Eat well, feel well, stay well (The STREAM Trial) Protocol

Version 1

Sponsor:	University of Southampton
Funder:	National Institute for Health Research
NIHR Reference:	RP-PG-0614-20004
ISRCTN reference:	
Ethics reference:	
Dates:	1 May 2019 – 31/12/2021

Protocol authorised by:

Name: Prof. Paul Little **Role:** Chief Investigator

Signature: **Date:** **29/05/19**

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

This study is funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research programme (grant ref No RP-PG-0614-20004). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

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FUNDER This trial is funded by NIHR PGfAR [RP-PG-0614-20004]

Protocol Information

This protocol describes the STREAM study and provides information about procedures for entering subjects. The protocol should not be used as a guide for the treatment of other subjects; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the trial, but sites entering subjects for the first time are advised to contact the study team at **Primary Care and Population Sciences** to confirm they have the most recent version.

Compliance
This study will adhere to the principles outlined in the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It will be conducted in compliance with the protocol, the Data Protection Act and all other regulatory requirements, as appropriate.

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1 List of Abbreviations

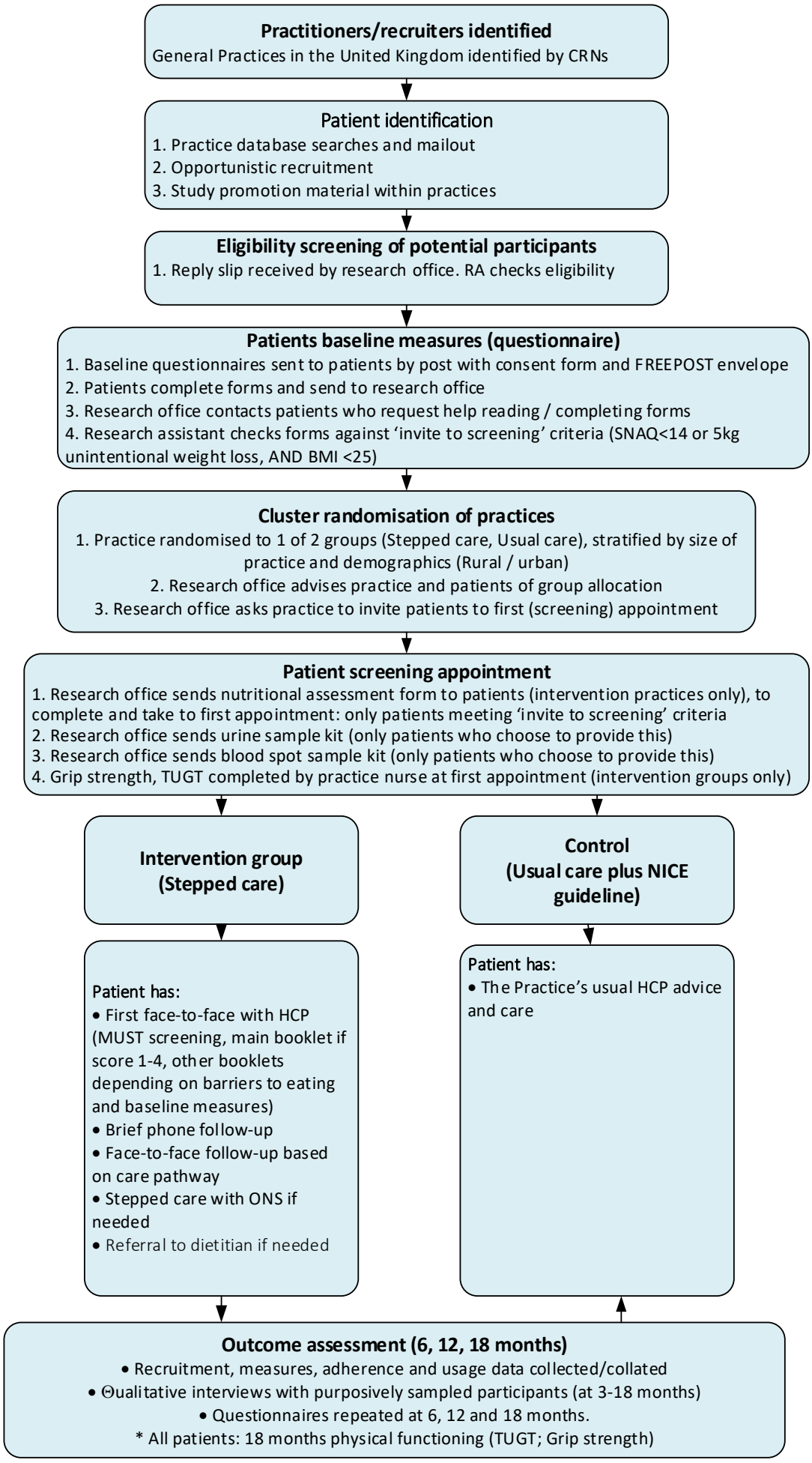
BCT	Behaviour Change Techniques
BMI	Body Mass Index
CI	Chief Investigator
CTCAE	Common Terminology Criteria for Adverse Events
DI	Digital Intervention
DMEC	Data Monitoring and Ethics Committee
FFQ	Food Frequency Questionnaire
GDS4	Geriatric Depression Scale, 4 item
GP	General Practitioner
HCP	Healthcare Professional
ICC	Intraclass Correlation Coefficient
ICMJE	International Committee of Medical Journal Editors
MST	Malnutrition Screen and Treat
MUST	Malnutrition Universal Screening Tool
NHS	National Health Service
NIHR	National Institute for Health Research
ONS	Oral Nutritional Supplement(s)
PCPS	Primary Care and Population Sciences
PCRN	Primary Care Research Network
PGfAR	Programme Grants for Applied Research
QIPP	Quality, Innovation, Productivity and Prevention
R&D	Research & Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SF-36	RAND 36-Item Health Survey Instrument
SMD	Standardized Mean Difference
SNAQ	Simplified Nutritional Appetite Questionnaire
SOP	Standard Operating Procedure
SSI	Site Specific Information
WEMWBS	Warwick–Edinburgh Mental Well-being Scale
TMG	Trial Management Group
TSC	Trial Steering Committee
TUGT	Timed Up and Go test

Keywords: Malnutrition risk; Patient information, Quality of life, Digital intervention, Malnutrition screen and treat

2 Trial Synopsis

Title:	**Screen and TREAt for Malnutrition (STREAM) Programme**
Sponsor:	University of Southampton
Sponsor Ref Number:	253810
Funder:	NIHR PGfAR
Trial phase:	Intervention study phase 3/4
Indication:	Risk of Malnutrition
Primary Aim:	To assess whether nutrition screen and treat policies for primary care are effective among an at risk free living older population in primary care
Objectives:	1) To undertake a cluster randomised controlled trial in primary care to determine whether nutritional intervention following screening for nutritional risk in older adults is practical, acceptable and effective. 2) To determine whether nutritional intervention following screening for nutritional risk in older adults is likely to be cost-effective in primary care.
Trial design:	Randomised controlled trial
Sample size (split by treatment group):	1110 at nutritional risk participants (555 in intervention group, 555 in usual care group)
Inclusion Criteria:	**Patients will:** Be aged ≥ 75 years AND have one or more of these major medical or social problem(s) increasing nutritional risk: (COPD; cerebrovascular disease; cardiac failure; CKD (stage IIIb/IV/V); chronic gastrointestinal disorders and liver disorders including Crohn's disease and constipation (but not functional conditions e.g. IBS); hospital discharge in previous 3 months; Parkinson's disease; current depression; excessive polypharmacy (10+medications); living alone.
Exclusion Criteria:	1. Terminal disease 2. Ongoing primary treatment for cancer 3. Diabetes or non-diabetic hyperglycaemia 4. Established dementia 5. Using oral nutritional supplements (ONS) 6. Established nutritional support 7. Unable to consent
Intervention	Eat well, feel well, stay well intervention
Control Group:	Usual care plus provision of **NICE guideline 32: Nutrition support for adults** to General Practices
Follow up duration	18 months
Total Number of Sites :	Approximately 110 sites (GP surgeries)

Participant flow diagram



3 Schedule of observations and procedures

Measure	Baseline /eligibility screening (Research team)	Baseline at visit 1 (General practice team)	6 month follow-up	12 month follow-up	18 month follow-up
Month	0				
Patient socio-demographic measures	X				
HCP demographic measures	X				
Clinical measures – only 'at risk' intervention group until 18 months follow-up					
Weight					
Height		X			X
Timed up and go test (TUGT)		X			X
Grip strength		X			X
Clinical measures – all 'at risk' patients in both groups		X			X
Urine Sample (optional)	X				
Blood spot sample (optional)	X				X
					X
Patient self-report measures – only 'at risk' intervention group					
Weight	X		X	X	X
Height	X				
Weight loss	X				
Current/recent acute illness	X		X	X	X
Infections (RTIs; UTIs; Skin; Stomach upset)	X		X	X	X
Vitamin / supplement use	X		X	X	X
SF36 measure of quality of life	X		X	X	X
SNAQ appetite questionnaire	X		X	X	X
Food Frequency questionnaire	X		X	X	X
Geriatric depression scale (GDS4)	X		X	X	X
Wellbeing (SWEMWBS)	X				X
Intervention usage	X		X	X	X
Barriers to eating	X		X	X	X
Psychological measures	X		X	X	X

(Risk awareness, outcome expectancy, self-efficacy, problems for adherence (PETS))					X
Perceptions of support (Modified Enablement questionnaire)					
Patient self-report measures – only random sample of 'low risk' participants					
Weight	X				X
Height	X				
Weight loss	X				
Current/recent acute illness	X				X
Infections (RTIs; UTIs; Skin; Stomach upset)	X				X
Vitamin / supplement use	X				X
SF36 measure of quality of life	X				X
SNAQ appetite questionnaire	X				X
Food Frequency questionnaire	X				X
Geriatric depression scale (GDS4)	X				X
Wellbeing (SWEMWBS)	X				X
Intervention usage	X				X
Barriers to eating	X				X
Psychological measures (Risk awareness, outcome expectancy, self-efficacy, problems for adherence (PETS))	X				X
Perceptions of support (Modified Enablement questionnaire)					
Frailty (measured using EFi from electronic systems)	X				X
HCP objectively recorded measures					
Usage of training pages				X*	
Support provision				X*	
HCP self-report measures					
Self-efficacy, sense of competence, outcome expectations	X			X	X

Confidence in the acceptability of the intervention	X			X	X
Economic measures					
Patient quality of life (SF12 taken from the SF36 measure)	X		X	X	X
Costs of food, help with cooking / shopping, drugs / vitamins	X		X	X	X (NR)
Health professional time using website					X (NR*)
Patient time using website					X (NR*)
Qualitative process analysis					
Patient experience and views			X	X	
HCP experience and views of intervention			X	X	

Key:

NR = Notes review

*Intervention groups only– measured via Lifeguide website and/or support log

4 Lay Summary

About 10-15% of people over the age of 65 living at home are at risk of malnutrition. In particular, poor appetite is an important risk factor for malnutrition and for weight loss, and a risk factor for the development of infections, hospital admissions and even longer term mortality. This may be because they are not getting enough to eat, or because they are not eating enough of the right food.
We have developed an approach ('intervention') to help doctors and nurses in general practice to check if older adults who live at home are at risk of malnutrition. They can then offer support to those who need it. Our intervention, called 'Eat well, feel well, stay well', includes booklets and other materials for older adults, and support for health professionals. The support for health professionals includes guidance about when to see patients, and for those more severely at risk when to use oral nutritional supplements.

The intervention was developed by experts who looked at previous literature to find what helps or hinders older adults eating well, and what is likely to work best in general practice. The intervention was improved after feedback from people aged over 65 years, patients and healthcare professionals.

In the study, we aim to assess the effectiveness of the intervention. All patients get a brief intervention with patient booklets and follow-up, but individuals who are at much greater risk will have the brief intervention plus oral nutritional supplements (ONS) for short spells when they are unwell. For comparison we will follow a group of patients who have the usual care that is provided by their doctors' surgery. We will assess outcomes including the number of infections people get, change in eating patterns, weight and quality of life. We will also compare patients and health professionals' experiences of being in these different groups.

5 Study background

Malnutrition probably affects about 13% of older people living at home (NCCAC, 2006). Malnutrition Screen and Treat (MST) policies for those at risk of malnutrition have not been fully tested in primary care, but may be effective and cost-effective.

The problem: eating patterns and malnutrition

Eating patterns that result in insufficient intake of calories or nutrients can cause ill health, but may also develop due to ill health, particularly among people with long-term conditions (NCCAC, 2006). Insufficient calorie and nutrient intake leads to loss of weight and strength, making people more susceptible to infections, falls, heart and breathing problems and worse mental health (NCCAC, 2006). The combination of ageing processes and the increased likelihood of having one or more long-term conditions means that malnutrition is most common among older people and the risk of malnutrition rises with age (Favaro-Moreira et al., 2016). In 2006, the National Institute for Health and Care Excellence (NICE) noted that malnutrition was increasing as the number of older people increases (NICE, 2006).

Identifying Screening tools

MUST

The Malnutrition Universal Screening Tool (Elia, 2003) is one of the checklists recommended by NICE to identify people at risk of problems related to malnutrition (NICE, 2006). Screening involves taking brief details of weight and height and calculating body mass index (BMI). People at significant risk of malnutrition are defined as any of the following:

- BMI less than 18.5 kg/m^2
- Unintentional weight loss greater than 10% within the last 3–6 months
- BMI less than 20 kg/m^2 plus unintentional weight loss greater than 5% within the last 3–6 months.

A re-analysis of the National Dietary and Nutrition Survey (NDNS) from 1994-5 suggested that 6.3% of people over 65 living in the community are probably at moderate risk of malnutrition with 5.8% at high risk (Elia & Russell, 2009; Elia & Stratton, 2009). Nutrition risk and health outcomes were related, and in a 3 month period 58% of patients at low risk, 65.6% of patients at moderate risk and 71.7% of patients at high risk visited their GP. Also, 18.9% of low-risk patients were admitted to hospital over a year compared with 42.6% of people who were at high risk. These comparisons indicate that an effective intervention is needed to address nutrition risk among older people living at home, in order to improve patient outcomes and reduce healthcare use.

Is MUST optimal for screening?

The difficulty of using MUST as an initial screening tool is that it relies on measurement by a health professional. An ideal initial screening in community settings would be to use simple questionnaires to identify those at nutritional risk.

We have used the feasibility study of the STREAM protocol among more than 500 adults in primary care to test whether a 'proxy' MUST questionnaire tool (weight or appetite loss in the last 6 months or looser fitting clothes and/or who can provide a reported height and weight with an estimated BMI of less than 20) could be used to identify individuals to go on and be screened by the practice nurse. However the feasibility study demonstrated that the proxy version was not effective in identifying individuals who were 'MUST positive' - it only identified around half of MUST positive individuals, and only half of those who were 'proxy' MUST positive turned out to be MUST positive when assessed by the nurse. It was also clear that there were relatively few individuals who were MUST positive, which raises questions both about the proxy version of MUST, and whether MUST is the most useful tool to most efficiently identify individuals who are at nutritional risk in community settings.

Is using the SNAQ appetite tool an alternative to using MUST?

Predicting weight loss in community settings is likely to be important: 10-12% of individuals in the community over the age of 60 are likely to lose 5% of body weight (M. M. Wilson et al., 2005), and this is more common in the older age groups. Weight loss is important in that an average of 5% over 12 months has been shown in several studies to be an independent predictor of mortality and poor physical functioning in older adults(LeBlanc et al., 2018; Newman et al., 2001; Wedick, Barrett-Connor, Knoke, & Wingard, 2002), and those who are not normal weight at baseline who then lose more weight are at higher risk of poor outcomes(de van der Schueren, de Smoker, Leistra, & Kruizenga, 2018; Newman et al., 2001).

The SNAQ (Simplified Nutritional Appetite Questionnaire) tool to assess appetite predicts weight loss, and so could be a feasible alternative to the use of MUST or the 'proxy' MUST questions. The SNAQ Tool comprises four simple questions regarding appetite and can be self-completed. It was developed to predict weight loss of 5% or more over 6 months, and has been shown to do so effectively with a sensitivity of 82% and specificity of 86% (M. Wilson et al., 2005). It is therefore likely that lower appetite in itself is a reasonable predictor of poor outcome. The ability of SNAQ to predict poor outcome has been confirmed in secondary care among 179 participants by members of our team: 42% of participants had a low SNAQ score (<14, indicating poor appetite), and a low SNAQ score was associated with a significant increased risk of hospital acquired infection (OR 3.53;

95% CI: 1.48, 8.41; p=0.004) and with risk of death (HR 2.29; 95% CI: 1.12, 4.68; p = 0.023) by 6 months of follow-up (Pilgrim et al., 2016). In our feasibility study we found fewer individuals than in secondary care with a low SNAQ score , but nevertheless low SNAQ scores are common (of the order of 20%) and were associated with low quality of life. It is however unclear whether providing a simple intervention will moderate outcomes in such individuals, particularly in primary care. We now propose to test this in the main STREAM trial.

Malnutrition Screen and Treat (MST) strategies

The review which underpins NICE guideline 32 outlined limited evidence for malnutrition screen and treat strategies, particularly for older people living at home (NCCAC, 2006). The reviewers found two controlled before-after studies in hospital (Jordan, Snow, Hayes, & Williams, 2003; Rypkema et al., 2004) and one cluster randomised controlled trial (RCT) in primary care from the USA (A. A. Moore, Siu, Partridge, Hays, & Adams, 1997). In Jordan et al's (2003) study, recording of weight increased, and referral to dietitians decreased with MST, but no patient outcomes were reported (Jordan et al., 2003). In the other study, MST resulted in weight gains and less hospital acquired infections (Rypkema et al., 2004). In the RCT, there were no improvements in malnutrition detection rate or nutrition intervention by health professionals (A. A. Moore et al., 1997). The review authors concluded that the evidence available at that time was not strong enough to support MST and called for more high quality studies. NICE recommended Malnutrition Screen and Treat (MST) policies for hospitals, but recommended that further studies were needed in primary care (NICE, 2006).

More recent studies have shown promising short-term effects of interventions targeting malnutrition risk factors in the community. Beck and colleagues found that twelve weeks of home visits from dietitians after hospital discharge had a positive effect on functional and nutritional status (Beck et al., 2013). In their RCT, Beck et al (2016) found that multidisciplinary treatment of nutritional risk factors in older people in nursing homes and receiving home-care could have a positive effect on quality of life, muscle strength, and oral care over 11 weeks. Badia et al's (2015) Octabaix study, a RCT with 24 month follow-up in primary care in Spain, tested an intervention for older people which targeted potentially modifiable malnutrition risk factors. The intervention had a positive effect on nutritional status, though there were no significant differences in outcome between intervention and control group, longer-term benefits were less certain and the authors highlighted the need for preventive interventions. A more recent trial (van der Pols-Vijlbrief, Wijnhoven, Bosmans, Twisk, & Visser, 2017) showed no effect on the 12 item short form (SF) physical scale, but a significant impact on the SF mental component and borderline effects on physical function, but much lower societal costs.

Oral supplements to prevent or treat malnutrition

One intervention that has previously shown promise for malnutrition risk is the prescription of oral nutritional supplements (ONS). A review commissioned by NICE in 2006 concluded that ONS were effective for older hospital patients, but ONS studies carried out in the community were small, included highly selected patients or were poorly designed, reducing confidence that ONS is effective outside the hospital setting (NCCAC, 2006).

Since the NICE recommendations (NICE, 2006), more studies have been published which suggest that nutrition interventions may be beneficial for people with eating patterns that put them at risk of malnutrition. An updated systematic review of studies with 3790 mostly older patients in mostly secondary care settings concluded that there were benefits from high protein supplements (Cawood, Elia, & Stratton, 2012). Benefits included reduced complications and less hospital admissions. Other benefits were increased weight, grip strength and energy and protein intake.

Two studies in the community have been completed since the NICE review (Kim & Lee, 2013; Parsons, Stratton, Cawood, Smith, & Elia, 2016). Kim and Lee measured power, balance and strength, and Parsons and colleagues measured dietary intake and quality of life, but health outcomes were not measured in either study. The researchers found that supplement use seemed to reduce the progression of functional decline (Kim & Lee, 2013), and appeared cost-effective in care homes (Parsons et al., 2016). However, it remains unclear whether supplements are effective for people living in their own homes.

Rationale for the present study

The key question is whether it is effective to screen home-living older people who live alone or have medical problems or have recently left hospital, identify those at risk of developing malnutrition and then give them nutritional support.

Participants will receive a brief lifestyle intervention, iteratively developed with input from patients and Healthcare Professionals. The authors of the studies described above provided no evidence of the iterative development which is needed for complex interventions, and we know how important this is from previous successful studies in our group (P Little et al., 2016). As part of the complex intervention we will test a targeted and stepped protocol for oral nutritional supplements (ONS): most people are unlikely to need ONS and can be managed with clinical management and dietary advice. We propose additional targeted use of ONS for individuals at the highest risk (fulfilling MUST criteria). The method we propose is to match the existing evidence from secondary care: to first give short courses of ONS supplements when people have less appetite due to inter-current illness (such as flu, infections and COPD exacerbations); this would be followed by a systematic plan, escalating to regular ONS use, or stopping ONS, based on patient needs.

Using the internet

LifeGuide is an open-source software package for creating interactive web-based interventions to support healthy behaviour (Lucy Yardley et al., 2009). Previous LifeGuide web-based interventions have been successfully used to provide training for health care professionals to deliver effective interventions to patients, e.g. Antibiotic prescribing (P Little et al., 2013) and weight reduction (P Little et al., 2016). We have therefore used LifeGuide as an efficient, easy-to-use, acceptable way of providing training and ongoing support for healthcare professionals to deliver the 'Eat well, feel well, stay well' intervention.

The internet is now used successfully by older adults for disease self-management, (Stellefson et al., 2013) and may have a role in delivering the intervention materials that we are developing for patients. However, we have currently developed printed materials, as this is likely to be the most accessible medium for a broad older adult population with varying socio-demographic characteristics.

Feasibility study

The 'Eat well, feel well, stay well' intervention has been developed for the STREAM programme. 'Eat well, feel well, stay well' is a brief intervention, consisting of dietary advice and support from healthcare professionals in primary care. It was iteratively developed using the person-based approach (L. Yardley, Ainsworth, Arden-Close, & Muller, 2015). We also explored the feasibility and acceptability of the procedures for both patient and health care staff for the planned main trial. Both the intervention and the procedures are such that we can now progress to the main trial.

The results of the feasibility indicated that it is most appropriate to run a two-arm trial, with a single intervention group where individuals at nutritional risk will be invited to screening based on: 1) a low SNAQ score or who report losing 5Kg unintentionally, and 2) have an estimated BMI less than 25 (since with normal weight are at less risk of poor outcomes (Newman et al., 2001)).

In terms of outcomes, SNAQ identifies a group of individuals likely to get more infections, so it is reasonable to assume that the intervention could reduce intercurrent illness and potentially, attendance at the GP and hospital admissions. We have therefore included infections as one of the primary outcomes that will be measured during the trial.

Further details about the results of the feasibility study, and how they informed this trial, can be found in Appendix B.

6 Trial Objectives

We aim to assess effectiveness of an intervention in primary care to encourage the use of malnutrition screen and treat (MST) policies for older people living in their own homes. The aim of the 'Eat well, feel well, stay well' intervention with the targeted use of ONS is to help staff in general practices to support behaviour change and improve the quality of life of older people who are at risk of malnutrition.

Main research objective:

1) To undertake a cluster randomised controlled trial in primary care to determine whether nutritional intervention following screening for nutritional risk in older adults is practical, acceptable and effective.

Secondary questions:

2) To determine whether nutritional intervention following screening for nutritional risk in older adults is likely to be cost-effective in primary care.

7 Trial outcomes

Data collection

Postal questionnaires at baseline and follow-ups (6, 12, 18 months) will take up to 30 minutes to complete. Participants who are to be followed up, and who return incomplete questionnaires, will be asked once by post or email if they are willing to complete the missing sections. Optional urine samples and blood spots will be taken by the participants at baseline and 18 month follow up.

7.1.1 Participants 'at risk', based on answers to baseline questionnaire

In person baseline measures will be taken by the practice nurse at first screening appointment in the intervention group only. The **usual care (control group)** will complete questionnaires at baseline and follow-ups, as for the intervention groups (SF-36, SNAQ appetite questionnaire, Food Frequency questionnaire, GDS4, psychological measures).

7.1.2 Participants at 'low risk' based on answers to baseline questionnaire

Those not identified as at nutritional risk from the questionnaire will be at low risk, so there is little point in intensively following up all such patients. However, since they have been exposed to screening it will still be useful to follow-up a sample at 18 months, to monitor any changes over time. We will follow up a random sample of 225 such patients in intervention and control groups (i.e. 450 in total), at this time.

Outcome measures

Primary outcomes

We have two co-primary outcomes for the trial: quality of life (QOL), and the proportion of participants experiencing an infection that can be prevented.

1) Quality of Life: Elderly adults with low appetite and significant comorbidities report low quality of life and we anticipate that improved diet may help to increase or stabilise quality of life. Quality of life has been measured in previous studies, so we will also be able to compare our results to other intervention studies. Some caution is needed for quality of life as the sole primary outcome in a primary care sample, since in a less unwell sample QOL is perhaps less likely to change (and/or further upstream in the pathway of illness), and previous studies have critiqued the use of Quality of Life measures in the comorbid population(Murphy, Hollinghurst, Cowlishaw, & Salisbury, 2018). Nevertheless, we have evidence from our feasibility study for the relationship between low SNAQ scores (our primary screening tool) and quality of life, supporting the use of quality of life measures.

2) Infections: Infections are common and particularly important in the elderly population, not only as an outcome in their own right but because they result in significant changes in cognitive function which do not necessarily recover. We anticipate that improved diet may help to reduce the quantity and/or duration of infections.

Secondary outcomes

Secondary outcomes include: Timed up and go test (TUGT); Grip strength; analysis of blood and urine samples; change in weight; change in malnutrition risk score (MUST); change in appetite (SNAQ); change in food intake (quantity and quality - FFQ); change in depression score (GDS4); current / recent acute illness; number of falls; number of regular medications; health service use; ONS use (prescribed or over the counter over the last year); hospitalisation; frailty (EFI score); psychological measures.

Health professional collected measures

	Baseline*	18 month follow-up**
Weight, height, MUST score	Yes	Yes
Timed up and go test (TUGT) (Mathias, Nayak, & Isaacs, 1986; Podsiadlo & Richardson, 1991),	Yes	Yes
Grip strength, using a handgrip dynamometer (three measurements from both hands) (Vaz, Thangam, Prabhu, & Shetty, 1996)	Yes	Yes

Notes: * Collected by nurse or HCA at first appointment (screened patients in intervention practices).

** Collected by independent nurse at 18 months for all in the 'follow-up' sample (those at nutritional risk in intervention and usual care groups and random selection of 'low risk' patients)

Self-collect measures

	Baseline	18 month follow-up
Optional urine sample – three morning samples self-collected over 10 days and posted direct to lab	Yes	Yes
Optional blood spot sample -self-collected at home on one occasion	Yes	Yes
Infections diary (self-report diary indicating type, duration and severity of infections)	Diary started at baseline and returned to research office at 18 month follow-up	

Notes: all the 'follow up' sample

Other data collected at baseline 6, 12 and 18 months in the 'follow-up' sample in all groups (unless stated otherwise in Schedule of observations)

Measures for Primary outcomes

1) **SF-36** as a measure of quality of life (Ware & Sherbourne, 1992). physical quality of life will be the primary outcome in the full trial, but the mental domain of SF-36 will also be measured.
2) **a) Proportion experiencing an Infection during the follow-up period** (Respiratory Tract Infections including COPD exacerbation; Urinary Tract infections; skin infections) based on recall of an episode of infection (defined as having at least 2 consecutive days with symptoms suggestive of an infection). We have shown it is feasible to measure this (P. Little, Stuart, & Hobbs, 2015) with good agreement between outcomes measured after 1 month and after 4-6 months (i.e. recall is reliable).

2) b) Other indices of infections. We will ask participants to document the number of infections and the duration of symptoms (in total and the number of days with bad symptoms) in a simple diary (P. Little et al., 2015). We will also document infections for which participants see their GP or attend A&E from the notes review.

Measures for secondary outcomes:

1) Proxy measures of malnutrition risk:
    - Current actual and/or estimated height and weight for BMI calculation,
    - Weight change (eg. Looser or tighter clothing / rings / belts)
    - Current / recent acute illness
    - Falls
    - Number of regular medications
2) SNAQ appetite questionnaire (4 items) (M. Wilson et al., 2005)
3) Food frequency questionnaire (20 items) (Robinson et al., 2016)
4) Geriatric Depression Scale (GDS4) (4 items) (D'Ath, Katona, Mullan, Evans, & Katona, 1994),
5) Wellbeing – WEMWBS (Scotland, 2006)
6) Psychological measures, informed by the logic model from the development phase of the study (self-efficacy, risk awareness, outcome expectancy).
7) Demographic questionnaire, including: Health service use and drugs, including taking ONS (prescribed or over the counter over the last year), taking multivitamins, details about recent hospitalisation, current drugs.
8) Frailty (EFI) score (baseline and 18 months only)

Notes review at 18 months in all groups

- Demographic information: medical problem(s) increasing nutritional risk (see inclusion criteria).
- Frailty (EFI) scores
- Health service use covering primary care visits, A&E, outpatient attendance and hospitalisation and drugs, including ONS, details about recent hospitalisation

Implementation process assessment

Consistent with the new MRC guidance for process evaluation of complex interventions(G. Moore et al., 2014) (), we will use mixed methods to evaluate implementation of the intervention. Data collection will be minimally intrusive, but will include: objective measures of health professional implementation of key behaviours, including:

- Self-report measures of theory-based determinants of healthy professional implementation (outcome expectancies, sense of competence, self-efficacy).
- Self-reported assessment of key patient behaviours (adherence to key components of agreed treatment plans and follow-up) using the validated Patient Experiences of Therapy Scale.
- Self-reported assessment of theory-based determinants of patient behaviours (self-efficacy, outcome expectancy, perception of supporter).

Qualitative process analyses

- During the main trial, we will interview 16-20 patients with different levels of adherence for in-depth understanding of patients' perspectives and influences on the experience and outcomes, employing the dimensions of our theory-based logic-model as prompts. Initial inductive thematic analysis (Braun & Clarke, 2006) will be followed by exploring how inductively derived themes map onto/elaborate/diverge from our theoretical predictions, to relate our context-specific insights to generalizable theoretical constructs. Qualitative findings will be triangulated with the quantitative analyses (G. F. Moore et al., 2015). We will examine how and why our qualitative findings converge with, complement or contradict the quantitative findings, for example by comparing patient experiences with trial outcomes.

- We will also use the qualitative data to offer possible explanations for mechanisms of action within the trial and quantitative findings, such as patterns of engagement and adherence. To inform future implementation we will also ask patients, and a sample of primary care staff (which we anticipate from previous experience will require between 12 and 20 staff), for their views on how this intervention could best be implemented and sustained in practice, exploring possibilities for primary care and community self-management support.

Quantitative process analyses

- We will assess reach (uptake; sample characteristics), self-reported adherence (Kirby, Donovan-Hall, & Yardley, 2014), predictors of adherence and outcomes (age; gender; education; comorbidities; frailty, illness and treatment perceptions (Kirby et al., 2014) (Horne, Weinman, & Hankins, 1999; Moss-Morris, 2002); self-efficacy to overcome identified barriers). The questionnaire data will be used to assess adherence to the intervention by participants. Notes data will record implementation by staff. We will examine the influence of baseline characteristics (particularly demographics) on engagement with the intervention and outcomes, and the psychological variables likely to moderate engagement (risk awareness, outcome expectancy, self-efficacy – see above). We will also employ multi-level modelling to investigate how process measures relate to outcomes.

8 Participant Identification and Recruitment

On the very conservative assumption that those at risk are at least 15% of the population we will aim to recruit approximately 7400 patients by predominantly postal invitation in order to identify at least 1110 patients at nutritional risk (i.e. with a SNAQ score below 14 or who report losing 5Kg of weight unintentionally; with BMI<25; - all based on answers to the baseline questionnaires). Eligible patients will be identified from around 110 general practices found by the Clinical Research Networks (CRN). Practices will be selected to ensure that small and large, rural and urban, and practices with lower Index of Multiple Deprivation scores are represented. Lead GP(s) or nurse(s) will be identified at each site. Before any practice can begin recruitment, a Lead GP or nurse must be identified.

The following documents must be in place and copies sent to the local STREAM Trial Coordinator (TC):

- A signed Study Agreement (Research lead and sponsor signature)
- Completed Delegation log outlining Roles and Responsibilities

Once the above documents are received and we are ready for the practice to start, the STREAM TC will send a green light email to the lead GP or nurse. A copy of this email must be filed in each centre's Site File. The practice will be able to begin recruiting patients in to the study once the providers have completed the online STREAM training components.

Practice and Health care professional (HCP) identification

Initial identification

- Practice databases will be searched for potentially eligible patients (see inclusion/exclusion criteria). Lists will be screened by GPs for exclusion criteria prior to mail out,

- Patients will also be identified by asking practice staff to invite patients they think are likely to be at nutritional risk prior to randomisation (and to document the reason why they regard them to be at risk)

Opportunistic identification in intervention practices.

Practices can help identify participants who may benefit most from the intervention in two ways:

1) Once an intervention practice is in the process of inviting individuals for screening appointments (who have been selected prior to randomisation), individuals who have not yet been screened can be flagged electronically when they attend for unrelated appointments or can be asked in person whether they would consider screening.

2) Once practice staff have completed intervention training for STREAM, they may be aware of particular individuals at nutritional risk for whom the study would be appropriate. We ideally need to capture such individuals (who will be treated separately in analysis). Thus, following randomisation and training healthcare professionals can recruit participants opportunistically.

To aid opportunistic identification, staff may:

- Flag items relevant to the inclusion criteria in patients' notes,
- Display study adverts in practices to alert eligible carers, or people they care for, about the study. Patients responding to the study advertisements can email the research team, for further information. Patients who would like one, will then be sent a study information pack (invitation letter, participant information sheet and reply slip) to complete and return to the research team.

Inclusion criteria

1. Patients aged ≥ 75 who are either living alone or have one or more major medical or social problem(s) known to increase nutritional risk. These are: Chronic Obstructive Pulmonary Disease (COPD); cerebrovascular disease, including stroke; cardiac failure; Chronic Kidney Disease (stage IIIb/IV/V); chronic gastrointestinal problems or chronic liver disease, including inflammatory bowel diseases and constipation (but excluding functional conditions e.g. IBS); recent hospital discharge in the last 3 months; Parkinson's disease; current depression (in the last 12 months); or excessive polypharmacy (10 or more medications) (Favaro-Moreira et al., 2016).
2. A proportion of participants (n=1110) will be identified as being at high risk of malnutrition, based on their questionnaire answers (with a SNAQ score of less than 14 or who report losing at least 5Kg of weight in the previous 6 months, and whose estimated BMI is less than <25), and in the intervention group only these individuals will be invited to screening and assessment.
3. English needs to be good enough to understand the study materials, as funding for the trial does not allow for translation.

Exclusion Criteria

Participants will be excluded if they:

- Have used ONS in the last 6 months,
- Have terminal disease,
- Are having ongoing primary treatment for cancer,
- Have diabetes or non-diabetic hyperglycaemia,
- Have established dementia (this group would be substantially different mandating involvement of the carers, and different outcomes),
- Are receiving established nutritional support,
- Are unable to consent,
- Institutionalised patients.

9 Registration and Randomisation Procedures

Screening and Eligibility Assessment

Letters of invitation, participant information sheets and reply slips will be sent from the practice via Docmail (a mail-merge style service) to potential participants. The duration between participants being informed of the study and their consenting will be at least as long as it takes for the reply slip to be returned and the questionnaire pack to be sent out. If participants do not want to be sent further information, they will have the option to indicate their reasons on the reply slip.

Consent

Consent will be sought from participants by post. Consent forms, along with baseline questionnaires will be sent to eligible participants who indicate on their reply slip that they would like to take part. Participants will be asked to contact the research team if they have any questions (clear contact details will be included in study documents). Participants will be asked to return the completed consent form to the research team with a completed baseline questionnaire. Patients can also request optional phone help filling out questionnaires.

The consent form will include three optional statements:

1. Agreement that participants may be contacted later by the research team for nested qualitative interview participation. Patients who agree to take part in the interviews will be asked to sign a further consent form prior to the interview, after they have had any questions answered by a researcher.
2. Agreement that participants would like to provide urine samples at the start of the study and 18 months later.

3. Agreement that participants would like to provide blood spot samples at the start of the study and 18 months later.

Randomisation, blinding and code-breaking

Cluster randomisation of Practices will be carried out using computer generated random numbers once patients' completed baseline questionnaires are received by the research office, to reduce the likelihood of selection bias. The few patients who return questionnaires after the practice is randomised will be allowed to participate since their invitation was blind to randomisation status.

Practices will be allocated to one of the two arms:

1. Brief 'Eat well, feel well, stay well' intervention, plus targeted ONS for a minority of individuals according to protocol
2. Usual care.

At the point of consent patients will be blind to practice allocation. All patients who consent at one Practice will receive the same intervention.

The research team will contact participants by letter, email or phone about which group they are assigned to. Participants assigned to the intervention arm will also be sent a nutritional assessment form to complete and take to their first appointment. The research team will also alert the patient's GP surgery. The research team or surgery will contact patients by letter, email or phone, to arrange appointments, or the patient will be asked to make an appointment with their GPs surgery. Where possible, staff will address barriers to attendance.

Follow-up measures

Those participants that will be followed up will be" at risk" participants in both intervention and usual care group, plus a random selection of 'not at risk' from both groups). Participants will be reminded to complete follow-up measures by the research team by letter, email or phone or will be contacted by the surgery. If the participant indicates that they would not be willing to complete further measures, no further contact will be made regarding follow-ups. All intervention group and control group patients who are 'at risk', plus a random selection 'not at risk' from both groups will be contacted to participate in the follow-ups, whether or not they have used the intervention.

Each participant will be sent a £10 high street gift voucher with the 18-month follow-up questionnaire. The usual care group will be given access to the patient leaflets and other materials after the end of follow-up.

The intervention is branded: “Eat well, feel well, stay well”.

Staff support tool

The brief training provided by the support tool will be completed by all staff before delivering the intervention. The tool will be accessed online using Lifeguide software ("Lifeguide online,") (Hare et al., 2009; Lucy Yardley et al., 2009). Components include a malnutrition screen and treat (MST) care pathway, how to carry out screening using MUST, the CARE approach to support and encourage patients (Bradbury et al., 2017), and when and how to prescribe oral nutritional supplements (ONS). An MST kit will be provided, including charts to use with MUST, printouts of key pages from the support tool, and folders, booklets and other materials to offer to patients.

Usual care group

Participants will continue to have the normal existing medical support provided by their GP surgery. The Practice will be provided with a link to the online version of NICE guideline 32, ‘Nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition’. Practices will be alerted if the guidelines are updated.

Intervention group

Patients who are at lower risk based on their questionnaire responses will not be invited for screening. Patients who are at nutritional risk from their baseline questionnaire will be invited for a screening appointment by a health professional. Patients will be assessed for underlying problems using a nutritional assessment proforma, and referred where necessary.

Patients will be offered printed booklets addressing their needs, a brief phone follow-up, and brief face-to-face appointments with a practice nurse at intervals, depending on their MUST score at the screening appointment.

Patient booklets

Eight patient booklets will be available:

1. Main booklet to encourage change in eating patterns,
2. Goal booklet, with techniques to support patients in planning, carrying out and maintaining change in eating patterns,
3. Four optional booklets, targeting specific barriers to eating well that have been identified from qualitative studies and interviews with older people,
4. Two booklets outlining how and when to use ONS (only for those receiving ONS).

Health professionals will provide all patients with the main booklet and goal booklet. They will also support patients in choosing optional booklets most relevant to their circumstances, and support patients in thinking about and carrying out the advice provided in the booklets.
Participants will also be prescribed a targeted course of oral nutritional supplements (ONS) if needed: ONS is only targeted to those individuals who cannot modify their food patterns or who are at higher risk. For example, patients with a MUST score of 3 and an acute illness such as an infection or COPD exacerbation will be prescribed ONS for two weeks; patients with a MUST score of 4 (high risk) will be prescribed ONS for three months, and the prescription will be reviewed at their next Practice appointment.
See **Appendix A** for a detailed diagram, incorporating TiDIER guidelines (Hoffmann et al., 2014).

Sample size. We propose co-primary outcomes of Quality of Life, and the proportion of individuals experiencing an infection. 'Success' is conceptualised as either outcome being significantly different between groups. The comparisons of most interest are the intervention group versus control group for individuals who are at risk (BMI<25; low SNAQ score or history of unintended weight loss) who are either invited to screening (intervention group) or not invited to screening (control group).

Quality of Life. We conservatively assume a modest QOL improvement compared to the control group based on prior reviews (a standardised effect size of 0.33 i.e. a small to moderate effect size). From current piloting 20-25% of individuals will be selected for screening, and most who are invited will attend for screening (80% attended, but if we assume conservatively 75% will attend). We also assume those who are not screened do not benefit, which will therefore mean a reduction in the effect size to a standardised effect size of 0.25. Assuming 10 participants per practice who are at risk, an ICC of 0.03 (inflation factor 1.27: (1+ ((10-1)*0.03)) 612*1.27=777 at risk participants are needed, or 1110 allowing for up to 30% loss to follow-up (for alpha 0.025; power 80%). If the at-risk subgroup is very conservatively at least 15% of the target population then approximately 7400 participants are needed who agreed to participate following the initial postal invitation from approximately 110 practices.

Infections. Approximately 70% of at-risk individuals in the target age group are likely to suffer respiratory infections during the course of a year (P. Little et al., 2015) and some will also have one of the other common infections (i.e. including urinary and skin infections), so we assume at least 80% will have an infection. We assume that this could be reduced by 15% to 65% among those screened but the observed reduction due to incomplete uptake of screening could be 68.5%; if so then the above sample size will provide 80% power for alpha 0.025 for the reduction in the number of individuals experiencing an infection.

Low risk individuals. For individuals who are not at higher nutritional risk based on their questionnaire responses at baseline, most of the analysis will be descriptive. However, it will be useful to compare changes in key outcomes over time: comparing low risk patients with higher risk patients in the control group (to address the issue of whether the trajectory of low risk participants is different from high risk patients) and between lower risk participants in both intervention and control practices (to document any possible intervention effect among low risk patients who are being managed in intervention practices). For the comparison between low risk patients in each study group, since low risk patients are not being screened we do not need to allow for attrition to invitation in reducing the apparent effect size, and we do not need to allow for clustering. If we randomly select a minimum of 146 participants per group who are not at risk (or 418 allowing for 30% loss to follow-up) this will allow us to detect a 0.33 SD difference (for 80% power, alpha =0.05) in the primary outcome comparing low risk patients in intervention and control practices. To allow for some leeway in our assumption we aim to randomly select 450 participants who are lower nutritional risk (225 from intervention, 225 from control practices). This sample size will also have similar power for the comparison between lower risk and higher risk patients in the control group.

Assessment and follow-up of participants in the 'follow-up' sample

Measures will be administered for all participants at baseline. 'At risk' participants (i.e. those with BMI <25 who also have a SNAQ score <14 or 5kg unintentional weight loss) will be followed up at 6 and 12 months, and a random selection of 'low risk' participants will be followed up at 18 months, unless otherwise stated (see Schedule of Observations and Procedures). Clinical outcomes will be assessed by the practice nurse or healthcare assistant at baseline and by an independent research nurse at 18 months. Patient-reported outcome measures will be completed and returned to the research office by post. Non-respondents will receive three reminders by post, email or phone. Website usage by healthcare professionals (STREAM measures) will be recorded automatically in Lifeguide.

An independent research nurse, blind to study allocation will complete the in-person follow-up assessments. All participants (including withdrawn participants who have consented to follow-up appointments) will follow the procedure outlined below:

- Participants will be sent questionnaire with £10 voucher 18 months post randomisation
- Approximately three weeks before the follow-up appointment is due, the research nurse will contact the patient to arrange an appointment. Appointments may be scheduled to take place in the patients' home or usual GP practice.
- The research team or research nurse will send confirmation of the follow-up appointment to the patient.

- If the patient indicates that they would not be willing to complete a follow-up, no further contact will be made with the patient regarding the follow-up appointment.

10.1.1 Discontinuation/Withdrawal of Participants from Study

Participants have the right to withdraw from the study at any time. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

- Withdrawal of consent,
- Terminal illness.

If a participant withdraws having completed the baseline questionnaires, their data will be retained to evaluate potential differences and reasons for attrition.

When participants indicate that they wish to withdraw, we will write to ask whether they wish to withdraw from the whole study or will agree to be followed up , or specific parts of it (e.g. supplying blood/urine samples, qualitative study).

10.1.2 Definition of End of Study

The end of study is the date of the last follow-up of the last participant.

11 Statistics and Analysis

Description of Statistical Methods

SPSS, Stata and Excel software will be used to evaluate outcomes.

The Number of Participants

We will aim to recruit 1110 high risk patients, half in each group (usual care, intervention).

Analysis of Outcome Measures/Endpoints

The overall aim is see if screening for, and treating, participants at risk of malnutrition is effective and cost effective for older patients with major medical problems. The overall study population can be classified using the results of a simple postal questionnaire as not at risk, or at risk (at risk: SNAQ <14 or loss of 5Kg unintentionally and BMI <25).

In order to best inform future screening policy, we need to assess the effectiveness and cost-effectiveness of different approaches to screening, for example, whether participants at 'low risk' may benefit from screening. We will therefore carry out three analyses:

1) Primary analysis of 'higher risk' individuals: Participants identified as 'at risk', based on answers to baseline questionnaires in intervention practices will be compared with those 'at risk' in control practices.
2) Secondary analysis: We will compare outcomes of participants who are 'at risk' with those who are 'not at risk'.
3) Secondary analysis: individuals not at risk. We will compare outcomes among those individuals identified by the questionnaire as 'not at risk' from intervention compared to usual care practices.

Methods of analysis. A detailed statistical analysis plan will be developed prior to completion of data collection. ITT analysis using multiple linear regression will control for how identified by screening (from the invitation or by opportunistic recruitment), practice clustering, and potential confounders. We will explore the nature and pattern of missingness and use multiple imputation methods as appropriate.

We will also explore which factors at baseline (e.g. age, deprivation, living alone, pattern of morbidity etc.) best predict higher risk individuals in order to guide efficient targeting in future, and will triangulate the mixed methods process data to describe implementation fidelity and understand contextual factors associated with successful and problematic implementation and outcomes.

Health economic analyses

Quality of life is the primary outcome for the effectiveness and cost-effectiveness analyses, and this should capture any impacts on morbidity. Consideration will be given to use of the secondary outcome in cost effectiveness analyses. Given that most of patients are likely to be elderly and retired, the choice of perspective is that of the NHS and PSS, as per NICE.

The outcomes are costs, cost per clinical outcome, and cost per QALY gained.

In the first year of the STREAM Programme, we conducted literature reviews of economic studies, mainly updating the NICEs CG32. The paucity of the cost effectiveness literature, reviewed by NICEs CG32, limited the scope for pre-trial modelling. However, what available literature there has informed the modelling structure, and qualitative work will help make sure we have identified key resource drivers. The model follows the patient's clinical pathway initially populated from the literature review, but then will be updated by the results from the full trial. We will investigate whether a Markov model or discrete event simulation modelling is more appropriate for the underlying problem. The model will represent the clinical pathway for a patient with malnutrition, particularly emphasising the associated morbidity and mortality associated with the condition.

Notes review will document resources required for MST (ONS; new medication prescribed; consultations; admissions; outpatients). Nurses will document data on screening and interventions (staff time; training; internet usage; equipment used). Resource use will be weighted by its unit cost.

We will derive utility scores from the full SF36, translated into SF6D. The methods for converting SF36 to SF6D are outlined in the SCHARR website (Sheffield.ac.uk/SCHARR/). QALYs will be estimated by means of area under the curve.

Bootstrapping will generate incremental cost effectiveness ratios (ICERs). Cost differences between intervention and control groups will be adjusted for baseline characteristics using generalized linear modelling. Cost-effectiveness acceptability curves will be produced to reflect the probability of the intervention will be cost-effective at different given willingness-to-pay value per QALY gained. Major assumptions will be tested in sensitivity analyses.

Should the trial show the hypothesised differences in outcomes, beyond trial modelling will be carried out. The model will be used to explore the long-term cost-effectiveness beyond the trial period and in more broad settings.

Qualitative Transcription and analysis

Interviews and focus groups will be audio-recorded (where applicable) and transcribed verbatim to allow for fidelity checks, to examine the acceptability and feasibility of support, and to inform potential intervention modifications. At this point the transcriptions will be anonymised (identifiable data removed) and participants' transcripts will be given pseudonyms so that they can be easily discussed between team members while protecting participants' identities. To ensure that we remain open to and grounded in users' perspectives we will carry out inductive thematic analysis of all textual data (Joffe & Yardley, 2004), triangulated where appropriate with self-report and web usage data, and with discussion among team members (including our PPI representatives) to reach inter-rater agreement on themes and elaborate our interpretations (Joffe & Yardley, 2004). Themes will then be related to the theoretical frameworks that have informed our intervention planning (i.e. Social Cognitive Theory, Self Determination Theory, Health Action Process Approach, Normalisation Process Theory).

12 Data Management

12.1 Access to Data

Access will be granted to authorised representatives from the Sponsor or host institution for monitoring and/or audit of the study to ensure compliance with regulations.

12.2 Data Recording and Record Keeping

Data collection will be via file download from secure websites (Lifeguide). Manual data will be input into secure databases by research staff, and filed in locked filing cabinet(s) in a locked room at University of Southampton. Anonymised data will be retained for a period of 5 years after publication and thereafter destroyed. Data with personal information will be deleted after the study period and write-up are complete (maximum 10years after study end).

12.3 Serious Adverse Events

12.3.1 Definitions

For this study Serious Adverse Event (SAE) is defined **as** any untoward medical occurrence or effect that at any dose:

- Results in death
- Is life-threatening – refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires hospitalisation, or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Other important medical events - based upon appropriate medical judgment, they may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

12.3.2 Causality

An SAE occurring to a research participant will be reported to the STREAM Study team where, in the opinion of the Principal Investigator at site, the event was related to administration of any of the research procedures , and was an unexpected occurrence. The causality assessment of the event should always be undertaken by a medically qualified doctor who is delegated to do so as indicated on the trial delegation log.

12.3.3 Expectedness

For the purposes of this trial no SAE's are considered expected.

12.3.4 Non serious AEs and exemptions

- Non-serious AEs will not be collected.
- SAEs NOT DIRECTLY related to the Trial are not required to be reported, this includes deaths and hospital admissions as assessed by PI at site as being not related to the trial website intervention. In such cases deaths will be reported using an End of Study form and will be sent directly to the trial team as per SOP.

- Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened, elective procedures for a pre-existing condition will not be classed as an SAE unless deemed related to the trial. Hospital admissions that are not directly related to the trial do not need to be reported.

12.3.5 Reporting

GP Practices will inform the STREAM Study Team of any SAEs considered to be related to the trial immediately but at least within 24 hours of becoming aware of the event occurring.
SAEs should be reported using the trial specific SAE Report Form and completed in as much detail as possible and faxed/emailed to the STREAM Study Team:

Fax 02380 701125 or email stream@soton.ac.uk

Note that the initial report can be made by phone but this must be followed up as soon as possible with a paper report form.

The STREAM Programme Manager will notify the appropriate REC should an SAE be considered related to the trial and unexpected within 15 days of the receipt of the report.
Follow Up
All SAEs will be followed up until resolved or an end of trial criteria is met (e.g. patient withdrew from study
All SAEs will also be sent to the PSC.

13 Quality Assurance Procedures

The study may be monitored, or audited in accordance with the current approved protocol, relevant regulations and standard operating procedures.

14 Ethical and Regulatory Considerations

As with many intervention studies, there is the potential to cause distress simply by raising worrisome topics. In this particular intervention, we will focus on diet-related issues, which may be sensitive for some people. To address this, there is a statement in the participant information suggesting that if participants feel distressed, they can talk to a friend, family member, their GP or a charity such as Age UK. Participation and engagement with the intervention are optional and participants can avoid it if they choose to.

Another potential concern is that some participants may change their behaviour in an unhealthy manner (e.g. too much poor quality food). As with any intervention, there is the potential for

participants to do too much, or, 'overdo' the ideas and tasks supplied. Therefore, the designers of the content have included encouragement to set realistic goals which are tailored to the needs of the individual. In the booklets patients are also advised to discuss changes with their GP or nurse.

Before starting the study, participants are informed that they can withdraw at any time without giving a reason. Usual care practices (and therefore participants) will be given access to 'Eat well, feel well, stay well' once their study participation has ended.

Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

Approvals

The protocol, informed consent form, participant information sheet, participant letters, and any proposed advertising material will be submitted to appropriate Research Ethics Committees (REC), Health Research Authority (HRA) and host institution(s) for written approval. The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants' ID number. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

Expenses and Benefits

Practice staff will receive staff support costs for their time spent supporting patients during this study. The online training module for practice staff will be supplied free of charge to those taking part in the research. Patient participants will receive a £10 gift voucher with the 18 month

questionnaire. Participants who also take part in the qualitative interviews will each receive a further £10 gift voucher for their time.

15 Finance and Insurance

Funding

Funding for this study is provided by the NIHR.

Insurance

The University has a specialist insurance policy in place which would operate in the event of any persons suffering harm as a result of their involvement in the research.

16 Publication Policy

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the NIHR. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

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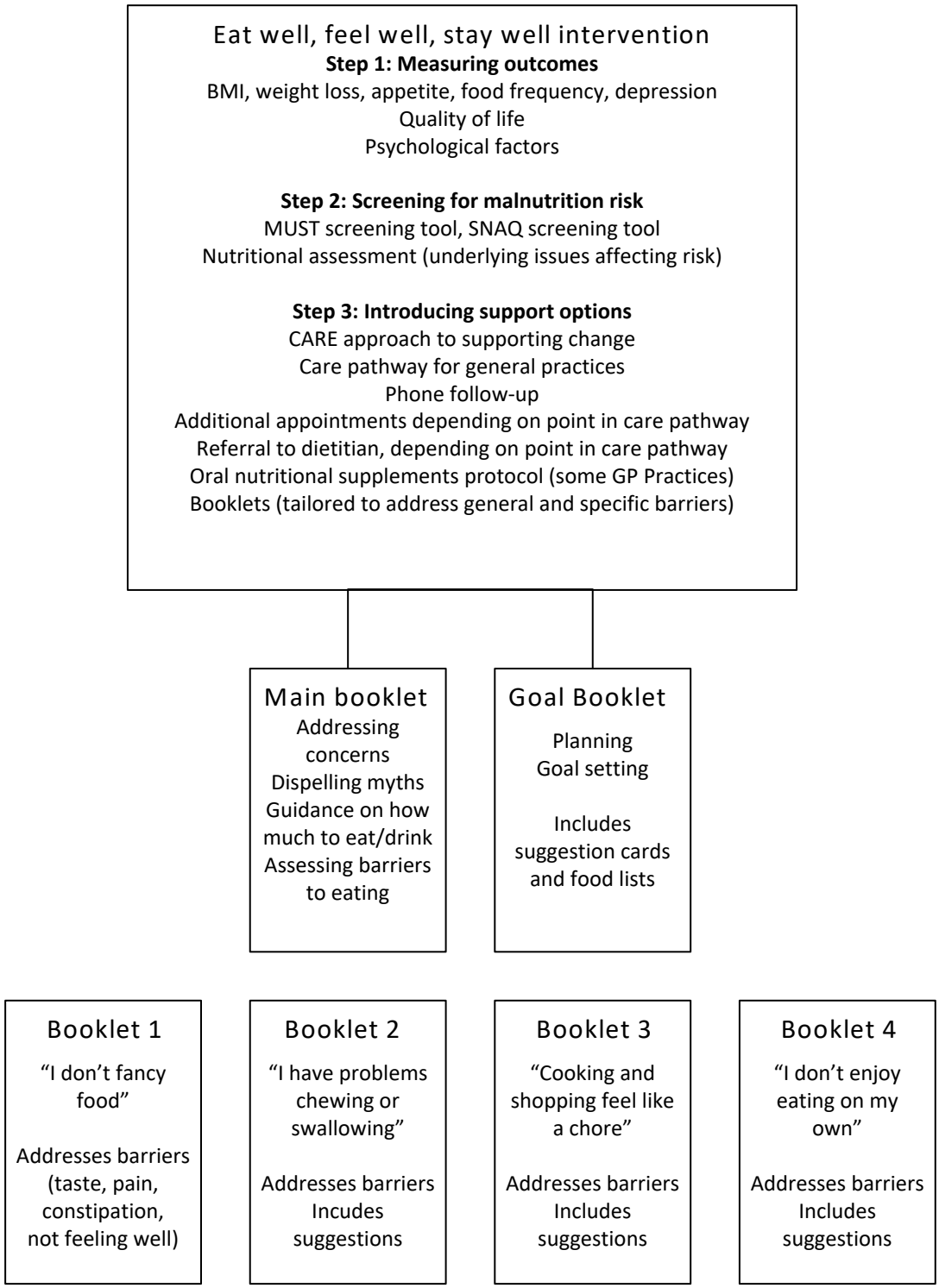
18. Appendix A: Eat well, feel well, stay well Intervention Outline



19. Appendix B: Findings from feasibility study that informed this randomised controlled trial

In terms of the feasibility of identifying higher risk individuals we wrote to nearly 3500 patients over the age of 65 with comorbidities likely to increase nutritional risk; nearly 1300 replied; and more than 500 were eligible and consented i.e. 20% of individuals approached with a 'cold calling' intervention are likely to agree to take part. 80% of those invited for screening attended screening, CRN nurses have carried out blinded follow up measures with 135/150 patients (90%) randomly selected from participants who are due to complete follow-up, and seven month follow-up questionnaires were received from 137 of a planned 150 patients (91%). Therefore, the protocol is not only feasible but provides high consent, high uptake of screening, and high follow-up rates. However, only 8% of the sample were 'proxy' MUST positive (see above), and the proxy MUST questionnaire performed poorly in identifying individuals who were MUST positive as measured by the nurse (sensitivity and positive predictive value both approximately 50%). MUST positive individuals were also not common (8%), and very few individuals who were MUST positive scored more than 1 (i.e. very few would be eligible for ONS supplementation based on current protocols).

However, poor appetite as measured by the SNAQ questionnaire was much more common (20%). Since SNAQ has been used effectively in community settings to predict weight loss we therefore propose using the SNAQ questionnaire to identify individuals at high risk.

We originally proposed two intervention groups, one comprising dietary advice alone and one with targeted ONS for intercurrent illness. The feasibility testing is ongoing, so we may find more individuals who would be eligible for ONS under current guidance, but it seems unlikely that there will be enough individuals requiring ONS to justify two intervention groups.

We therefore propose a single intervention group where individuals at risk will be invited to screening based on: 1) a low SNAQ score or who report losing 5Kg unintentionally, and 2) have an estimated BMI less than 25 (since with normal weight are at less risk of poor outcomes (Newman et al., 2001)). Those screened will be given assessment and dietary support; those individuals who are eligible for ONS are also offered ONS for intercurrent illness initially as in the original proposal.

In terms of outcomes, SNAQ identifies a group of individuals likely to get more infections, so reasonable to assume that the intervention could reduce intercurrent illness and potentially, attendance at the GP and hospital admissions. 10-20% see the GP each year (Millett, Quint, Smeeth, Daniel, & Thomas, 2013), but the number of respiratory tract infections individuals experience where they do not see the GP is much more common – in total with around 70% of our target population reporting one or more infections in a 4 month winter period (P. Little et al., 2015). Infections are not only likely to be reduced by improving nutrition, but they are very disruptive to normal life, and they are also associated with much more important longer-term effects –

particularly cognitive decline in the elderly. Cognitive decline occurs both following severe infections (Annane & Sharshar, 2015) but also following upper respiratory infections (Bucks et al., 2008), and is probably mediated by systemic inflammatory processes (Cunningham et al., 2009).

We have evidence for the relationship between low SNAQ scores (our primary screening tool) and QOL, supporting the use of QOL measures. Thus we have maintained QOL as one of our primary outcomes, but specified a slightly lower effect size than we specified in our original application. The rationale for infections as a co-primary outcome is not just that infections are one of the key determinants of deterioration in the elderly – particularly for cognitive decline – but that we have evidence that low SNAQ scores are likely to predict the incidence of subsequent infections.

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