapist assessment/education/motivation/specific exercises, restorative/adaptive processes, but the overall effectiveness depends on, for example, wider support from GP, occupational therapist, family and carers. Related interventions such as comprehensive geriatric assessment (CGA) are typically based around a specialist multidisciplinary process, to identify

an individual's medical, functional, social and psychological needs to agree a plan for treatment and follow-up; these will be included in the review.

Interventions that would not be considered eligible for inclusion are those where:

- the intervention is either not initiated, or not mainly provided, in the community, or neither e.g. interventions delivered in outpatient, day hospital, inpatient and intermediate (post-acute) care settings;
- the intervention includes only one component (intervention practices, structural elements and contextual factors) e.g. if any of the following are delivered as single component interventions: a drug; treadmill training; yoga; provision of information; cataract surgery for visual impairment; hearing aid for hearing impairment; medication review; nutritional supplements;
- the intervention is not targeted at the individual person, with provision of appropriate specialist care e.g. general staff education (not training in a patient-level intervention), practice-level reorganisation, operational, managerial or IT interventions, public health messages;
- a focus of the intervention is not sustaining (maintaining or improving) independence. Sustaining independence will include maintaining or improving independence in basic activities of daily living (washing, dressing, grooming, toileting, walking, climbing stairs, etc), or maintaining or improving independence in instrumental activities of daily living (gardening, managing finances, outdoor mobility, gardening, etc), or both, excluding a focus on only one of these specific activities (e.g. walking only). For example, interventions that primarily address cognitive deficits, mood disorders, or both, unless they also aimed to improve overall independence; disease focused case management of older people with specific long-term conditions, for example diabetes, COPD or depression.

The evidence base for falls prevention is well established, including in a recent NMA [16], so interventions in which the primary focus is falls prevention will be excluded (although falls will be a key secondary outcome).

Comparators

Usual care, "placebo" or attention control, or a different complex intervention meeting our criteria.

Outcomes

Studies will only be included where outcome data were measured at a minimum 24 weeks (approximately 6 months) timepoint. For all outcomes, data will be extracted and categorised for three timeframes shown in Table 1.

Table 1. Timeframes for analysis

Label	Target timepoint	Range
Short term	6 months	24 weeks to 9 months
Medium term	12 months	> 9 months to 18 months
Long term	24 months	> 18 months

Where more than one timepoint is reported for an outcome within a range specified above we will use the timepoint nearest to the target timepoint.

Main outcomes

- Living at home, defined either as a reported study outcome, or the inverse of care home admission and mortality if reported separately;
- Activities of daily living (basic/instrumental);
- Home-care services (non-healthcare professional) usage;
- Hospitalisation;
- Care home admission;
- Costs;
- Cost-effectiveness.

Additional outcomes

- Health status/health-related quality of life;
- Depression;
- Loneliness;
- Falls;
- Mortality.

Because of the large number of outcomes and multiple timeframes, our summary reports will prioritise results from the main outcomes in the medium term (around 12 months). Furthermore, we will limit analyses of additional outcomes and hospitalisation to the medium-term timeframe only. We anticipate that the medium term will be of particular interest to commissioners and older people, will be most likely to allow sufficient time for effects to be realised but not washed out, and when most data will be available. We plan to conduct sensitivity analyses and meta-regression for the medium-term timeframe initially and to extend these to short- and long-term networks in the presence of significant findings.

Search strategy

We have developed a search strategy with our information specialist, covering CENTRAL, MEDLINE, EMBASE, CINAHL, PsycINFO databases and trial registers.

The search contains the following sections:
1. Elderly or frail
2. Home-based or community interventions
3. RCT filter
4. 1 AND 2 AND 3

Restrictions by publication status or language will not be used.

We will scan reference lists of included papers.

Study selection

Search results will be imported into Rayyan software. Two independent researchers will assess title and abstract of records. We will obtain full text articles for all potentially eligible trials. Two researchers will independently assess inclusion against our pre-specified criteria, resolving disagreements by consensus. We will contact study authors if further information is required.

Data collection process

Two independent researchers will extract data using a piloted data extraction form in a purpose-built Microsoft Access database. Characteristics of included and excluded studies tables will be produced in Review Manager 5. Summary of findings tables will be produced in GRADEPro.

Intervention grouping

We will group interventions for NMA in a three-stage process.

1. We will use the Template for Intervention Description and Replication (TIDieR) framework to summarise reported interventions [17]. The TIDieR framework includes 12 key items.
    - Brief name of intervention.
    - Rationale, theory or goal of the elements essential to the intervention.
    - The physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery/training of intervention providers.
    - The procedures, activities and/or processes used in the intervention, including any enabling or support activities.
    - The expertise, background and any specific training given to each category of intervention provider.
    - The modes of delivery (such as face-to-face or by some other mechanism) of the intervention, and whether it was provided individually or in a group.
    - The types of location where the intervention occurred, and any required infrastructure.
    - The amount and intensity of intervention delivered, including number of sessions, their schedule, duration and dose and the overall timeframe.
    - Details of any individual/group adaptations, personalisation or titration.
    - Details of any changes made to the intervention during the course of the study.
    - Strategies to achieve fidelity or adherence and planned assessment of fidelity
    - Extent of intervention fidelity achieved.

2. We will complete a content analysis of the summarised interventions using the TIDieR framework in nVivo 12 to inform provisional groupings [18].

3. We will develop provisional intervention groupings based upon the service organisation or structure (e.g., team structure), key patient care processes (e.g., assessment, follow-up), and specific patient care interventions (e.g., exercise, ADL practice, relaxation). We will present our provisional groupings to experts including policy makers, commissioners, older people and carers for open discussion. We will revise our groupings based on these discussions. The intervention types will become the nodes in the NMA.

The three stage intervention grouping process will be led by co-applicant Gladman, a highly experienced clinical academic community geriatrician and trialist, including in the design and evaluation of complex interventions [21-23], nominal group methods, and organisation of community services for older people [24].

Although the critical features will be identified in the intervention grouping process we anticipate groupings may consider intervention content, method of working (e.g. multidisciplinary team meetings), key staff members (e.g. medical, nursing, therapy, social care), delivery method (e.g. groups, individual), location (home, day centre), delivery context (e.g. post-discharge care, proactive home visits), intervention duration/intensity.

Assessment of frailty

We anticipate that a range of validated instruments and operationalised measures will be used to identify pre-frailty and frailty in included trial populations of some studies. Examples of such frailty measures include: the use of the Fried phenotype model, the Tilburg Frailty Indicator, Groningen Frailty Indicator, Study of Osteoporotic Fractures criteria, Chinese Canadian study of health and aging clinical frailty scale, Hebrew Rehabilitation Center for Aged Vulnerability Index, Vulnerable Elders Survey, Brief frailty measure derived from the Canadian study of health and aging or a formally produced Frailty Index. We will classify the trial population in accordance with the frailty measure, so long as it is developed or validated according to the modern meaning of frailty and not as a generic term for being old or disabled. We will report methods used for each study, including cutpoints for identification of pre-frailty and frailty.

We also anticipate that many studies will not formally have described study populations in terms of frailty. In such circumstances two reviewers with extensive clinical academic frailty expertise (AC & JG) will independently use the well-validated phenotype model as a framework to categorise study-level frailty profile (not frail; pre-frailty; frailty) of trial participants if the relevant variables are reported [25]. The model is based on five characteristics (weight loss; exhaustion; low energy expenditure; slow gait speed; low grip strength). Evidence of ≥3 indicates frailty, 1-2 pre-frailty and 0 not frail. In the remaining studies where neither a recognised frailty measure nor the variables needed to apply the frailty phenotype categorisation are reported, the two reviewers will independently attempt to classify the populations based on trial eligibility criteria and/or reported baseline characteristics closely linked to frailty including gait speed, hand grip strength, mobility, activity or disability levels. Any disagreements will be resolved by consensus.

In categorising study level frailty, we recognise that trials may include participants across different frailty categories, so as well as ‘not frail’, ‘pre-frail’ and ‘frail’, our categories will also include ‘not frail and pre-frail’, ‘pre-frail and frail’ and ‘all’.

Our main analysis of the impact of frailty will only include trials that used a validated measure. Trials in which the reviewers allocated a study-level frailty level on the basis of eligibility criteria and/or baseline characteristics will be examined in secondary analyses.

Risk of bias within individual studies

Two reviewers will independently assess risk of bias (RoB) in each result of interest from each included study, using Cochrane’s RoB 2 - a revised tool for assessing risk of bias in randomised trials [26]. For cRCTs, we will additionally assess identification/recruitment bias, and the other issues such as loss of clusters detailed in section 23.2: Assessing risk of bias in cluster-randomized trials, of the Cochrane Handbook Version 6 [10].

For each domain, a judgement of high risk of bias, low risk of bias, or some concerns will be made, then an overall risk-of-bias judgement will be reached for each assessed result of interest, with any disagreements resolved by consensus.

Summary measures

For each trial and each outcome separately, effect estimates and confidence intervals (CI) will be extracted comparing intervention and control groups. For continuous outcomes, we will calculate the intervention effect as mean differences. We will consider using standardised mean difference if different measures are used for similar constructs.

For binary outcomes, we will calculate risk ratios (RR) and odds ratios (OR). For survival (time-to-event) outcomes, hazard (rate) ratios will be extracted. Any details about non-proportional hazards will also be extracted.

Outcomes at all timepoints will be recorded and categorised (around 6 months, 12 months, 24 months; see Table 1).

Planned methods of analysis

We will meta-analyse the extracted effect estimates using modules within R and Stata, such as metafor, metan, mvmeta and network. Random-effects meta-analyses will be conducted, to allow for potential between-study heterogeneity in each intervention effect [27]. Restricted maximum likelihood (REML) estimation will be used to fit all the models, with 95% CIs derived using the Hartung-Knapp Sidik-Jonkman approach, to account for uncertainty in the estimate of heterogeneity (tau-squared) [28].

Initially, for each outcome separately, we will perform a separate meta-analysis for each type of intervention, to provide summary effectiveness results based only on direct evidence. We will summarise Ors and RRs for binary outcomes, pooled (standardised) mean differences for continuous outcomes, and pooled HRs for survival outcomes. We will display forest plots, with study-specific estimates, confidence intervals and weights, alongside the summary (pooled) meta-analysis estimates, 95% CI, and (if appropriate) a 95% prediction interval.

Network meta-analysis

An NMA will then be conducted (for each outcome separately), using a multivariate random-effects meta-analysis framework via the network module in Stata using REML estimation [29]. This allows both direct and indirect evidence to contribute toward each intervention effect (treatment contrast), via a consistency assumption. The within-study correlation of multiple intervention effects from the same trial (i.e. in multigroup trials) will be accounted for, and a common between-study variance assumed for all treatment contrasts in the network (thus implying a +0.5 between-study correlation for each pair of treatment effects). If possible, sensitivity to relaxing this assumption will be examined using model fit statistics. We will produce summary (pooled) effect estimates for each pair of treatments in the network, with 95% CI, and the borrowing of strength statistic to reveal the contributions of indirect evidence. For binary outcomes, if possible, we will do an NMA of both OR and RR, to check the robustness of conclusions to the choice of effect measure.

Based on the results, the ranking of intervention types will be calculated using resampling methods, and quantified by the probabilities of being ranked first, second, …, last, together with the mean rank and the Surface Under the Cumulative Ranking curve (SUCRA).

Assessment of inconsistency

The consistency assumption will be examined for each treatment comparison where there is direct and indirect evidence (seen as a closed loop within the network plot). This involves estimating direct and indirect evidence, and comparing the two [5,6,30]. The consistency assumption will also be examined across the whole network using ‘design-by-treatment interaction’ models, which allow an overall significance test for inconsistency. If evidence of inconsistency is found, explanations will be sought and resolved.

Risk of bias across studies

If there are 10 or more studies in a meta-analysis, funnel plots will be presented to examine small-study effects (potential publication bias). Egger's, Peter's and Debray's test of asymmetry will be used for continuous, binary and survival outcomes, respectively.

Examination of frailty impact

Meta-analysis results will initially be presented for all levels combined, then for frailty/pre-frailty where reported data permit. Impact will be further examined by extending the standard and NMA to a meta-regression, with frailty/pre-frailty as a study-level categorical covariate allowing effects of frailty/pre-frailty to vary for each treatment effect, to quantify if intervention effects vary according to population-level frailty.

All analyses to examine frailty impact will initially be restricted to trials using a validated measure. Sensitivity analyses will 1) be restricted to trials using the phenotype model to identify pre-frailty/frailty as an internationally-established reference standard, 2) include trials that used either a validated or an operationalised measure of frailty, 3) include all trials, including by study-level categorisation of frailty status.

Additional analyses

We will also run additional sensitivity analyses to present results of more recent evaluations, restricted to trials in the last 15 years. Meta-regression will be used to quantify differences in summary effects between studies at low risk of bias and other studies, and between those with shorter and longer lengths of follow-up. A multivariate network meta-analysis will be considered to accommodate all outcomes simultaneously, to examine if conclusions remain the same after accounting for the correlation amongst outcomes [31]. As mentioned, we will consider how relaxing the assumption of common between-study variances improves model fit.

Confidence in cumulative evidence

We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, adapted for NMA, to rate evidence quality informed by the Confidence in network meta-analysis (CINeMA) approach for dichotomous and continuous outcomes [11,32-34,43,44]. We have worked with our PPI Frailty Oversight Group to identify key outcomes for the systematic review and NMA from the perspective of older people, so plan to include all outcomes in the overall GRADE evidence profile where feasible. Our assessment of quality of treatment effects will enable generation of GRADE evidence profiles for our individual intervention groupings for each outcome separately.

For dichotomous and continuous outcomes, we will generate assessments of risk of bias, heterogeneity between study estimates (known as inconsistency in GRADE), indirectness, imprecision, incoherence and reporting bias (known as publication bias in GRADE) Using CINeMA. We will then produce a GRADE rating for each estimate. As we will include RCTs and cRCTs, the starting point will be a high-quality evidence rating. For each assessment, we will downgrade evidence quality on the basis of concerns in these domains, but accounting for the interconnectedness between domains to avoid excessively downgrading the overall rating [43].

For time to event or rate data, we will use the GRADE for NMA approach. The assessment of quality of treatment effects will include presentation and rating of the quality of direct and indirect treatment estimates separately and combined in NMA [34], with a focus on first order loops for assessment of indirect treatment estimates. Using GRADE, we will downgrade evidence quality on the basis of risk of

bias, inconsistency, indirectness, imprecision and publication bias. We will make an overall judgement on whether the quality of evidence for an individual outcome warrants downgrading on the basis of study limitations in each of the domains, aligned with GRADE guidance [33].

Specifically, we will not consider imprecision when rating the direct and indirect estimates to inform the combined NMA rating, aligned with recent guidance [11]. Furthermore, in the presence of incoherence between direct and indirect estimates, we will assess the certainty of evidence of each estimate to guide whether or not the network estimate is downgraded [11].

Summary of economic evidence

We will follow the brief economic commentary framework recommended in the Cochrane Handbook, version 6 [45], extracting and summarising brief details of the analytic perspective, time horizon, evaluation type(s), main cost items, currency, price year, any reported details about discounting and sensitivity analysis, the principal findings which apply to this review's time periods and outcomes of interest, and verbatim text of conclusion of each identified study. We will then compare and contrast the findings from similar interventions (classified in the same intervention group) and between different intervention groups, based on the conclusions of these studies.

We will use the definitions stated in the "Glossary of Terms for Health Economics and Systematic Review" from the Campbell and Cochrane Economics Methods Group [46] to classify the three full economic evaluation types [47]– cost-effectiveness analysis, cost-utility analysis, and cost-benefit analysis. We will classify analysis of comparative costs for alternative interventions in monetary value of the resources used as cost analysis (partial economic evaluation) [45, 48]. We will identify the cost item categories reported in each of these studies and use these to identify the evaluation perspective. The cost items will be classified into four categories: health sector costs, other sector costs, patient and family costs, and productivity impacts [45, 48]. An evaluation that included the monetary expenses on health and/or social care will be regarded as adopting a health and social care system perspective. If non-monetary, intangible resources for care or economic impacts associated with the intervention were also included in the total costs, e.g., informal care provided by family or friends, productivity loss, the evaluation perspective will be classified as societal. Additionally, we will extract the intervention cost items if they were provided separately. We will not further assess the quality of the identified economic evaluations [45].

4. Dissemination, outputs and anticipated impact

Dissemination

We propose multiple strategies for dissemination with content adapted for the audience:

i) Policy makers, commissioners, managers, clinicians, patients and public

These are our most important groups to maximise impact of outputs. We have strong existing links with NHS England through Prof Martin Vernon (National Clinical Director for Frailty and Integration) and David Bramley (Deputy Head of Long-term Conditions Unit). Joint lead applicant Clegg also has strong links with NHS RightCare through his contribution to development of the NHS RightCare Frailty Pathway, working with Alex Thompson (Frailty Pathway Topic Lead). We will continue to work in partnership with NHS England and NHS RightCare to influence national policy on healthy ageing and management of frailty. We will build on existing links to disseminate findings through the FutureNHS Collaboration Frailty in Primary Care Network, CCGs, Local Authorities, Age UK and the British Geriatrics Society. We will build on our

existing links with NHS England and NHS RightCare to incorporate review findings into an updated National Toolkit, which will include guidance on how evidence-based services for older people should be designed and commissioned, including for people living with pre-frailty and frailty.

Joint lead applicant Clegg is a member of the NICE Multimorbidity Guideline Development Group and British Geriatrics Society & Royal College of General Practitioners Fit for Frailty Guideline. This will ensure that review findings can be widely disseminated to impact on planned updates of these national guidelines, and aligned publications including the British Geriatrics Society toolkit for primary care.

In addition, our dissemination strategy will include a social media communication plan. We will maintain a Twitter account and online blogs to provide project updates and a summary of the final results. We will work with our PPI representatives, to tailor findings to the needs of different stakeholders and disseminate them through a series of lay summaries, presentations at conferences, including at the national INVOLVE conference and our own annual conference, and academic peer reviewed papers.

ii) Researchers

We will disseminate the research findings via key scientific conferences (e.g. British Geriatrics Society; British Society of Gerontology; Royal College of General Practitioners Annual Conference; annual conference of the Society for Academic Primary Care). Talks, meetings and workshops will be organised as appropriate with involvement from local lay, clinical and professional groups. At the end of the project we will produce a final report and academic papers. In collaboration with our PPI representatives, we will develop a short summary of the results, which will be made available and distributed to wider stakeholder organisations.

Outputs

- Robust evidence on the effectiveness of community-based complex interventions to sustain independence for older people, stratified by frailty.
- Evidence on the most effective configuration of services, to inform planning and delivery of community-based services for older people, aligned with the NHS Long Term Plan.

Engagement of patients, NHS and the wider population

We have excellent existing links with older people living with frailty, carers, health and care planners, practitioners and policy makers. These include through the national frailty collaborative that has been established by joint lead applicant Clegg as part of the Yorkshire & Humber AHSN Improvement Academy Healthy Ageing theme. Members of the collaborative include GPs and other primary care practitioners, secondary care clinicians, CCG leads, local authority representatives, public health clinicians, lay members and voluntary sector staff. We have strong links with NHS England through our collaborative work to develop the infrastructure and supporting guidance for the 2017/18 GP contract to enable national frailty identification and management.

Entry of outputs into the health and social care system

We have an excellent track record of rapid translation of research outputs into clinical practice. For example, joint lead applicant Clegg led the development, validation and national implementation of the electronic frailty index (eFI), which has been made freely available to every general practice in England and around 95% of all UK practices. This work supported national policy change through the 2017/18 General Medical Services GP contract, and influenced the 2019 NHS Long Term Plan [2]. Additionally, Cochrane Reviews authored by joint lead applicant Crocker and co-applicant Forster [15,35] and co-

applicant Gladman [36] have been highly influential, informing the 2016 Royal College of Physicians National Stroke Guidelines [37].

Entry of research outputs into the health and social care system has been supported through the national frailty collaborative established by joint lead applicant Clegg. The collaborative has engaged with health and social care professionals, local authorities and 75 CCGs nationally to develop and implement new models of care for older people. This national engagement will facilitate outputs of our proposed systematic review and NMA into the UK health and social care system.

Further support required to maximise impact

Joint lead applicant Clegg is leading the NIHR CLAHRC Yorkshire & Humber Primary Care-based Management of Frailty theme and co-applicant Gladman is leading the NIHR CLAHRC East Midlands Caring for Older People and Stroke Survivors theme. This has included joint working to establish a national cross-CLAHRC ageing and frailty research collaborative, with national representation. We will use this cross-CLAHRC network, and additional implementation expertise within CLAHRC Yorkshire and Humber, to maximise impact of research outputs.

Possible barriers for adoption and implementation

We have considered and addressed the key barriers as a core component of our application. A key barrier to implementation of findings from previous evidence syntheses has been that previous reviews have not used NMA to summarise whether different types of interventions have differential effects on outcomes. This has limited usefulness for policymakers, health and social care commissioners and providers. A key objective for our review and NMA is to generate robust evidence on how interventions might best be configured to improve outcomes, maximising potential for widespread adoption and implementation. Furthermore, we plan to establish an Expert Reference Panel including policymakers, commissioners, practitioners, older people and carers as part of our Intervention Grouping process. This will ensure that the critical features of interventions to be included as NMA groupings/nodes will be closely aligned with future implementation. Our Expert Reference Panel will also help ensure that potential research beneficiaries understand the value of our research findings for improving care, supporting rapid translation of outputs into practice.

Immediate and longer-term impact

The clear focus on ageing well and frailty in the 2019 NHS Long Term Plan means that there will be immediate and longer-term interest in designing and commissioning evidence-based services based on the outputs of the review. The results of our proposed systematic review and NMA will therefore remain highly relevant and important to the needs of the NHS and social care in the future.

5. PROJECT TIMETABLE

-6-3m:	Run searches; screen records; obtain papers; assess eligibility.
3-20m:	Summarise studies; extract data; intervention grouping & frailty assessment.
20-24m:	Prepare data for analysis synthesise data in meta-analysis/network meta-analysis.
21-26m:	Write-up/dissemination.

6. PROJECT MANAGEMENT

We will establish a project management group (PMG), including the co-applicants and PPI representatives. The PMG will meet monthly across the duration of the project.

7. ETHICS

Formal ethics approval is not required for this systematic review and network meta-analysis.

8. PATIENT AND PUBLIC INVOLVEMENT

PPI in developing the proposal

We have established a PPI Frailty Oversight Group (FOG) as part of our NIHR Collaboration for Leadership in Applied Health Research and Care Yorkshire & Humber (NIHR CLAHRC YH) programme: Primary Care Management of Frailty in Older People. The FOG has a structure that provides connections to the whole spectrum of older people, with a focus on those living with frailty to enable meaningful, public involvement in our research projects.

The FOG comprises a core reference group of five key individuals (Marilyn Foster, Anne Grice, Christopher McDermott, Akhlaq Rauf, and David Walker), who also provide advocacy as lay representative older people on the Bradford Older People's Partnership, the Bradford Self-Care and Prevention Board, general practice Patient Participation Group and BME representation for the Local Authority. The FOG meets with joint lead applicant Clegg and our CLAHRC Project Manager on a quarterly basis to discuss ongoing and new research projects. Additional PPI engagement activity also takes place in the interim period between meetings. As experienced lay members who also provide representation on a range of local organisations and groups, FOG members can quickly and effectively connect the research team to other relevant organisations, groups and individuals depending on the specific needs of the study. Our work to develop the FOG as a novel model of PPI engagement has been recognised through publication in a peer-reviewed journal [38].

We have consulted our FOG throughout the development of this application, and discussed plans in detail at our quarterly meetings in December 2018 and April 2019. Specific examples of how our oversight group have influenced the application include:

- Emphasising the selection of a wide range of outcomes of importance for older people, with a key focus on independence and wellbeing, alongside service-orientated outcomes such as hospitalisation, length of stay and care home admission.
- Preparing the study plain English summary to ensure an easy to read overview.
- Proposing using the extensive community links of the FOG to help identify lay representatives for our planned intervention grouping Expert Reference Panel and Project Management Group (PMG).

PPI throughout the research project

We plan active patient and public involvement across the duration of the planned research project, including:

i) Research design and methods
We plan an intervention grouping Expert Reference Panel with PPI representation from older people and carers alongside policymakers, commissioners, practitioners, trialists and biostatisticians. The panel will convene to reach consensus on intervention types that are potentially useful service models. The intervention types will become the nodes in the network meta-analysis.

ii) Management of the research

We plan PPI representation on our planned Project Management Group (PMG), which will include all co-applicants and meet on a monthly basis across the duration of the project. This will ensure that we have active lay representation to help steer management of the research.

iii) Contributing to study reporting and dissemination
We have an excellent track record of PPI input into study reporting and dissemination of findings. This has included co-presentation of previous research findings at national conferences, and co-authorship of academic outputs. We will work closely with our Frailty Oversight Group (FOG) and PPI representatives to co-produce and co-present study outputs, including through a range of local and national lay publications.

iv) Training and support
We have developed and delivered a bespoke PPI training package as part of our NIHR CLAHRC programme, based on INVOLVE guidance. We will adapt this training programme and tailor to the individual needs of PPI members. We have included costs for PPI travel and attendance at Expert Reference Panel and PMG meetings, based on INVOLVE guidance.

9. PROJECT AND RESEARCH EXPERTISE

We have a research team with expertise spanning academic geriatric medicine, community services for older people, rehabilitation, Cochrane Reviews and network meta-analysis. We have excellent PPI representation through our Frailty Oversight Group and links with national policymakers, commissioners and practitioners are well established.

Andrew Clegg: Clinical Senior Lecturer and Honorary Consultant Geriatrician, Academic Unit of Elderly Care and Rehabilitation, University of Leeds, leading a large portfolio of internationally-recognised ageing and frailty research spanning intervention trials, observational research and big data, holding research grants totalling £13M. Expertise in systematic reviews and meta-analysis, including as Cochrane Review lead and co-author. Joint lead applicant with overall responsibility for research delivery and outputs.

Tom Crocker: Career Development Fellow, Academic Unit of Elderly Care & Rehabilitation, University of Leeds & Bradford Institute for Health Research, with applied qualitative and quantitative health services research methods and extensive expertise in systematic review and meta-analysis techniques, including leadership of Cochrane Reviews. Joint lead applicant with responsibility for management of the systematic review and meta-analysis, and research outputs.

Joie Ensor: Lecturer in biostatistics, Primary Care and Health Sciences, University of Keele, with expertise in meta-analysis techniques including network meta-analysis.

Anne Forster: Head of Academic Unit of Elderly Care & Rehabilitation, University of Leeds, NIHR Senior Investigator and academic physiotherapist with expertise in Cochrane Reviews and complex intervention trials.

John Gladman: Professor of the Medicine of Older People, University of Nottingham, with expertise in configuration and delivery of community services for older people, Cochrane Reviews, frailty and complex intervention trials, Nominal Group consensus methods.

Richard Riley: Professor of biostatistics, Primary Care and Health Sciences, University of Keele, with expertise in network meta-analysis and meta-regression.

10. Success criteria

We will measure success by delivery of our main aim, to synthesise evidence on the effectiveness of community-based complex interventions for older people, including the effect of frailty and pre-frailty, and group interventions to identify the best configuration types.

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APPENDIX 1. PROTOCOL AMENDMENT HISTORY

Protocol version no.	Date issued	Author(s) of changes	Details of changes made
2.0	22/5/2020	TC, AC, JG, Rri, JE, AF, NL, MJ, EP, Rra, RB.	Research questions reworded for consistency of language with the aim and title of the study. Eligibility criterion regarding focus on independence broadened to include interventions that focus on independence regardless of whether that is the main aim of the intervention. This change was because there often is no single main aim of an intervention (in contrast with a study), Clarified our definition of RCT/cRCT. Clarified that interventions mainly but not entirely delivered in the community are eligible. Revised our explanation of independence to specifically relate to independence in activities of daily living, as this is a well understood, individually meaningful aim, less interdependent on the wider healthcare context than other meanings, and therefore more generalisable across trials. Clarified that placebo includes attention control in our Comparators criterion. Other minor changes.

3.0	9/10/2020	TC, AC, JG, Rri, JE, AF, NL, MJ, EP, Rra, RB.	Change from one primary and eleven secondary outcomes to seven main and five additional outcomes (with the same overall set of outcomes), to assist with summarising the critical evidence in line with GRADE recommendations. The selection of main outcomes was based on feedback from PPI representatives. Change to the plans for intervention grouping. We have revised our plans to conduct the intervention grouping within the research team rather than using an expert reference panel as there is insufficient tacit expertise on how it is most appropriate to group these interventions for network meta-analysis and the volume of data that will be produced by our analysis would be inappropriate for consideration by an expert panel. The previously planned approach would probably result in ill-defined groupings and will be better based on careful consideration of the extracted descriptions of interventions. Having developed groupings, we will then seek to refine these on the basis of feedback in open discussions with experts to ensure their clarity and suitability. Rename outcome “Home care requirement” to “Home-care services (non-healthcare professional) usage”, to clarify kind of home care as well as its measurement by what is delivered rather than assessed need, as the former is what is commonly measured and was intended by us. Change 6 months minimum follow-up to 24 weeks (2 weeks earlier) to avoid excluding relevant studies. Remove “or led by” from the text about ineligible interventions to allow for university-led interventions or hospital-employed community-based staff. Correct error in the reference for cluster trial sources of bias from section 23.2 to 23.1.2 Add “each result of interest from” to risk of bias section as this is the process for the revised risk of bias tool. Additionally, change “outcome” to “result of interest” for clarity.

4.0	12/11/2021	AC, TC, JE, AF, JG, Rri, RB, MJ, NL	Label timepoint categories as short, medium and long term. Adjust definitions of timepoint categories slightly by reducing the lower bounds of the medium- and long-term categories, to put timepoints only slightly shorter than the target timepoints (12 and 24 months) in the same group as the target timepoints (e.g. 21 months is now grouped with 24 months not 12 months). Specify medium-term timepoint as primary timepoint for summary reporting due to multiplicity of outcomes and timepoints. We have based these changes on our knowledge of the reported timepoints, most of which are at the target timepoints. We have not examined the effect measures to inform these changes. Add detail to the approach for assessing frailty. Update project timetable and end date. Remove barriers to proposed work section as duplicating other sections and now outdated. Remove mention of Nominal Group methods from PPI section left over from changes made in version 3.0 of the protocol. Correct minor typo: delete duplicate “use the” from Intervention grouping section.
5.0	25/01/2022	AC, TC, JE, AF, JG, Rri, RB, NL	Add CINeMA to the approach to GRADEing the confidence in the cumulative evidence. This change will allow automatic consideration of the relevant concerns for continuous and dichotomous outcomes, accounting for the contributions of direct and indirect evidence, instead of judging these. This will increase transparency as well as reducing workload.

6.0	03/03/2022	AC, TC, JE, AF, JG, Rri, RB, NL	Add methods based on the Cochrane Handbook to summarise economic evidence. No methods were previously specified for handling economic evidence (though costs and cost-effectiveness were specified as outcomes of interest) and it is rarely appropriate to conduct meta-analysis of such outcomes [Shields, G.E., Elvidge, J. Challenges in synthesising cost-effectiveness estimates. Syst Rev 9, 289 (2020). https://doi.org/10.1186/s13643-020-01536-x]. Limit some outcomes and additional analyses to main timeframe (medium term) due to escalating number of analyses. Change 'timepoint' to 'timeframe' when referring to a category of timepoints. Update project timetable and end date.