1. Full title and details of project

Development and evaluation of the electronic frailty index+ (eFI+) tool: integrated prognostic-decision modelling to target interventions for older people with moderate or severe frailty

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Sponsor

University of Leeds

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Ethics information

The University of Leeds Ethics Committee have advised that as the study plans secondary analysis of routine data using datasets with existing ethics approvals and no access to personal data that separate Ethics Committee approvals are not required.

Protocol version	Date	Ethics approved version
1.0	24/01/2019	N
2.0	02/09/2019	N

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2. Summary of research

Research questions

i) How should eFI components be combined with additional routine primary care data to develop prognostic models for predicting key outcomes of requirement for home care, falls/fractures, nursing home admission and mortality in older people with moderate or severe frailty?

ii) Can model predictive performance be improved through addition of data from measures that are practical for primary care use, but not available in routine data?

iii) How should risk predictions from the prognostic models be translated into a decision analytic model (DAM) to guide clinical management?

iv) What is the potential cost-effectiveness of implementing interventions targeted at subgroups of older people with frailty in routine NHS care?

Background

Lead applicant Clegg led the eFI development, validation and national implementation. This has been translated into major NHS policy change through inclusion in the 2017/18 GP contract, which supports frailty stratification using the eFI, and NHS Long Term Plan.

Aim

To develop and evaluate the eFI+, a prognostic tool supplementing the original eFI including 4 integrated prognostic-decision models. The eFI+ will stratify older people with moderate or severe frailty into subgroups most likely to benefit from key interventions (community rehabilitation; falls prevention; comprehensive geriatric assessment; advance care planning).

Methods

Design

Prognostic model development, internal validation and external validation using large datasets (ResearchOne, SAIL databank, Leeds Data Model) and cohort study data (CARE75+), with linked DAM and health economic analysis.

Population

Patients ≥65 with moderate or severe frailty, defined by the existing eFI.

Key outcomes

12-month outcomes for prognostic models:

- New/increased home care package
- Emergency Department (ED) attendance/hospitalisation with fall/fracture
- Nursing home admission
- All-cause mortality

Statistical methods

i) Prognostic modelling

We will build 4 separate prognostic models for our 4 key outcomes by combining the eFI with additional individual-level routine data, informed by reviews to identify prognostic factors. Each model will be developed and internally validated in one large dataset, to adjust for potential overfitting, with subsequent external validation of predictive performance in a second large dataset.

Separately, we will use CARE75+ (n≈1,200) to investigate additional predictive value of clinical measures practical for primary care (e.g. gait speed, activities of daily living, loneliness).

ii) Decision analytic model (DAM)

We will translate the prognostic models into a framework to support clinical decision-making, in co-production with stakeholders/PPI. We will integrate prognostic models with effect size estimates from systematic reviews/meta-analyses to identify relevant thresholds of predicted risk, above which implementation of our key interventions would be warranted.

iii) Health economic evaluation

12-month and long-term cost effectiveness models will be developed, informed by the DAM.

Timelines

-6m-0m: Obtain datasets
1-5m: Data preparation, imputation
6-23m: Prognostic model development, internal validation, external validation; economic model development
24-29m: DAM development; examination of net-benefit/cost-effectiveness
30-32m: Write-up/dissemination

Impact

Potential for major impact, building on our track record of eFI national implementation and NHS policy impact.

3. 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 (1). Frailty is an especially problematic expression of population ageing. It is a condition characterised by loss of biological reserves and vulnerability to adverse outcomes, including loss of independence, falls, care home admission and mortality (2). These outcomes have considerable impact on quality of life of older people, their carers, the NHS and social care.

Around 10% of people aged 65 and over have frailty, rising to around 50% of people aged over 85 (3). Around 90% of older people living with frailty experience mobility problems, and over 50% have difficulties with washing, dressing or housework (4). Estimates indicate annual NHS and social care costs for an older person with severe frailty are £6,955, compared with £1,237 for a fit older person (5). Total annual NHS and social care spending on frailty is estimated at £15 billion

(5). UK and international guidelines support routine frailty identification in primary care to allow timely and targeted proactive care (6-8).

To enable routine frailty identification, lead applicant Clegg led the development, validation and national implementation of the electronic frailty index (eFI) using routine primary care electronic health record (EHR) data (9). The eFI incorporates 36 deficits (clinical signs, symptoms, diseases, disabilities, impairments), constructed using around 2,000 primary care Read codes. An eFI score is calculated by the presence or absence of each individual deficit as an equally weighted proportion of the total possible, and can be used to identify frailty categories (not frail, mild frailty, moderate frailty, severe frailty), which predict risk of nursing home admission, hospitalisation and mortality. The eFI is supported in the 2016 NICE multimorbidity guideline and 2014 British Geriatrics Society & Royal College of General Practitioners Fit for Frailty Guideline (6, 7).

This work supported major NHS policy change, through the 2017/18 GP contract, which includes identification and management of people living with moderate and severe frailty as a key requirement for general practice based primary care. The 2017/18 GP contract supports population-level frailty stratification using the eFI (10). The success of the eFI national implementation and adoption has influenced the recently published NHS Long Term Plan (11). The Plan specifies supporting people to age well as a key objective, with a greater focus on proactive care based on population health management, including use of the eFI.

However, the eFI has some limitations, including equal weighting of deficits, and cumulative adding of deficits that are assumed not to improve or resolve. Additionally, the original validation did not investigate key outcomes, such as loss of independence or falls, and established prognostic factors for these outcomes are not necessarily included in the eFI. For example, 19 potentially relevant deficit variables (e.g. back pain, mood problems, self-care problems) were also identified but not included in the eFI, either because prevalence did not increase from age 65 to 95, or overall population prevalence was low. Furthermore, whilst the use of routine data to generate an eFI score is a major strength, measures of mobility (e.g. gait speed, timed-up-and-go test) functional impairments (e.g. activities of daily living) and social concerns (e.g. loneliness) that may improve eFI predictive performance are less likely to be completed routinely in primary care.

3a. Evidence explaining why the research is needed now

The commissioning brief for this call specifies research to develop a tool based on the eFI components that can identify subgroups of older people most likely to benefit from a range of interventions aimed at improving their independence. The brief specified that the new tool may be supplemented by other routinely available data, or simple clinical measures practical for use in primary care.

We propose to develop the eFI+, which will include four integrated prognostic-decision models to identify subgroups of older people living with moderate or severe frailty who are most likely to benefit from four evidence-based interventions. The prognostic modelling will include supplementing the eFI with established risk factors for key outcomes (new/increased requirement for home care; ED attendance/hospitalisation with fall or fracture; nursing home admission; all-cause mortality) and exploring how addition of clinical measures practical for use in primary care

improves model performance.

Our selection of interventions is aligned with the brief, informed by the evidence review and additional systematic review/meta-analysis data. The evidence supporting our four selected interventions is outlined below:

i. Community-based rehabilitation
Evidence indicates that community-based exercise interventions (12, 13) and community-based occupational therapy (14) alone or in combination (15) improve independence for older people living with frailty, although those with severe frailty and dementia may not benefit (16).

ii. Falls prevention
Network meta-analysis indicates multicomponent falls prevention interventions reduce injurious falls and fall-related hospitalisation (17). Various intervention packages (e.g. combined strength and balance training with vision assessment and treatment; multifactorial assessment and treatment with calcium/vitamin D supplementation) may have differential effects, which will be incorporated into our decision model.

iii. Comprehensive geriatric assessment (CGA)
CGA is a multidisciplinary approach to identify medical, functional, social and psychological needs to develop a shared plan for treatment and follow-up. CGA is supported in national frailty guidelines (7) and may reduce care home admission and mortality (6, 18, 19).

iv. Advance care planning (ACP)
A 2016 systematic review of ACP for older people in the terminal stage of life reported improved quality of care and reduced healthcare use (20).

We considered additional interventions, including evidence from a 2018 systematic review and meta-analysis on interventions for older people with functional impairments and mental health problems, co-authored by co-applicant Walters (21), and de-prescribing. However, the evidence base in the context of frailty was too limited to support prognostic modelling and decision analysis for those with moderate to severe frailty.

4. Aim, research questions and objectives

Aim

To develop and evaluate the eFI+, a prognostic tool supplementing the original eFI including 4 integrated prognostic-decision models. The eFI+ will stratify older people with moderate or severe frailty into subgroups most likely to benefit from key interventions (community rehabilitation; falls prevention; comprehensive geriatric assessment; advance care planning).

Research questions

i) How should eFI components be combined with additional routine primary care data to develop prognostic models for predicting key outcomes of requirement for home care, falls/fractures, nursing home admission and mortality in older people with moderate or severe frailty?

ii) Can model predictive performance be improved through addition of data from measures that are practical for primary care use, but not available in routine data?

iii) How should risk predictions from the prognostic models be translated into a decision analytic model (DAM) to guide clinical management?

iv) What is the potential cost-effectiveness of implementing interventions targeted at subgroups of older people with frailty in routine NHS care?

Objectives

i) To develop and externally validate the eFI+ in terms of predictive performance for key outcomes (requirement for home care, falls/fractures, nursing home admission and all-cause mortality) using routinely available data in three large databases (Secure Anonymised Information Linkage (SAIL) databank; ResearchOne; Leeds Data Model (LDM)).

ii) To use existing data from the Community Ageing Research 75+ (CARE75+) national cohort study (n≈1,200) to investigate how simple clinical measures practical for use in primary care settings, but not currently routinely completed, might improve the predictive performance of the eFI.

iii) To generate four integrated prognostic-decision models, by linking thresholds of predicted risk from the prognostic models to the four selected interventions. This will be done by translating treatment benefit to absolute risk by combining the risk predictions from the models with intervention effect size estimates reported in systematic review/meta-analysis data. We will then examine the net benefit of this DAM compared to other strategies using a co-production approach in partnership with stakeholders and PPI representatives.

iv) To investigate cost-effectiveness of key interventions and prioritise interventions based on overall cost-effectiveness and service delivery.

5. Research plan/methods

Health technologies being assessed

The eFI+ will be developed using components of the original eFI, supplemented with additional routine primary care EHR data, and guidance on the added benefits of implementing simple clinical measures in routine primary care practice. The eFI+ will be suitable for rapid implementation in UK primary care EHR systems, building on existing close links with system suppliers (SystmOne/EMISWeb/Vision/Microtest).

We will develop, then internally and externally validate the eFI+ using the Secure Anonymised Information Linkage (SAIL) databank, the ResearchOne database, and the Leeds Data Model (LDM). These datasets enable investigation of home care packages and nursing home admission as key outcomes for prognostic modelling, and indicators of loss of independence in frailty, which is not possible using other national primary care datasets (CPRD, THIN or QResearch).

In addition, we will analyse Community Ageing Research 75+ (CARE75+) cohort study data (CI Clegg, n≈1,200) as the only national cohort study to include eFI scores (22), to investigate how

simple measures that can be assessed in primary care, but are not available in routine EHR data (e.g. gait speed, timed-up-and-go test; activities of daily living; loneliness) may improve prediction.

Study design

Prognostic model development, internal validation and external validation using routine primary care research data (ResearchOne), linked datasets (SAIL databank and LDM) and cohort study data (CARE75+), with integrated Decision Analytic Modelling, including health economic analysis. Co-applicants Riley and van der Windt are founders/members of the Prognosis Research Strategy (PROGRESS) partnership. The prognosis research framework developed by PROGRESS informs the design and analysis methods of our study (23, 24).

Data sources

We plan to use four data sources, outlined in Table 1 for clarity. Professor Ronan Lyons and Ashley Akbari (SAIL co-director/Senior Analyst), Dr Chris Bates (ResearchOne lead data scientist) and Frank Wood (LDM lead) are collaborators, and have confirmed access to data and feasibility of plans. Dr Andrew Clegg (lead applicant) is the CI of CARE75+.

Table 1. Databases to be used for prognostic modelling, including key outcomes included in database and access.

Database	**Description**	**Outcomes**	**Access**
Secure Anonymised Information Linkage (SAIL) databank	Anonymised records from around 5 million people in Wales, with linked primary care, ED attendance, hospital admissions, outpatient data, social care, Welsh Care Homes Dataset, and ONS mortality data. SAIL includes eFI summary scores and individual components.	•New/increased home care package •ED attendance/ hospitalisation with fall/fracture •Nursing home admission •All-cause mortality	Host: SAIL databank Analysis: Remote secure access
ResearchOne	Nationally representative, de-identified data from around 6 million primary care electronic health records on the TPP SystmOne clinical system. ResearchOne includes eFI summary scores and individual components.	•Nursing home admission •All-cause mortality	Host: The Phoenix Partnership (TPP) Analysis: Secure research environment, Leeds Institute of Data Analytics, University of Leeds
Leeds Data Model (LDM)	Anonymised, linked primary, secondary, community and social care data from 810,000 patients across 108 practices in Leeds, including eFI summary scores and individual	•New/increased home care package •ED attendance/ hospitalisation with	Host: Data Services for Commissioners Regional Office (DSCRO) Analysis: Secure

	components.	fall/fracture	research environment, Leeds Institute of Data Analytics, University of Leeds
Community Ageing Research 75+ (CARE75+) cohort	National prospective cohort study (n≈1,200) collecting detailed sociodemographic information, frailty measures (including eFI scores), simple instruments suitable for use in primary care (e.g. gait speed, timed-up-and-go test; activities of daily living; informal care; loneliness), and key outcomes at six, 12, 24 and 48 months. CARE75+ is a very rich dataset that provides a highly efficient method to investigate how simple instruments might augment eFI performance.	• Activities of daily living • Mobility • Health-related quality of life • New/increased home care package • Informal care • Falls • Hospitalisation • Nursing home admission • All-cause mortality	Host: Bradford Teaching Hospitals NHS Foundation Trust Analysis: Secure research environment, Leeds Institute of Data Analytics, University of Leeds

Eligible population

Patients ≥65 years with moderate frailty (eFI score 0.24 to 0.36) or severe frailty (eFI score >0.36) and registered with a ResearchOne, SAIL or LDM practice on 1st April 2018. Lookback period will include the complete primary care EHR to first registration, and linked data (SAIL and LDM). Outcomes will be assessed over a 12-month period to 31st March 2019.

All CARE75+ participants with moderate frailty (eFI score 0.24 to 0.36) or severe frailty (eFI score >0.36) will be eligible.

Key outcomes for risk prediction

Outcomes for risk prediction (all 12 months)

- New or increased home care package
- ED attendance/hospitalisation with fall or fracture
- Nursing home admission
- All-cause mortality

Predictors

Components of the eFI, supplemented with variables available within routine primary care EHR data and clinical assessment measures practical for use in primary care.

Selection of additional variables available within routine EHR data and clinical assessment measures practical for use in primary care will be informed by an ongoing systematic review of prognostic factors in older people with frailty, led by co-applicants van der Windt and Riley, funded by the NIHR School for Primary Care Research Evidence Synthesis Working Group (25).

Systematic review findings will be supplemented with additional targeted scoping reviews of the literature to identify additional prognostic factors.

We will establish an Expert Reference Panel (ERP) including representation from older people, GPs, practice nurses, primary care EHR IT experts and commissioners to review candidate additional predictors. Results from the ongoing systematic review and scoping reviews will be presented to the ERP to guide selection of additional predictors that are feasible for implementing into routine primary care EHR systems as part of the eFI+. The ERP will also ensure that any additional clinical assessment measures that are not available in routine data would be practical as part of routine primary care practice and acceptable to older people living with moderate or severe frailty. The panel will also provide clinical steering on how time-variability of eFI deficits should be incorporated into the modelling.

Prognostic models

Each prognostic model will be developed and internally validated in just one of the databases, and then externally validated in a second database (see flowchart, supplementary document upload):

Model 1: Predicting new/increased home care package

Development/internal validation database: SAIL

SAIL includes linked social care data to enable modelling of new/increased home care packages at 12 months.

External validation database: LDM

LDM includes linked social care data to enable modelling of new/increased home care packages at 12 months.

Model 2: Predicting ED attendance/hospitalisation with fall/fracture

Development/internal validation database: SAIL

SAIL includes existing linkage to the Emergency Department Dataset (EDDS) and Patient Episode Database for Wales (PEDW), enabling modelling of ED attendance/hospitalisation with fall/fracture at 12 months.

External validation database: LDM

LDM includes linked secondary care data to enable modelling of ED attendance/hospitalisation with fall/fracture at 12 months.

Model 3: Predicting nursing home admission

Development/internal validation database: ResearchOne

ResearchOne includes nursing home residence as a routine variable, based on the Care Quality Commission list of registered UK nursing homes, enabling modelling of this outcome at 12 months.

External validation database: SAIL

SAIL has existing linkage to the Welsh Care Homes Dataset, enabling reliable identification of new nursing home admission at 12 months.

Model 4: Predicting all-cause mortality
Development/internal validation database: ResearchOne
All-cause mortality will be identified by date of death, which is reliably recorded in ResearchOne, enabling modelling of this key outcome at 12 months.

External validation database: SAIL
SAIL has existing linkage to the ONS mortality dataset, enabling identification of date of death.

Sample size for prognostic model development
SAIL and ResearchOne extracts will each include ≈600,000 patients aged 65 or over, with an estimated 72,000 having moderate frailty, and 24,000 severe frailty. LDM extract will include ≈150,000 patients aged 65 or over, with an estimated 18,000 having moderate frailty and 6,000 severe frailty.

For model development, a key indicator of the effective sample size is the number of outcome events. Previous research into the outcomes of interest, and feasibility estimates using CARE75+, ResearchOne and SAIL, inform estimates for anticipated number of events within 12 months.

- New or increased home care package: Anticipated 15,864 events in SAIL, based on 14.9% 12 month incidence in moderate frailty group (10,080 events), and 24.1% 12 month incidence in severe frailty group (5,784 events).
- ED attendance/hospitalisation with fall or fracture: Anticipated 8,064 events in SAIL, based on 7.4% 12 month incidence in moderate frailty group (5,328 events) and 11.4% incidence in severe frailty (2,736 events).
- Nursing home admission: Anticipated 2,160 events in ResearchOne, based on 2.0% 12 month incidence in moderate frailty group (1,440 events) and 3.8% 12 month incidence in severe frailty group (720 events) (9).
- All-cause mortality: Anticipated 12,216 events in ResearchOne, based on 10.6% 12 month incidence in moderate frailty group (7,632 events) and 19.1% 12 month incidence severe frailty group (4,584 events) (9).

Therefore, even when taking the lowest estimate of incident events by 12 months (for nursing home admission), for each outcome we would expect at least 2,160 events in each of ResearchOne or SAIL. This enables us to robustly estimate a prognostic model for each outcome even with up to 108 predictor parameters, corresponding to 20 events per potential predictor parameter (2160/20). This exceeds ‘rule-of-thumb’ recommendations of 10 or 15 events per predictor parameter (26).

Furthermore, conservatively assuming the new models will have a Nagelkerke R-squared of 15%, Riley’s sample size formula suggests that at least 7.5 events for each predictor parameter will ensure overfitting and optimism are minimized (27), when the outcome proportion is 3%. When increasing outcome proportion to 20% (home care package), 9% (fall/fracture), or 15% (mortality), the minimum sample size required is 18, 11.5 and 15 events per predictor parameter, respectively. We exceed all these, due to the large datasets available.

Further, we are likely to have fewer than 108 potential coefficients, as there are only 36 deficits

within the existing eFI model, plus an additional 19 further candidate deficits from the original eFI development, plus additional established risk factors for outcomes identified from the planned reviews along with demographic information (sex, age, deprivation). Thus, the sample size is sufficient to estimate all these predictor parameters, whilst also allowing potentially nonlinearity for continuous predictors and clinically plausible interactions.

Sample size for external validation

Current recommendations are that at least 100 events and 100 non-events (ideally 200) are required for prognostic model external validation (28, 29). Our estimates indicate considerably more than this, such as 2160 events for the least prevalent outcome of care home admission in SAIL and ResearchOne, and 540 in LDM (which will only be used for external validation of models).

Missing data

Handled using multiple imputation and Rubin's rules, under a missing at random assumption, including outcome in the imputation model (30, 31), accounting for practice clustering.

Analysis plan

i) Prognostic modelling

We will build 4 separate prognostic models within the development datasets to predict risk of our 4 key stated outcomes in individuals with moderate or severe frailty as the startpoint.

For each outcome, for those with moderate frailty (eFI score 0.24 to 0.36) or severe frailty (eFI score >0.36) we will develop and internally validate a prognostic model containing just eFI (as a whole as it currently stands) and then containing components of eFI (included as predictors) along with additional routine primary care EHR data following systematic/scoping reviews and Expert Reference Panel assessment. The regression model will be logistic regression or flexible parametric survival (32, 33), for binary or time-to-event outcomes (as appropriate when we observe the database coding and censoring etc.), to produce outcome risks by 12 months. Where necessary, outcomes affected by competing events (e.g. mortality) will be accounted for using a competing events models, within the flexible parametric framework. Practice-level effects influencing patient outcomes will be captured using random effects. Where sufficient information is provided, we will also extend the models to consider longer-term outcomes, such as nursing home admission or overall mortality risk by 5 years, to facilitate the subsequent economic modelling of longer term impact.

Due to the large sample size, overfitting is expected to be small, but we will adjust for it using penalisation via a global shrinkage factor estimated via bootstrapping. Where variable selection is considered important for parsimony, we will rather use penalisation via elastic net. Internal validation will use bootstrapping of the entire development dataset, and optimism-adjusted estimates of predictive performance produced for calibration (e.g. calibration-in-the-large, calibration slope, Observed/Expected), discrimination (e.g. C-statistic) and overall (e.g. Nagelkerke R^2) performance of predicted risks. Continuous variables will not be categorised and potential non-linear effects examined using splines or fractional polynomials. Non-proportional hazards for predictors will also be examined with interaction terms with time. We will then examine how the eFI might be improved by incorporating additional predictors available from routine primary care EHR

data into the model, based on improvement in model fit and predictive performance. Given potential for heterogeneity, we will explore use of latent class models, which can help identify relevant subgroups and may enable the design of targeted regression models that rank by need.

All models will be externally validated in a different database. Predictive performance statistics will be derived as described above (e.g. C-statistic, calibration slope), alongside calibration plots showing agreement between observed and predicted risks, across the spectrum of predicted risks, using a loess non-parameter smoother. To further validate our models, we will evaluate consistency in predictive performance across different geographical areas and general practices, using individual participant data meta-analysis and cross-validation techniques (34). Where necessary, recalibration approaches will be considered to improve predictive performance in particular regions.

Separately, we will use the CARE75+ dataset to investigate the additional predictive power of clinical assessment measures of prognostic factors identified from the reviews that are practical for use in routine primary care (e.g. gait speed, timed-up-and-go test, activities of daily living, social isolation/loneliness). Key outcomes of new/increased home care package, self-reported falls, nursing home admission and all-cause mortality will be investigated. Other outcomes sensitive to improvement of independence among older people with moderate and severe frailty will be also assessed. These include activities of daily living, measured using the Nottingham Extended Activities of Daily Living (NEADL), and mobility. Stata and R will be used for all analyses, and the TRIPOD reporting guidelines adhered to when writing up (35).

ii) Decision modelling

Prognostic models will be translated into a framework to guide clinical decision making by identifying relevant thresholds of predicted risk, above which implementation of our stated interventions is warranted. Our approach will be based on extracting intervention effect size estimates from available systematic review/meta-analysis evidence, combined with predicted risks from the models. That is, assuming intervention effects are constant across all individuals on the relative scale (which is typically a reasonable viewpoint (36)), we will identify which individuals stand to benefit most (in terms of absolute risk reduction) from the intervention conditional on their predicted risk from the model.

Our Expert Reference Panel (ERP) including older people, GPs, practice nurses, primary care EHR IT experts and commissioners will help guide translation of prognostic models, ensuring that routine service delivery is prioritised. This will allow us to generate a decision analytic model (DAM), which will be examined using decision curves and net benefit in the external validation datasets (37). This will allow a comparison of overall benefit versus harms, against other strategies such as ‘treat all’ and ‘treat none’. Sensitivity analysis will be undertaken for a range of possible scenarios, including relaxing the assumption of a constant relative intervention effect. The DAM will inform the proposed economic evaluation.

iii) Health economic evaluation

The health economic evaluation will be conducted in two stages. Both stages will involve ongoing input from our Expert Reference Panel to ensure that there is relevant clinical, commissioner and

PPI input into the economic evaluation. The objective of the first stage is to provide a short-term, 12-month comparison of the cost-effectiveness of the scenarios identified by the DAM. For the second stage, we will extend our analysis to a long-term cost-effectiveness evaluation of these scenarios. Plans will build on ongoing health economic modelling work, using ResearchOne and CARE75+ data led by co-applicants Hulme and Nikolova as part of an NIHR Programme Grant, for which lead applicant Clegg is CI (NIHR RP-PG-0216-20003).

We will use an individual-based state-transition model. In each 12-month period an individual can be in one of three states: living at home, in a care home, or dead. Living at home is our primary outcome for being independent and is defined as not being in a care home or dead. Conditional probabilities for care home admission and death will be taken from the prognostic models. Care home admission and death are absorbing states. Care home average costs and quality of life will be extracted from published sources. Falls and increased home care packages are assumed to modify only the transition probabilities between states. Expected costs of falls and increased home care packages, conditional on interventions, will be computed using estimates from the prognostic models.

Stage 1: Short-term economic evaluation
We will estimate expected costs and benefits for each scenario at individual level over the period of 12 months and then compute population averages to compare different scenarios.

The benefit measure used in the economic evaluation will be quality-adjusted life years (QALYs), using utilities taken from the Euroqol 5-dimension health questionnaire, 5-level version (EQ5D-5L) (38). EQ5D-5L scores will be frailty-specific utilities obtained from CARE75+ data, which collects quality of life measures for older people with frailty at the individual level at baseline, six, 12, 24 and 48 months. The impact of our four key outcomes will be accounted for by applying a utility decrement, estimated within a regression framework using CARE75+ data, along with previously published estimates. Interventions are assumed to impact only probabilities of changing states, not Quality Adjusted Life Years (QALYs). We will check robustness using estimates for QALY change due to identified interventions, taken from available systematic reviews/meta-analyses. A secondary analysis will use utilities derived from the short-form 6-dimension health questionnaire (SF-6D) (39), which is also collected in the CARE75+ study.

Determinants of costs are: 1) implementation costs of the interventions, 2) administrative costs of the interventions, 3) healthcare costs (excluding costs of falling), 4) home care package costs, 5) nursing home costs, 6) falls, and 7) informal care.

All costs will be estimated on an annual basis. Resource use will be derived from ResearchOne, SAIL, LDM and CARE75+ and unit costs obtained from national databases (e.g. NHS Reference Costs (40), PSSRU (41), British National Formulary (42)). Informal care costs will be obtained from CARE75+ data. We will address parameter uncertainty using probabilistic sensitivity analysis and will present results as incremental cost effectiveness ratios (ICERs), expected net benefits and cost effectiveness acceptability curves.

Stage 2: Long-term economic model

The long-term model is an extension of the short-term model. We will extend our one-year analysis to 50 annual cycles. In our long-term model we assume that all changes in health status due to falls/fractures and related ED attendances/hospitalisations are adequately reflected by changes in frailty on a yearly basis, and do not need to be added as separate variables in the conditional probability estimation.

Time-varying transition probabilities will be obtained from the prognostic models to account for the change in age and frailty with time (43). Evolution of frailty will be constructed as a set of outcomes for changes in frailty score with corresponding probabilities obtained from the data, adjusted for age, frailty, gender and deprivation. We will use the frailty evolution model of Mitnitski et al (44) and extend it by adjusting for the number of falls/fractures over the period of a year, gender and deprivation. Given the frailty model estimates, we will construct different frailty trajectories with and without intervention. Based on these trajectories, we will construct a sequence of transitional probabilities with associated utilities/costs for these outcomes. Calculation of costs and QALYs will be aligned with Stage 1. We will perform sensitivity analysis regarding administrative costs of the interventions as a fraction of initial cost. Costs and outcomes will be discounted at 3.5% per annum as per NICE recommendations. Extrapolation will use the NICE Methods Guide and ISPOR Task Force on Cost Effectiveness Modelling (45).

Project oversight

We plan a Project Steering Group (PSG) including PPI representatives, primary care clinicians, commissioners, geriatricians, social care staff, therapists, Age UK, NHS England, and Electronic Health Record programming experts. Led by Prof John Gladman, the group will meet six monthly, with a focus on project progress and delivery against agreed timelines.

6. Dissemination, outputs and anticipated impact

Dissemination

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). 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 frailty policy. 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 study findings into an updated National Frailty Toolkit, which will include guidance on operational implementation of the eFI+, and National Frailty Pathway.

Lead applicant Clegg is a member of the NICE Multimorbidity Guideline Development Group and British Geriatrics & Royal College of General Practitioners Fit for Frailty Guideline. This will ensure that study 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 purposely designed project website and social media communication plan. The website will include an overview of the project, working papers on the substantive and methodological aspects, and a discussion board. 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 academic peer reviewed papers.

ii) Researchers
We will disseminate the research findings via key national (e.g. British Geriatrics Society; Royal College of General Practitioners Annual Conference; annual conference of the Society for Academic Primary Care) and international conferences (e.g. International Association of Geriatrics and Gerontology). 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

- The eFI+, a novel tool incorporating four integrated prognostic-decision models to identify and stratify older people with moderate or severe frailty who are most likely to benefit from key interventions.
- Guidance for GPs and other primary care practitioners for making informed decisions regarding optimal intervention for high risk subgroups of people with moderate or severe frailty.
- Guidance for evidence-based commissioning of interventions for older people living with moderate or severe frailty.

Engagement of patients, NHS, social care 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 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 health and care system
We have an excellent track record of rapid translation of research outputs into clinical practice. This is exemplified through our previous national implementation project to make the eFI available to every general practice in England, and 95% of all UK general practices, at no additional cost. Following national implementation of the eFI, NHS England data indicate over 2.5M older people have been assessed for frailty, and around 1M have been identified as living with moderate or severe frailty.

Through our national implementation project, we have built strong and enduring links with the four providers of UK primary care electronic health record systems (SystmOne, EMISWeb, Vision, Microtest). These existing links mean that we are extremely well positioned for rapid implementation of the eFI+ into the health and care system. We will work closely with our EHR provider partners to incorporate the eFI+ into GP templates and decision-making tools, ensuring that the entry of the eFI+ into clinical practice facilitates efficient care processes, relieving pressure on primary care at a time when resources are stretched. We plan to implement the eFI+ on the same terms of the existing eFI license agreement, ensuring availability at no additional NHS cost.

Further support to maximise impact

Lead applicant Clegg is leading the NIHR CLAHRC Yorkshire & Humber Primary Care-based Management of Frailty theme. This has included establishment of a cross-CLAHRC frailty 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.

Co-applicants Riley and van der Windt are founders and key investigators in the Prognosis Research Strategy (PROGRESS) partnership. This is an MRC funded, international, interdisciplinary collaboration developing understanding in research into prognostic factors, risk prediction models, and predictors of differential treatment response. We will use the support developed through our strong links to the PROGRESS partnership to maximise impact of study outputs, including international dissemination of novel methods and findings.

Possible barriers for adoption and implementation

We have considered and addressed the key potential barriers for adoption and implementation. A key potential barrier to adoption and implementation in primary care is failure to ensure that the eFI+ helps guide primary care decision-making in partnership with older people living with frailty. We have included strong primary care clinician, commissioner and PPI representation across our project. This includes in our Expert Reference Panel (ERP), who will help guide selection of additional variables for inclusion in the eFI+ and additional measures that are both practical for use in primary care and acceptable to older people. Our ERP will also co-produce the decision analytic model in preparation for health economic evaluation. This will help ensure that wider primary care providers and commissioners are able to better grasp the potential value and importance of the eFI+. Strong stakeholder representation will also ensure that key individuals are able to drive eFI+ national adoption and implementation. We plan to co-produce relevant supporting eFI+ guidance materials with NHS England and NHS RightCare, ensuring that end users are able to operationalise the tool in routine clinical practice.

A critical potential barrier to implementation is failure to consider the requirements of primary care electronic health record providers at all stages of project development. The existing strong links with providers of primary care EHR systems, and plans for representation on the Project Steering Group across the duration of the project means that we are extremely well positioned to address this critical potential barrier.

Immediate and longer term impact
We anticipate major potential for immediate and longer-term impact, in line with the major national impact achieved through our previous national eFI implementation.

The 2019 NHS Long Term Plan includes supporting people to age well as a key objective, with a greater focus on proactive care based on population health management for people living with frailty. The contemporary national health and care focus on frailty, including in the Long Term Plan, means that there will be sustained interest in identifying and commissioning evidence-based frailty services. This means that the eFI+ has potential to achieve major, sustained impact, as it will guide robust commissioning of evidence-based interventions for older people living with moderate and severe frailty, including cost-effectiveness.

Our links with the four leading providers of primary care EHR systems, and existing license agreement with these partners, means that we will be able to rapidly implement the eFI+ into primary care EHR systems, at no additional cost to the end NHS user, with immediate impact.

7. Project timetable
-6m-0m: Obtain datasets
1-5m: Data preparation, imputation
6-23m: Prognostic model development, internal validation, external validation; economic model development
24-29m: DAM development; examination of net-benefit/cost-effectiveness
30-32m: Write-up/dissemination

8. Project management
The co-applicants will form the project management group (PMG), under the chairmanship of the lead applicant. Our PPI co-applicant, Willi Riha, will provide lay representation on the PMG, so that management of our planned study can be informed by personal insight and experiences. The PMG will meet on a monthly basis across the duration of the research project.

Project oversight will be provided by our planned project steering group (PSG) meeting every six months including PPI representatives, GPs and other primary care practitioners, commissioners, geriatricians, social care staff, therapists, Age UK, NHS England, and Electronic Health Record programming experts. Financial management will be undertaken through our well-established systems at the University of Leeds. Dr Clegg will be the signatory for financial matters and will meet at least quarterly with the designated finance officer.

9. Ethics
We have considered relevant ethical, governance, data access and data security as a key component of application development. Professor Ronan Lyons and Ashley Akbari (SAIL co-director/Senior Analyst), Dr Chris Bates (ResearchOne lead data scientist) and Frank Wood (LDM lead) are named collaborators, and have confirmed access to data and feasibility of plans. Dr Andrew Clegg (lead applicant) is CARE75+ CI.

For SAIL data, we will submit an application for internal review by the SAIL team, prior to external review by the Information Governance Review Panel (IGRP). Once approval is in place, remote access to SAIL data will granted to named Keele University researchers via a Virtual Private Network (VPN) for data analysis.

For ResearchOne data, we will submit a ResearchOne data request form, which will be considered by the ResearchOne Ethics Board. For LDM data, will submit a detailed data application to DSCRO. For CARE75+, we will submit a data request to the CARE75+ Data Review Committee (DRC), which includes both academic and PPI input. Once relevant approvals are in place for ResearchOne, LDM and CARE75+, bespoke data extracts will be transferred and stored separately within the highly secure research environment of the MRC Medical Bioinformatics Unit, Leeds Institute for Data Analytics, University of Leeds using well-established procedures, for analysis by the University of Leeds team.

10. Patient and public involvement and engagement

PPIE involvement 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 (CLAHRC) programme: Primary Care Management of Frailty in Older People. The FOG has a structure that provides connections to the whole spectrum of older people living with frailty and their carers to enable meaningful, public involvement and engagement in our frailty 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 meet with lead applicant Clegg and our CLAHRC Project Manager on a quarterly basis to discuss ongoing and new research projects. Additional PPI engagement activity takes place in the interim period between meetings. As experienced lay members who also provide representation on a range of local organisations and groups, the FOG are able to network the research team quickly and effectively 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 (46).

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

- Emphasising the selection of a wide range of interventions and outcomes spanning health and social care, with a key focus on independence for people living with moderate and severe frailty.
- Identifying that simple instruments practical for use in primary care must be practical for older people living with moderate and severe frailty to complete, in addition to being feasible for use in primary care settings.
- Preparing the study plain English summary to ensure an easy to read overview.

- Using community links to help identify our named PPI co-applicant, Willi Riha, as an older person who has recent and relevant experience with NHS care following a fall and fractured ankle. Mr Riha has a background in computer science, as a retired lecturer at the University of Leeds, so is well positioned to make a valuable contribution to an analytically complex research project.

PPI involvement throughout the research project

i) Research design and methods

Our PPI co-applicant, Willi Riha, will be a core member of the Project Management Group (PMG), which will include all co-applicants and meet on a monthly basis across the duration of the research project. This will ensure that we have active lay representation throughout the project, supporting PPI input into ongoing research plans.

We plan an Expert Reference Panel (ERP) with lay member representation alongside clinician and commissioner representatives. The ERP will review additional variables for inclusion in our prognostic models, and additional measures that are potentially suitable for primary care completion. This will help ensure that any additional measures are acceptable to older people living with frailty, as well as feasible as part of routine primary care practice. The ERP will also co-produce our planned decision analytic model, to ensure that it will inform better targeting of interventions from the perspective of older people living with frailty as well as from a clinical and commissioning perspective.

ii) Management of the research

In addition to PPI representation on our PMG and Expert Reference Panel (ERP), we will establish a Project Steering Group (PSG) including lay members and Age UK representatives alongside a range of clinicians, commissioners, and primary care electronic health record system representatives. The inclusion of lay members and voluntary sector representatives will ensure appropriate research management from the perspectives of older people living with frailty and carers alongside the service delivery, commissioning and policy perspective.

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 PPI partners and Age UK, with whom we have a longstanding history of successful partnership working, 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 package and tailor to the individual needs of PPI members. We have included costs for PPI travel and attendance at PMG, ERP and PSG meetings, based on INVOLVE guidance.

11. Project and research expertise

We have a research team with expertise spanning clinical academic geriatric medicine, primary care, rehabilitation, biostatistics, analysis of large datasets, prognostic modelling, models of stratified care, health economics and PPI. Lead applicant Clegg led the development, validation and national implementation of the eFI. Co-applicants Riley and van der Windt are founders/members of the Prognosis Research Strategy (PROGRESS) framework.

Andrew Clegg: Clinical Senior Lecturer and Honorary Consultant Geriatrician, University of Leeds, leading a large portfolio of internationally-recognised frailty research spanning intervention trials, observational research and big data, holding research grants totalling £13M. Lead applicant with overall responsibility for leadership, management and outputs of the research project.
Milica Bucknall: Lecturer in Statistics, Keele University with extensive expertise in analysing large datasets, including using the eFI.
Simon Conroy: Professor of Geriatric Medicine, University of Leicester, with expertise in large dataset analysis and interpretation of evidence for decision modelling.
Claire Hulme: Professor of Health Economics, University of Exeter, and health economics lead, with expertise in health economic evaluation relevant to older people, and decision modelling.
Sara Humphrey: General practitioner with extensive experience in service commissioning for older people with frailty, and involvement in frailty-related research.
Silviya Nikolova: Lecturer in Health Economics, University of Leeds, and experienced econometrician, with expertise in economic modelling using eFI.
Samuel Relton: Research Fellow in Health Services Research, University of Leeds, with expertise in large, complex dataset analysis for prognostic model development and validation.
Suzanne Richards: Professor of Primary Care Research with expertise analysing complex health and social care data, and assimilation of research evidence for decision modelling.
Willi Riha: PPI co-applicant and senior citizen, with experience as an NHS patient & previous computer scientist.
Richard Riley: Professor of Biostatistics, Keele University, and co-founder of Prognosis Research Strategy (PROGRESS) framework, with extensive expertise in prognosis research, risk prediction modelling and decision analysis. Lead biostatistician, Keele University hub.
Danielle van der Windt: Professor of Primary Care Epidemiology, Keele University, and member of PROGRESS framework group, with extensive expertise in prognosis research and the design and evaluation of stratified models of primary care.
Kate Walters: Professor of Primary Care and Epidemiology, UCL, and clinical GP, with expertise in frailty, big data and primary care for older people.
Robert West: Professor of Biostatistics, University of Leeds, with expertise in big data analysis, latent class modelling and missing data approaches. Lead biostatistician, University of Leeds hub.

12. Success criteria and barriers to proposed work
We will measure overall success by delivery of our main aim, to develop the eFI+ as a novel tool comprising four integrated prognostic-decision models, with linked health economic evaluation.

Key potential barriers and mitigating factors:
1) Obtaining datasets for prognostic model development and external validation
We have carefully selected our planned data sources to ensure that we are able to develop, internally validate and externally validate prognostic models to predict our key outcomes of interest

(requirement for new or increased home care package; ED attendance/hospitalisation with fall/fracture; nursing home admission; all-cause mortality). We have selected data sources that include existing data linkage across primary care, secondary care and social care, and ensured that external validation will be in a second independent dataset. We have confirmed access to data and feasibility of our plans with the lead data scientists for our planned data sources, who are also named study collaborators (Professor Ronan Lyons and Ashley Akbari (SAIL co-director/Senior Analyst); Dr Chris Bates (ResearchOne lead data scientist) and Frank Wood (LDM lead)). Lead applicant Clegg is CI for CARE75+. We have allowed six months set-up to complete regulatory approvals required to access data.

2) Availability of eFI scores and components in planned datasets
We have considered this critical barrier to delivery at the planning stage. The eFI algorithm is based on around 2,000 Clinical Terms Version 3 (CTV3) codes that are used to construct 36 individual deficit variables. The eFI score is calculated by the number of deficits present as an equally weighted proportion of the total possible (e.g. if 9/36 deficits are present, eFI score = 0.25). The eFI algorithm has already been implemented in ResearchOne, SAIL and LDM, meaning that the existing eFI components and scores are available for eFI+ prognostic model development and validation. This includes the capability to calculate historical eFI scores at any timepoint in the dataset.

Additionally, eFI scores are already collected prospectively as part of the CARE75+ study. This is critically important, because scores are not routinely logged in the primary care electronic health record, so it is not possible to retrospectively extract eFI summary scores for historical cohort studies or trials. We are also at an advanced stage of full linkage of CARE75+ to the SystmOne primary care electronic health record. This will provide access to full primary care clinical information for around 1,000 cohort participants, including the 2,000 CTV3 codes that comprise the eFI algorithm, and relevant outcome data.

3) Intellectual property and licensing
The University of Leeds holds background IP for the eFI, with lead applicant Clegg the named IP lead. We have an existing licensing agreement that has been agreed with all the key system suppliers as part of the national eFI implementation, whereby the eFI is made available at no cost to the system suppliers on the basis that a premium charge is not then applied to the end NHS user. We anticipate that foreground IP for the eFI+ will continue to be held by the University of Leeds, and that the existing license agreement will continue to apply. This model of IP and licensing means that there is potential for maximal NHS benefit from the project, and maximal impact of the research.