STUDY PROTOCOL

ELDER

STUDY

Short title: ELDER

Full Title: Improving the oral hEalth of oLder aDults using milk supplEmented with fluoRide and probiotics: An interventional feasibility study and pilot RCT

Final V1.4, Date 20 September 2022

Sponsor reference number	35835071
Funder reference number	2021-280
IRAS Project ID	316798
REC reference	

Protocol Development and Authorisation

Protocol Contributors	
The following people have contributed to design the ELDER Study protocol	
Name	Affiliation and Role
Vida Zohoori	Teesside University, Chief Investigator
Sherley John	Teesside University, Principal Investigator
Caroline Orr	Teesside University, Trial Microbiologist
Claudio Angione	Teesside University, Trial Data Analyst
Alan Batterham	Teesside University, Trial Statistician
Louise Jones	ENRICH - NIHR North East North Cumbria, Trial Advisor

Protocol Amendment History				
The following amendments and/or changes have been made to the ELDER Study protocol since the implementation of the first approved version				
Amendment No.	Protocol Version no.	Date issued	Author(s) revising the changes	Details of changes made
	.			

CI and Sponsor authorisation	
This protocol has been approved by:	
Chief Investigator	
Name	Prof. Vida Zohoori
Signature	
Date	(dd-mm-yyyy)
Sponsor approval	
Sponsor representative name	
Signature	
Date	(dd-mm-yyyy)

General Information This protocol describes the ELDER trial and provides information about the procedures for entering participants into the trial. The protocol should not be used as a guide or as an aide-memoire for the treatment/care of other patients/participants. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the care home managers at each trial site. Still, centres entering participants for the first time are advised to contact the clinical trial coordinator in the coordinating centre to confirm that they have the most up-to-date version of the protocol in their possession. Problems relating to the trial should be referred to the coordinating centre in the first instance.

Compliance This study will adhere to the conditions and principles outlined in the EU Directive 2001/20/EC, EU Directive 2005/28/EC and the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95). It will be conducted in compliance with the protocol, the UK Policy Framework for Health and Social Care Research, General Data Protection Regulation (GDPR) and Data Protection Act, 2018, Human Tissue Act 2004 and other regulatory requirements as appropriate.

Funding The ELDER trial is being funded by the Eklund Foundation for Odontological Research and Education, an organisation established to support international research and education in Dentistry.

This study is included in the NIHR CRN portfolio and therefore is supported by NIHR CRN North East and North Cumbria Network.

Administrative Information

Contact Details: Chief Investigator & Co-Investigators

Chief Investigator	
Vida Zohoori School of Health and Life Sciences Teesside University Middlesbrough United Kingdom	Professor in Public Health and Nutrition Director of the Centre for Public Health Research V.Zohoori@tees.ac.uk

Co-Investigators (Named Funding Applicants)	
Alan Batterham School of Health and Life Sciences Teesside University Middlesbrough United Kingdom	Professor of Health Science A.Batterham@tees.ac.uk
Caroline Orr School of Health and Life Sciences Teesside University Middlesbrough United Kingdom	Associate Professor (Research) in Microbiology C.Orr@tees.ac.uk
Christina Stecken-Blicks Faculty of Medicine Umea University Sweden	Professor in Paediatric Dentistry christina.stecksen-blicks@umu.se
Svante Twetman Department of Odontology University of Copenhagen Denmark	Professor in Odontology stwe@sund.ku.dk

Trial Data Analyst	
Dr Claudio Angione School of Computing, Engineering & Digital Technologies Teesside University Middlesbrough	Professor (Research) c.angione@tees.ac.uk

United Kingdom	

Contact Details: Trial Team

Teesside University (Trial Sponsor & Coordinating Centre)	
Principle Investigator & Clinical Trial Coordinator	
Sherley John School of Health and Life Sciences Teesside University Middlesbrough United Kingdom	Research Associate S.John@tees.ac.uk t. 01642 738328 | m. 0740987008
Trial Advisor	
Louise Jones Northumbria Healthcare NHS Foundation Trust Newcastle United Kingdom	Lead Community Research Nurse louise.jones@northumbria-healthcare.nhs.uk t. 01670 859042

CRN NIHR (North East North Cumbria)	
Lead Delivery Team Members	
Alex Ramshaw	Direct Delivery Team Lead LCRN North East and North Cumbria Core Team NIHR Clinical Research Network (CRN) alex.ramshaw@nihr.ac.uk m. 07759134490
Jill Deane NIHR LCRN North East North Cumbria	Senior Research Nurse – Team Lead (Primary Care) LCRN North East and North Cumbria Core Team NIHR Clinical Research Network (CRN) jill.deane@nihr.ac.uk/jill.deane2@nhs.net m.07824537347
Delivery Staff	
Delivery staff includes Clinical Trial Assistants and Research nurses assigned from the local NHS Primary Care Team (PCT) and Direct Delivery Team (DDT) - LCRN who would collaboratively support the ELDER trial.	

General queries and for the supply of trial documentation, please contact the Clinical Trial Coordinator

Clinical queries:

Clinical queries
All clinical queries should be directed to the Clinical Trial Coordinator who will direct the query to the most appropriate clinical person.

Trial Documentation:

Trial reporting
ELDER Monthly record will be complemented by trial staff and copies should be emailed to the below trial specific email address:
ELDER@tees.ac.uk

Serious Adverse Events:

SAR reporting
SAEs will be reported by the RN on the ELDER Monthly Record

Where an adverse event meets the definition of a SAR the Clinical Trial Coordinator should be informed immediately, and a SAR form should be completed by the responsible person and emailed to the ELDER Trial email address
(See section 10.5 for more details).

Email: ELDER@tees.ac.uk
Mobile number: 07404 987008

Abbreviations

Term	Description
AE	Adverse Event
AR	Adverse Reaction
CH	Care Home
CHR	Care Home Resident(s)
CI	Chief Investigator
CRF	Case Report Form
CRN	Clinical Research Network
CTC	Clinical Trials Coordinator
CTIMP	Clinical Trial of an Investigational Medicinal Product
CQC	Care Quality Commission
DDT	Direct Delivery Team
DMC	Data Monitoring Committee
ENRICH	EmbeddiNg Research In Care Homes
GCP	Good Clinical Practise
ICF	Informed Consent Form
MAR	Medication Administration Record
MUST	Managing Undernutrition South Tees
NIHR	National Institute of Health Research
PCT	Primary Care Team
PI	Principle Investigator
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
PRCL	Primary Root Caries Lesion
RCT	Randomised Control Trial
REC	Research Ethics Committee
RN	Research Nurse
SAE	Serious Adverse Event
SAR	Serious Adverse Event
SIV	Site Initiation Visit

TMF	Trial Master File
TSC	Trial Site Coordinator

‡NB The terms will be used interchangeably throughout the document: Wherever the term clinical study is used, it shall be referred to as 'trial' or 'study'; similarly, the reference to Teesside University is used herein as 'coordinating centre' or 'sponsor organisation'; likewise, the reference to the trial team is used therein as 'trial staff' or 'research member'.

TRIAL SUMMARY

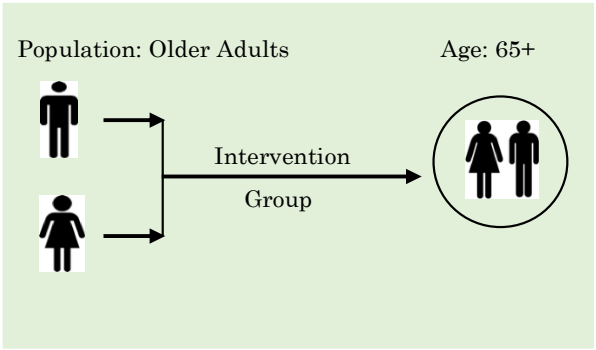
Title	**Improving the oral health of older adults using milk supplemented with fluoride and probiotics: An interventional feasibility study and pilot RCT**
Acronym	ELDER
Short title	ELDER
Trial configuration	Multi-centre, open-label, parallel-group, four-arm, prospective, cluster-randomised, placebo-controlled feasibility trial
Trial setting	Care homes in TeesValley (residential, nursing, mixed)
Planned sample size	240 participants
Eligibility criteria	**Care Home (cluster level) criteria:** ***Inclusions*** • Site: Tees Valley care homes for older people, with, without nursing or mixed • Size: ≥ 5 resident beds in the care home in total with mental capacity ***Exclusions*** • Care homes not located within the Tees Valley region • Care homes with inadequate resident capacity where there are < 5 beds in total **Care Home Resident criteria at trial entry:** ***Inclusions*** • Full-time resident in a care home • Age ≥ 65 years

	• No acute or immunocompromised medical condition • Able to give informed consent for participation • Tolerance for dairy products ***Exclusions*** • Residents who are receiving planned respite or end-of-life or palliative care • Residents who are < 65 years of age • Residents with any immunocompromised medical conditions • Residents who lack the mental capacity to provide informed consent • Residents who are currently taking/being prescribed regular probiotics • Residents with severe lactose intolerance • Residents who do not have a working level of oral English
Follow-up duration	The recruitment window will be open for three months from the official trial start date, and the follow-up schedule will begin from the time the participant gives written informed consent and would from then depend on the length of time the participant remains active in the trial. Participants will have a baseline assessment and endpoint assessment after nine months.
Planned trial period	The participants to drink milk supplemented with fluoride or probiotics or a placebo for nine months or until 30/12/23, whichever is sooner.
Trial Objectives	1. To evaluate the effect of milk supplemented with probiotics and/or fluoride on primary root caries lesions (PRCL) 2. To record rates of recruitment, retention, and completion. 3. To estimate variability for the potential outcome measures to inform sample size planning for a definitive trial
Trial Outcome	**Primary Endpoint**: 1. Acceptability of the supplemented milk and compliance with the intervention program

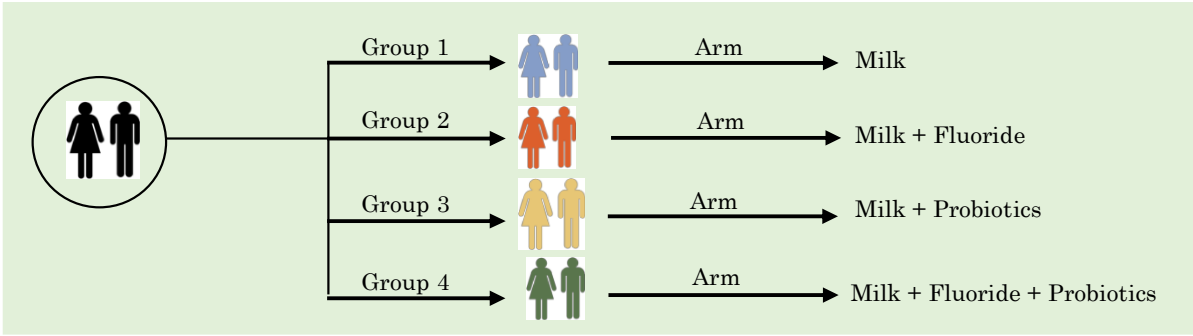
	2. Potential clinical dental results of the intervention, including root caries and gingival inflammation 3. Bacterial counts in saliva and plaque at baseline and over a subsequent 9-month period **Secondary Endpoint**: 1. Frequencies of infection 2. Use of antibiotics and unscheduled pain killers 3. Urgent care appointments (medical/dental) over the 9-month period of intervention
Description of Intervention	This intervention will include: Administration of the study product once daily for five days a week – milk supplemented with probiotics and/or fluoride or matching placebo for nine months or until 30/12/23, whichever is sooner

WORK FLOW DIAGRAM

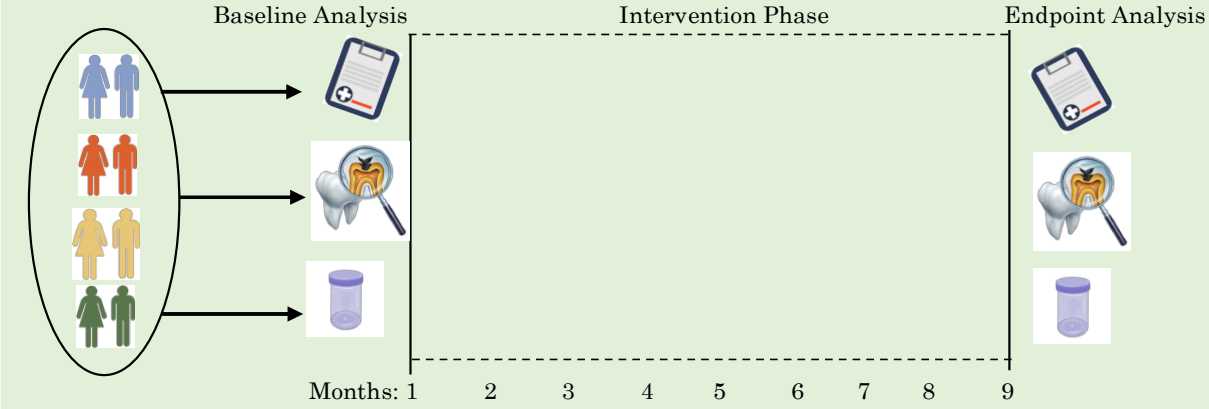
Recruitment



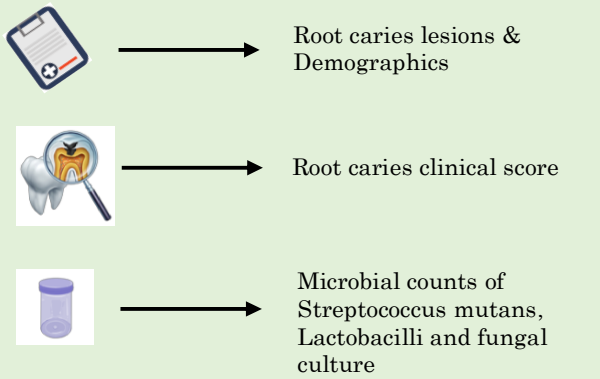
Intervention



Data Collection



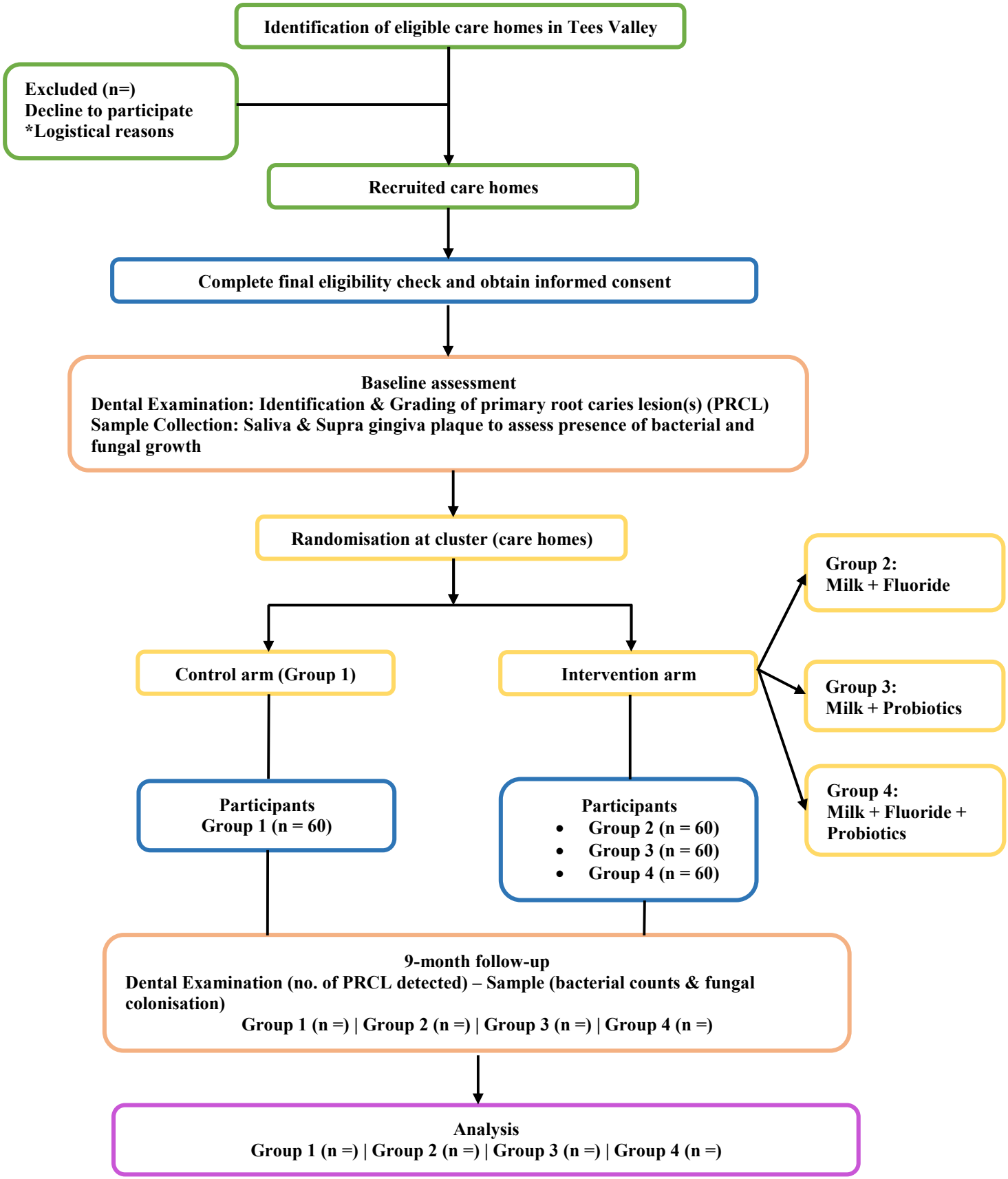
Data Analysis



Key

Medical and Dental records; Oral Examination; Saliva (Whole &/or oral swab) &/or Supragingival Plaque

PARTICIPANT FLOW DIAGRAM



*Care home staff, or managers did not respond to calls or emails/were too busy

1. INTRODUCTION

1.1 Background

Globally, ageing populations present significant public health implications, with non-communicable diseases (NCDs) becoming the leading causes of disability and mortality. Oral diseases are among the most common and preventable NCDs, resulting in inadequate nutritional intake, deteriorating quality of life, and the subsequent impact on longevity (1).

Data from extensive cohort studies on the oral health of older adults (2) depicts a worrying situation, with dental caries (tooth decay) persisting as a significant problem. The National Institute for Health and Care Excellence (NICE) guidance on oral health identified dental caries as a significant problem, particularly among older people in the UK (3).

The James Lind Alliance Priority Setting Partnership (4) listed "*prevention of tooth decay & reducing oral health inequalities at a community level* " and "*better oral care for the prevention/management of health conditions (e.g. malnutrition/chest infection)"* among their top 10 "Oral and Dental Health" priorities.

A NICE research recommendation is to explore "*community-based interventions, which are effective and cost-effective in improving oral health and reducing oral health inequalities among groups of adults at high risk of poor oral health*", including interventions to increase fluoride exposure (3).

Although fluoride remains the most effective and economic protective agent against dental caries, its effectiveness is boosted when combined with other anti-caries agents such as probiotics offering general health as well as cost-saving benefits (5).

Cow's milk is a nutritious drink, providing a good source of protein and micronutrients and contributing to optimal hydration (6). Due to its low potential for caries generation, milk has been recommended as a convenient and cost-effective vehicle for delivering fluoride to older people residing in the community (7).

Providing milk supplemented with fluoride and/or probiotics (S-milk) could offer a potentially cost-effective method for caries prevention in older adults, particularly those living in care homes.

1.2 Trial Rationale

There are currently 12.4 million people aged ≥65y in the UK; a figure projected to increase to 16.5 million by 2039 (8). Improvement in the oral health of adults over the last 40 years has resulted in the number of people retaining at least some natural teeth into old age increasing dramatically over this period. The UK Adult Dental Health Survey (9) showed that almost 78% of those aged ≥65y in England retained some natural teeth in 2009, compared with only 22% in 1978. However, the prevalence and incidence of dental caries in older adults have increased during the same period (9). In England, at least 1.8 million people aged ≥65 have an urgent dental condition, a number expected to increase to 2.7 million by 2040 (10). In addition, there are marked inequalities in oral health in England across this population, both by geography and by deprivation. Aside from the impact of poor oral health on older individuals' ability to eat, speak and socialise, poor oral health is also associated with other health conditions, including malnutrition and pneumonia (1), particularly in settings such as care homes.

Dental treatment for older people is complicated by co-morbidities and potential lack of access to usual dental care. This growing problem will consequently have significant financial repercussions for the

NHS. There is, therefore, a real and urgent need to find feasible and cost-effective population-based oral health preventive measures for older people.

Although the role of fluoride in preventing carious lesions has been well established (11), implementation of an effective individual- or community-based fluoride preventive measures has not occurred. Whilst effective professionally-applied interventions to prevent dental caries in older adults exist, there are significant barriers to their provision, particularly for care home residents (12). Furthermore, adults residing in care homes are often not supported with personal oral health care, including tooth brushing with fluoride toothpaste (13), and there are significant barriers to addressing this (14), including the need for carers to develop appropriate skills.

Whilst S-milk would address many of the concerns, the efficacy of any programme will depend on the practicalities around the provision and the feasibility, acceptability, and cost-effectiveness of the programme to key stakeholders. Our research will explore S-milk as a community-based oral health intervention to reduce inequalities among groups of older adults at high risk of poor oral health in geographical areas with the highest disease burden (North of England).

1.3 Existing studies and the research gap

Milk supplemented with fluoride has been shown to be effective with reductions in dental caries reported in all studies included in two systematic reviews (7, 15). However, the majority of these studies have focused on children.

Although the effect of probiotics on systemic health and medical disorders has been described (16), evidence for the caries preventive effect is more recent. Eight randomised controlled trials (RCTs) with dental caries as a primary outcome have been reported (17), of which four (18-21) used cow's milk as a vehicle for the provision of probiotics. These four RCTs reported a reduction of caries in the groups given milk supplemented with probiotics. Moreover, milk supplemented with both fluoride and probiotics was more effective than milk supplemented solely with either (20, 21). In older people (58-84yr) residing in the community, a daily intake of milk supplemented with fluoride and probiotic was effective at reversing primary root caries lesions over a 15-month period (21).

Additionally, studies have shown reduced frequencies of other health concerns in groups receiving milk supplemented with probiotics, such as middle ear infection (20), mouth thrush (22) and acute upper respiratory tract infections (23).

In addition to these benefits, milk is a good vehicle for introducing fluoride and/or probiotics in care homes, as it is included in guidelines as part of a healthier diet for older adults in care homes (24). However, studies have shown that the future success of a new food product depends on several factors, including consumer socio-demographics and motivations (e.g. health benefits) (25). It is therefore essential that older people are, first, accepting of S-milk

2. Aims, Objectives, and Outcome Measure

2.1 Hypothesis

1) Milk is an efficient, acceptable, and feasible vehicle to deliver fluoride and probiotics on a community basis.
2) Milk supplemented with fluoride and probiotics is more effective than milk supplemented with either fluoride or probiotics in improving the oral health of older adults.

2.2 Aim

This study aims to explore whether milk supplemented with fluoride and/or probiotics is sufficiently efficient, acceptable, and feasible to improve the oral health of older adults living in care homes.

2.3 Objectives

1) To evaluate the effect of milk supplemented with probiotics and/or fluoride on primary root caries lesions (PRCL)
2) To record rates of recruitment, retention, and completion.
3) To estimate variability for the potential outcome measures to inform sample size planning for a definitive trial.

2.4 Outcome Measures

The primary endpoints will be:

i. Acceptability of the supplemented milk and compliance with the intervention programme
ii. Potential clinical dental results of the intervention, including root caries and gingival inflammation
iii. Bacterial and fungal counts in saliva and supragingival plaque at baseline and over a subsequent 9-month period

The secondary endpoints will be:

i. Frequencies of infection
1. Use of antibiotics and unscheduled pain killers
2. Urgent care appointments (medical/dental) over the 9-month period of intervention

3. Trial Design

It is a multi-centre, open-label, parallel-group, four-arm, prospective, cluster-randomised, placebo-controlled pilot trial aiming to recruit at least 240 Care Home Residents (CHR). A cluster randomised trial is required, as an individually randomised trial would be subject to the threat of contamination (unintentional drop out and drop in across treatment arms due to mixing up milk) and managing four different kinds of milk within a single care home would be infeasible.

4. Trial Site Identification and Selection

Adult residential care homes and nursing homes registered for old age located in Tees Valley will be recruited for the trial. Initial scoping for ideal trial sites was done by screening the LCRN-NIHR ENRICH database system and from the local council and support sectors such as MUST using their contacts and email lists of care home registers and by engaging with commissioning groups within the local care home provider forum. An easy-read two-way question and answer format explaining the study background was prepared in simple English and circulated to all potential care home staff identified through this multiple ascertainment method, and depending on the area (case-by-case bases), a short drop-in session was organised. The potential care home managers, members from the regional care home forum, the commissioning team from the local council, and members from the Care Quality Commission (CQC) were invited and presented an opportunity to ask questions to the research team. The CTC and CI chaired and attended these sessions. These meetings thus informed the research team

of the possible uptake of care homes interested in the study. A site-identification list was prepared for CTC to contact potential trial sites individually and confirm participation. The care homes will also be identified through posters and media promotion of the trial using local council portals to increase study visibility and uptake within the regional care home sector.

The feasibility study will be undertaken in care homes across Tees Valley, which have provided consent to participate. In order to achieve the overall estimated sample size for the study, we aim to recruit care homes with an average of ten residents or five residents in each sister care home if they belong to the same chain of care homes. A minimum of four and a maximum of fifteen participants will be recruited at each care home.

The CI and CTC running the study will identify suitable care homes to take part in the trial. The specific inclusion and exclusion criteria for care home selection will be:

Care Home (cluster level) criteria:

Inclusions

- Site: Tees Valley care homes for older people, with- or without nursing or mixed
- Size: ≥ 5 resident beds in the care home in total with mental capacity

Exclusions

- Care homes not located within the Tees Valley region
- Care homes with inadequate resident capacity where there are < 5 beds in total

5. Trial Population

Care home residents in Tees Valley region of North East England. The residents (individual level) will be eligible to participate if they meet all of the inclusion criteria and may not enter the trial if any of the exclusion criteria listed apply.

Inclusion criteria

- Full-time resident in a care home
- Age ≥ 65 years
- No acute or immunocompromised medical condition
- Able to give informed consent for participation
- Tolerance for dairy products

Exclusion criteria

- Residents who are receiving planned respite (temporary care home resident) or end-of-life or palliative care
- Residents who are < 65 years of age
- Residents with any immunocompromised medical condition
- Residents who lack the mental capacity to provide informed consent
- Residents who are currently taking/being prescribed regular probiotics
- Residents with severe lactose intolerance
- Residents who do not have a working level of oral English

6. Enrolment and Randomisation

6.1 Enrolment

6.1.1 Recruitment Strategy through Middlesbrough and Redcar Care Home Commissioning Group (CHCCG)

To design the recruitment protocol of the study, initial Patient and Public Involvement (PPI) meetings have been undertaken within Middlesbrough and Redcar care home forums to determine the most appropriate and person-centred recruitment method for the care home staff and residents. These discussions occurred during early stakeholder engagement with care home managers and care home staff, who will be potential recruiters for the study. The meeting(s) addressed common research challenges encountered in care homes. Most of the strategies that have emerged were around methodological approaches and innovative approaches that could be implemented to reduce the loss to follow-up of potential recruits given the duration of the intervention phase. The strategies proposed were incorporated to co-design a workable protocol that could be embedded within the residential care plan of the residents without disrupting the care home organisational culture.

6.1.2 Recruitment Process

Trial recruitment for the ELDER Study will be a two-step process. The first step will be the recruitment of care homes. The trial staff (any team member listed) will contact eligible care homes (by email/phone/in-person) from the 'site identification list' generated to explain the study in detail, answer any outstanding questions about it, and invite them to participate. Potential care homes will be given at least three days to discuss the study to decide whether or not they wish to take part. A trial team member will contact eligible care homes again to confirm whether they would like to take part in the trial.

The second step of the recruitment process is recruiting eligible residents for the trial. Eligibility will be determined by a screening process undertaken in two stages. The first stage will be the identification of potentially eligible CHR. The care home managers (or their staff) will screen through the personal information stored in the care home records to identify those CHR who are eligible to join the trial as only they would have access to care home records. Once an initial eligibility check is completed at this stage, a member of the trial staff will complete the screening log, and the worksheet will be sent to the coordinating centre for review (please refer to section 6.2 for a detailed description of the contents included in the screening log). Care Home staff, will also assist with giving out trial information within the care home and liaise with the ELDER trial team to arrange appointments for a member of the trial staff to discuss the trial with them and obtain informed consent.

Potential eligible residents will be given the Participant Information Sheet (PIS) to read. The eligible resident will be given up to a week to decide whether they are interested in participating or not.

A member of the trial team will then be assigned to undertake the next phase (stage two).

In stage two, an informed consent discussion will take place with a member of the ELDER research team. After the allotted week, a research member will approach the resident to ask about their willingness to participate in the trial. If interested, the resident will complete the Informed Consent Form (ICF) for the pilot study.

Since only CHR with a capacity to consent will be recruited to the trial, the number of residents in many care homes in Tees Valley will be excluded; therefore, this would mean that in most care homes, as the upper limit is 15 CHR per care home, the trial team members will invite all eligible residents for participation in the study. In the case of care homes with larger capacity, then a sample of potentially eligible participants will be randomly selected by the trial team to be invited for participation to meet the aforementioned target figure.

6.1.3 Rationale for recruitment method

Due to the long-term follow-up period of the ELDER study and the potential vulnerability of the study population, there is a need to design a robust and structured recruitment methodology. Research in care homes, when compared with ageing research overall, remains relatively undeveloped, owing largely to barriers encountered during recruitment. The recruitment approach should, therefore, be tailored to this setting, and such an approach should recognise that the care home is a resident's home and the importance of a residential care plan as this is a careful construction of a resident's daily routine which when disrupted minimises participation (26-28). The ELDER study, therefore, acknowledges the significance of care home organisational culture and uses a person-centred recruitment method. The initial recruitment will be done by a member of the resident's direct care team, which allows the care home staff the flexibility to use their professional judgement as they know which of their residents to approach about participation. Moreover, the two-step recruitment approach allows the trial team to give the residents more information after already being aware of the research presented to them by their care provider. This also provides the option for the residents to ask questions at different times and consider their participation over a period of time, again an approach based on person-centredness.

6.2 Pre-Screening and Enrolment log

The coordinating centre will keep a comprehensive list of the following for each trial site

- number of residents who are ineligible and eligible to participate in the trial
- number of eligible residents who agree and disagree to participate
- number of residents approached and not yet approached about the trial

The screening log will enable the trial team to gather information on the recruitment process in different trial sites and detect biases, if any.

6.3 Informed Consent

The consent process is two-part - at the care home level and at the individual participant level - with both parts occurring before the randomisation of care homes to arms.

For care homes, the aforementioned recruitment process also describes the stages of informed consent. If the care home managers or staffs require more information regarding the trial, they will be provided with the study protocol and relevant literature evidence. No specific consent form will be provided to the care home staff if they consent to their care home to participate in the trial, as the protocol and study documents (refer to section 7) are legally binding documents.

Following a care home recruitment into the study, all potentially eligible residents will be fully informed about the trial through a participant information sheet supplemented with verbal explanations. A member of the ELDER research team delegated the responsibility to take consent will ensure that they adequately explain: the aim of the study, what it will involve for the participant; anticipated benefits; potential side effects of taking the study products and clarify any issue they may

be unclear about. They will also stress that participation is voluntary. The resident is free to decline participation and may withdraw from the trial at any time for any reason without prejudice to future care and with no obligation to give the reason for withdrawal. In care homes with residents who cannot read or write or where English is not their first language but can understand and speak English, information sheets can be read to them. The potential participant will be given time to consider the trial information and discuss their participation with others (i.e., family members if they wish). The potential participant will be given the opportunity to ask questions throughout the process.
Written informed consent will then be obtained by means of the participant's dated signature and countersigned by the person who presented and obtained the ICF. A copy of the fully signed ICF will be catalogued within the local care home trial site file, and a copy will be provided to the participant. The original signed form will be retained at the coordinating centre. Contact details of the trial team will be provided to participants/personal legal representatives should they have any questions about their ongoing participation in the trial.
Once consent has been obtained, a History Record Sheet will be filed to trace trial activity. Ideally, this would include the date of discussion, the name of the trial, a summary of the discussion, the version number of the PIS given to the participant, a copy of the signed ICF, and the date of consent received. This Sheet will be completed and periodically updated by the trial team.

Verbal consent: In the event that a resident is unable to make a mark or sign for themselves, verbal consent will be taken, and a senior care home staff member may attest to the ICF on their behalf. A member of the trial team, ideally the person who presents and explains the study, will witness, sign and date the ICF to approve that consent has been given.

Consent procedure for new residents: In case of new residents joining the care home prior to randomisation will still be considered potential participants if they meet the study eligibility criteria. Following eligibility confirmation by the care home staff, a research team member will follow the same process as described above to obtain informed consent.

6.4 Randomisation

The unit of randomisation is the care home (cluster). The care homes will be randomised based on a 1:1 ratio to each available intervention arm or control arm. Trial staff at each trial site will inform the coordinating centre when there are four eligible care homes as they will be randomised in a set of four or six if two sister care homes belonging to the same chain are recruited. As the unit of randomisation is a care home, and the number of participants in each care home is expected to vary, blocking will be used to ensure a close balance of the number of participants (and not necessarily care homes) assigned to each arm. The allocation for a particular trial site will only be revealed after gaining informed consent (i.e., both at the care home level and the individual participant level) and baseline data collection. This approach reduces the threat of post-randomisation selection bias in cluster trials, as individual participants consent to be randomised to one of the four arms rather than being told which arm they have been allocated to if consent is only sought at the level of the care home.

6.5 Blinding and concealment

As the ELDER trial is an open-label study, the participants, care home staff, and trial team (including the trial statistician and RNs conducting all assessments) will not be blinded to intervention assignment

due to the nature of the trial procedure. However, the dentist performing the baseline and follow-up dental examination will be blinded to intervention and outcome assignment. Release of allocation only following enrolment, resident consent, baseline data collection, and dynamic randomisation of care homes using minimisation will ensure allocation concealment.

7. Site set-up

Teesside University, which is coordinating the trial, will identify suitable care homes to take part in the trial. Each or a group (if they are a chain of care homes under single management or large care homes with one or more sister care homes or care home(s) contained within a regional sector) will have appropriately trained GCP delivery staff assigned either from the DDT or PCT from NIHR-LCRN. Each delivery staff will be responsible for the research activity and the participants within care homes for their assigned region(s).

Before setting up the study in care homes, the care home manager will be approached to obtain permission for the care home to take part in the trial and for all CHR to be approached about the trial. Care home staff will be required to complete a 15-minute trial training session with the PI or any member of the trial team before carrying out any research within their care home. Care home staff will help identify those CHR who are potentially eligible to join the trial, assist with giving out trial information within their care home, and liaise with either the site or trial coordinator to arrange appointments for the delivery staff team to discuss the trial with the residents and obtain informed consent.

The senior care home/nursing staff member will ensure that the coordinating centre has received the following documents

- Site-specific Non-Commercial Organisation Information Document (Care home agreement)
- Completed signature list and roles and responsibilities document
- Completed contacts list of all site personnel working on the trial

Upon receiving all of the essential document packages, the coordinating centre sends the Regulatory Greenlight Approval Letter to the care home lead detailing that the care home is now ready to recruit participants for the trial. The coordinating centre will also provide each care home with a site file, in which the confirmation letter and all participant-facing documents will be filed. The care home will also provide all documents required to recruit a participant for the ELDER trial and other trial supplies.

8. Trial Intervention

The consented care homes will be assigned randomly to one of the study arms: - (a) Group 1: non-supplemented milk (placebo), (b) Group 2: milk supplemented with fluoride (5.0 mg F/l), (c) Group 3: milk supplemented with probiotics (Lactobacillus), and (d) Group 4: milk supplemented with fluoride and probiotics. All subjects will be asked to drink a glass of plain/supplemented milk once daily, five days a week, for nine months. Fluoridated milk or probiotics, or placebo (referred to as the Study product) will be administered by the resident's routine caregiver during medicinal/meal rounds. The study product will be sourced from the manufacturer and transported to the study site. Fluoridated milk will be distributed in a small carton, and the probiotics will be provided as a powder in sealed sachets. The preferred route of administration is as follows:

1. The carton containing fluoridated milk is to be emptied into a tall glass and then consumed.

2. The probiotic powder is to be dispensed in a spoon, then added to a prepared glass of skimmed milk/fluoridated milk, mixed well and then consumed

Each care home will be provided with the manufacturer's dossier detailing the composition of the probiotic form and fluoridated milk. After allocation, probiotic sachets will be distributed to the care home at the beginning of the trial, whereas milk (both skimmed & fluoridated) will be distributed to the trial sites weekly. Participants admitted to the hospital would not be expected to continue taking the study product during their hospital stay.

8.1 Adherence

Data regarding participant's adherence to the study product will be collected from a number of sources:

- Consumption sheet*:* frequency/amount/quantity of a single glass of milk consumed by the participant will be recorded.
- Product count - the trial staff, will undertake regular counts of unused study products.

8.2 Acceptability and Compliance

A critical outcome is compliance with the intervention programme. We define compliance as consumption of the allocated milk on >50% of intervention days. This threshold approximates consuming the milk four in every seven days and is based on the implementation of milk fluoridation schemes in schools, where milk is provided only on school days which constitute approximately 53% of a calendar year. We define success with respect to compliance if 75% of the sample meets this criterion. Consumption of assigned milk will be assessed using a consumption sheet collected from the participants.

9. Trial Procedure

Care home staff involved in the trial will be trained in trial-specific procedures, including recording participant information and in delivering the study product to the participants. All study appointments will occur at the care home where the participant is a resident.

9.1 Data/Sample Collection and Assessment

Eligible participants will have an appointment arranged by their care home staff, at which informed consent will be obtained by the delegated research team member. The following data will be recorded, and samples collected from the trial participants:

- Oral examination: A clinical examination of the oral cavity will include the number of teeth with PRCL. The texture of the lesion will be assessed by visual and tactile examination and will be classified as an 'active' or 'inactive' lesion according to the Petersson and Baysan grading system (29-30). Any signs of gingival inflammation will also be recorded.
- Saliva: Given the age, most of the trial participants will present with a clinical condition called Xerostomia (dry mouth) that might result in their inability to provide an adequate quantity of saliva for microbial testing. Therefore, oral swab samples will be collected by swabbing the buccal mucosa and the anterior floor of the mouth under the tongue. However, from a subset of participants, in addition to an oral swab, whole stimulated saliva will be collected. The latter sample is not mandatory and will only be collected from participants willing to provide this additional specimen.

- Plaque: Supragingival plaque will be collected from a proportion of the teeth diagnosed and graded for PRCL. A sterile interdental brush will be used to scrape plaque from the tooth surface. The collection of supragingival plaque specimens is not mandatory, and a participant deciding not to provide this specimen will still be recruited to the trial.

Those participants with complete tooth loss (edentulous) will only provide saliva samples.

All samples of saliva collected will be cultivated at 37^{O}C for 48h and 96h to measure bacterial and fungal growth. All oral examination, recordings and biological sample collection will be performed by a senior dentist both at baseline and after a subsequent follow-up period of 9 months. A dental hygienist will also be present (not necessarily at all sites) to assist with data collection. The dental examiner, after completing the oral examination, will give these to the trial staff delegated to the respective trial site. The dental assessment will be recorded in a specifically designed record sheet which will be sent to the coordinating centre periodically after completion. All samples/data will be labelled with participant study ID before being sent to the coordinating centre for filling/storage and analysis. Only the research team and laboratory staff at the coordinating centre will have access to trial specimens. The CTC will ensure that the storage, analysis, and disposal of all biological samples will meet the requirements of the Human Tissue Act, 2004. Data collected will be transferred to trial-specific password-protected Excel files with the help of the CTC for subsequent data analysis.

- Medical and dental records: Participants' medical and dental background data will be collected from the care home records and continuously updated during the course of the trial. The dental history collected will include but is not limited to the number of reported episodes of tooth pain, discomfort, sepsis, and unscheduled visits to a dental office. In addition, general medical information such as data on non-scheduled medical episodes, use of pain medication, data on the frequency, recency, and occurrence of bacterial or fungal infections, report of any common bowel problems, domiciliary visits, and hospital admissions will be recorded monthly by the delivery staff into the relevant trial form. The dentist or any member of the research team will collect this information at baseline and then after nine months.

9.2 Discontinuation of trial intervention and loss of follow-up

Each participant has the right to withdraw from any aspect of the trial at any time. The participant's care will not be affected at any time by declining to participate or withdrawing from the trial. A clear distinction must be made as to what aspect of the trial the participant is discontinuing from, for example:

- Discontinue from the entire trial and do not want any data or samples already collected relating to them to be used
- Discontinue from the trial, study product and all subsequent trial follow-up (sample collection and data collection), but data and samples already obtained up to this point can be used
- Discontinue from study product and all subsequent sample and questionnaire data collection, but happy for routine medical and dental data to be collected.

The reason for participant withdrawal will be detailed in a Case Report Form (CRF) and reviewed by the CI and independent committee. Any queries relating to the potential withdrawal of a participant should be forwarded to the coordinating centre immediately.

Apart from the participant's individual choice to withdraw from the study, the trial intervention will be terminated if the participant

- Tests positive for CV-19
- Prolonged hospitalisation for any medical or surgical reasons not otherwise diagnosed at the time of recruitment
- Experiences in unexpected series of adverse reactions to the study product

‡NB All data collected prior to withdrawal will not be deleted and will be included in the analysis on the condition that appropriate consent is in place. Routinely collected health data will still be obtained for use in the study unless the participant explicitly states otherwise.

10. Safety Assessment

10.1 General Definition

Adverse Event (AE)
Any untoward medical occurrence in a clinical trial subject which does not necessarily have a causal relationship with this treatment [Dir 2001/20/EC Art 2(m)]. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (ICH-E2D Guideline).

Serious Adverse Event (SAE)
In research other than CTIMPS, an SAE is any adverse event that a) Results in death; (b) Is life-threatening*; (c) Requires hospitalisation or prolongation of existing hospitalisation; (d) Results in persistent or significant disability or incapacity; (e) Consists of a congenital anomaly or birth defect or (f) Is otherwise considered medically significant by the investigator. [The Medicine for Human Use (Clinical Trials) Regulations (2004) as amended; and the Dir 2001/20/EC Art 2(o)]
*Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe (ICH-E2D Guideline).
An SAE occurring to a research participant should be reported to the REC where in the opinion of the CI, the event was:

- Related – that is, it resulted from the administration of any of the research procedures, and
- Unexpected – that is, the type of event is not listed in the protocol as an expected occurrence.

Therefore, the relatedness or unexpectedness of an event will be reviewed by the CI at each site and wherein the opinion of the CI, the SAE will be classed appropriately and reported to the main REC. For ease of recording and reporting, in this study, an SAE thought to be probably or certainly related to the study product will be referred to as a Serious Adverse Reaction (SAR).

10.2 Causality

This study uses the following instruction to assign causality to report SAE (31)

Relationship	Description
Unrelated	No evidence of any causal relationship between the AE and the trial medication/study intervention
Unlikely	Little evidence to suggest there is a causal relationship (e.g., the event did not occur within a reasonable time after administration of the study product) or there is another reasonable explanation for the event (e.g., the participant's clinical condition or other treatment).
Possible	There is some evidence to suggest a causal relationship with the study product (e.g., because the event occurs within a reasonable time after administration of the study product), but the influence of other factors may have also contributed to the event (e.g., the participant's clinical condition or other treatments).
Probable	There is evidence to suggest a causal relationship with the study product and that the influence of other factors is unlikely.
Definite	There is clear evidence to suggest a causal relationship with the study product and that other possible contributing factors can be ruled out.
Not Assessable	There is insufficient/incomplete evidence to make a clinical judgment of a causal relationship

10.3 Expectedness

It is expected that participants in the trial will have a range of underlying comorbidities; therefore, adverse events that are deemed expected for this population (see section 10.3.2) will not be reported. However, there may be pre-specified adverse events expected based on the manufacturing information and current evidence studies of the study product that should be recorded and reported. The procedure to report and the record are covered separately elsewhere in this document (see section 10.5).

10.3.1. Summary of current manufacturer's information

SACCO System's safety information sheet published in 2016 states that the probiotic product *Lactobacillus rhamnosus* is not hazardous and is well tolerated even among children aged 1-5 years. Rare cases of secondary infection have been reported in immunosuppressed patients, but since the trial excludes residents with any immune compromised medical condition, we, therefore, do not expect any adverse events based on the current manufacturer's information.

10.3.2. Summary of current literature

Following an extensive review of current literature and also based on the evidence published by a recent article (32) that critically appraised all probiotics used for oral health, we conclude that the

probiotics strain used in ELDER is generally safe and well tolerated among both infants and the elderly.
Minor gastrointestinal symptoms such as abdominal cramping, bloating, soft stools, flatulence, and taste disturbance have been reported (33). If these events were to occur, they would be classed as expected AEs and would be classed as unexpected if these events were to meet the definition of SAR.

10.4 Reporting Period

The adverse event reporting period for this study begins as soon as the resident provides informed consent and ends one month after the final data collection. The study products (probiotics and fluoridated milk) being used in this trial is a well-established food supplement, and given the frailty of the study population with a wide range of healthcare needs, it's critical not to cloud any true emerging safety signals by collecting unrelated data. Therefore, safety reporting in this study will focus on SAEs that could be related to the study population, and only SARs that could be related to the study product will be assessed for expectedness. The onset of any AE will be apparent particularly to care home staff, as they know their residents and their medical conditions thoroughly and so can quickly identify any deterioration to a resident's health very early. The care home staff will be informed of the pre-specified events that could be expected with the study.

10.5 Collecting and Reporting procedure

10.5.1 Adverse Events

Care home staff will report all events that meet the definition of an AE other than those events that do not require reporting (see section 10.6). The care home staff should manage those events excluded from reporting according to routine care home procedures. If an adverse event has occurred, the care home staff should inform the trial staff immediately or during the regular monthly data collection visit. The trial staff will collect and report the data directly into the CRF paper form specific for recording AEs (HRA/Non-CTIMP safety report to REC form) and into the ELDER Monthly Record.

10.5.2 Serious Adverse Events

All SAEs will be collected as part of a routine monthly follow-up (recorded by the trial staff on the ELDER Monthly Record under a separate subheading 'Further Comments – CRF Information' and into an SAE form (HRA/Non-CTIMP safety report to REC form) from the time of consent until the 9-month follow-up period). The delivery staff will discuss SAEs with a second delegated assessor (CTC from the coordinating centre) to confirm the causality classification (definitely, probably, possibly, unlikely, not related). The details of the second assessment will be reported on the ELDER Monthly Record under Further Comments – CRF Information. If the two assessors have assigned a different classification for an event assessed, then the highest category of causality (most likely to be related) will be selected, and the CI will confirm the assessment.

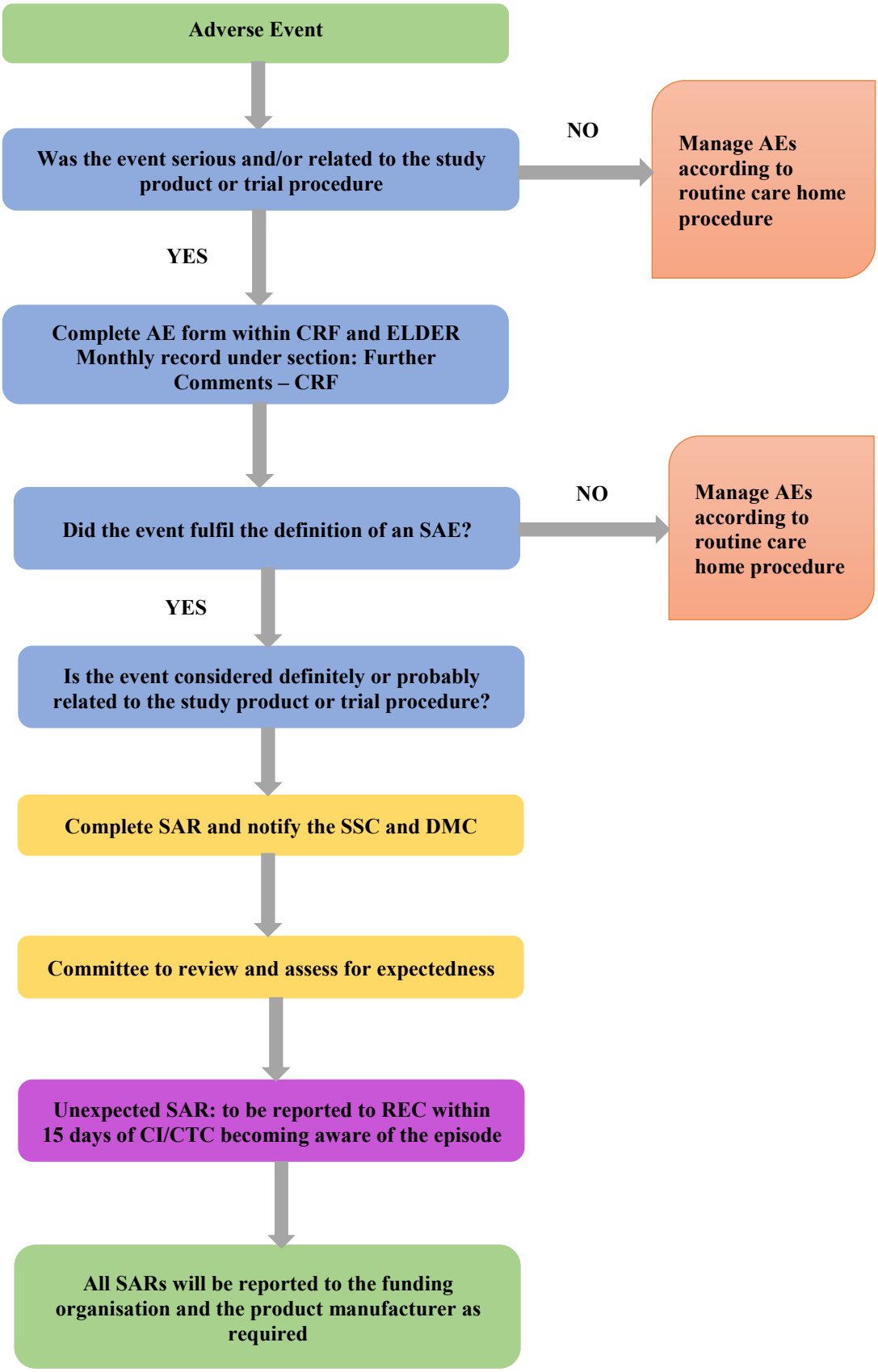
10.5.3 Serious Adverse Reaction

An SAE classified by the delivery staff/CTC and further confirmed by the CI as being probably or definitely related to the study product (diagnostic tests confirming septicaemia or the suspected pathogen is identified as the Bacillus strain used in the ELDER study product) will be classed as a SAR. In such cases, the trial staff should complete a purpose-designed SAR form, and the original

form returned to CTC within four days of the trial staff becoming aware of these events. The trial staff completing the report should include a detailed explanation of the event and supplement the report with clinical test results; if the hospital reports are not available at the time of reporting, the trial staff should forward the follow-up information as soon as possible to CTC, who would include these additional data in the appropriate report. Related and unexpected SAEs (i.e., all unexpected SARs) will be reported to the REC within 15 days of the CI/CTC becoming aware of the event. The CTC is responsible for additionally reporting SARs to the monitoring committee and the study product manufacturer (SACCO Systems) as appropriate.

Contact details for reporting SARs
Please Email to ELDER@tees.ac.uk, attention Clinical Trial Coordinator
Queries
Tel: 07404987008 (Mon to Fri 09.00 – 17.00)

SAE SAFETY REPORTING FLOWCHART



10.6 Events that do not require reporting

The study population will have a vast number of health events in the normal course of their care at this stage of life, and therefore it's important to distinguish between reporting events that could be connected with the trial intervention and those events that are frequently occurring in care homes and are unrelated. Such events which deemed unrelated to the study and will not be reported as AEs or SAEs, and these include:

- Agitation
- Allergic reaction (not related to study product)
- Anorexia, loss of appetite
- Bruising, ecchymoses
- Confusion
- Delirium
- Dehydration
- Fall with injury, with/without fracture
- Cardio vascular-related events
- Hypoglycaemia
- Hypotension
- Medication (non-trial) error
- Nursing care missed
- Pressure ulcer
- Skin tear, abrasion, breakdown
- Urinary tract infection with catheter

Similarly, pre-existing diseases or conditions present before the intervention that does not worsen will not be included as AE.

11. Statistical considerations

11.1 Sample size

The sampling frame adopted for this study is a non-random convenience sampling, depending on the availability within the 3-month recruitment window and their acceptance to participate in the study. This pilot RCT is not powered to detect intervention effects. The size of the study is sufficient to address the primary feasibility outcomes of acceptability of/compliance with the intervention and whether the potential oral health outcomes for a subsequent definitive trial can be captured robustly. The aim is to recruit up to 10 care home residents per home (a minimum of four and a maximum of fifteen) from care homes resulting in an estimated recruited sample of 240. This calculation was based on the calculations of a four-arm trial with three experimental treatments, with a normally distributed outcome, a standardised value of 0.6 being considered an interesting treatment effect, a significance level of 0.05, and Bonferroni's correction for multiple testing. The sampling size estimation was based on the required number of clusters (care homes) with an average consenting participant of 10.

11.2 Analysis of Outcome Measures

The proportion of participants complying with the interventions together with the Clopper-Pearson 95% confidence interval will be assessed. We shall apply generalised linear mixed modelling with

distribution and link function matching the outcome variable in question. Mean intervention effects will be presented with 95% confidence intervals for descriptive purposes only, with no inferences made regarding efficacy, as appropriate for a pilot.

12. Site Activation and Initiation

All members of care home staff facilitating the trial will also be required to sign a trial delegation log. Before commencing recruitment, all sites will undergo a process of initiation and have completed essential GCP and trial training. The coordinating centre must be informed immediately of any change in the care home research team.

13. Quality Control and Quality Assurance

13.1 On-site Monitoring

The trial staff would visit each site twice or thrice in a month, and the frequency of these periodic monitor visits depends on the trial site requirements and support required. The focus of these visits is to evaluate the site's performance (recruitment and retention rate), ascertain whether the study is conducted according to GCP and other regulatory and good practice guidance, and inspect for any protocol deviation. The monitor will specifically check if the source documents, trial records and CRF entries are accurately and legibly completed and maintained. The CTC will prepare a monthly trial monitoring update report that will be emailed to the CI and a copy filed in the communication log within the Trial Master File (TMF). The trial staff will remain in regular contact with the care home managers to check the study progress and resolve any queries.

13.2 Audit and Inspection

The trial will be included in the NIHR CRN portfolio and, therefore, will be permitted to their routine quality checks, audits, and regulatory inspection at trial sites as well as at the coordinating centre. The trial data may also be subjected to an internal audit by Teesside University under their remit as a sponsor. The trial team and care home managers will comply with these visits and provide access to source data and files.

14. End of trial definition

The end of trial is defined as the date of the last data captured from the last participant.

15. Trial Organisational Structure

15.1 Finance

The trial is funded by the Eklund Foundation for Odonatological Research. The research funding will be administered by Teesside University. The study provides oral hygiene kits to participants and to care home staff to encourage oral care among the care home residents. These kits are distributed by TePe free of charge to every participating site.

15.2 Sponsor

Teesside University is the study coordinating centre and will act as a sponsor for the trial. Delegated responsibilities will be assigned to specific members of the research team at the coordinating centre and the trial staff at the LCRN-NIHR delivery team.

15.3 Trial Management Group

The Trial Management Group (TMG) is responsible for the day-to-day running of the study at the trial sites. The group comprises all the members of the research team, such as the project staff from the coordinating centre (CI, CTC, Trial data analyst and statistician), TSC and the staff from the LCRN Delivery Team (i.e)the Leads and their delivery staff. The collective role of the TMG will include a) recruiting to time and target, b) distributing and monitoring the supply of study-related documents, site folders and study products to all participating centres, c) sample/data collection and management d) data entry, collation, and cleaning e) data analysis f) assure participant confidentiality and data security by observing data protection regulations g) conduct the trial in accordance with ICH GCP.
The TMG will meet monthly- every two months as deemed necessary to discuss the trial's progress. The CTC will meet with the RNs regularly in person, virtually or by telephone.

15.4 Study Steering Committee

The Study Steering Committee (SSC) will include national and international subject experts on different aspects of the project, representatives from the PPI group, local council staff and members of the funding organisation. The members' collective experience covers the fields of odontology, public health, nursing, medical statistics, primary care research and care home research around engagement, intervention implementation, and its regulations.
The SSC will be responsible for providing overall supervision of the ELDER Trial and taking up the executive role of approving any major study-related decisions. This includes a) reviewing and approving the trial protocol, amendments, and trial documentation; b) advice TMG by providing strategies to improve recruitment rate and deal with loss to follow-up numbers; c) providing solutions to deal with problems at trial sites, including handling protocol deviations; d) particular concentrate to guide the progression of the trial towards its agreed milestone and e) monitor if the safety of the participant is prioritised throughout the trial. In discharging its safety role, SSC will consider and act upon, as appropriate, according to the recommendation by the Data Monitoring Committee. These two groups will work in conjunction to decide, based on the safety report, whether a protocol modification is required to continue the study or if the study needs to be terminated prematurely, such as but not limited to a CV-19 outbreak. The SSC will assume primacy over DMC and will be responsible for ultimately deciding the final outcome.
The SSC will meet before site activation and quarterly or half-yearly after the start of the study. Meetings of the SSC may also take place on an ad-hoc basis if needed.

15.5 Data Monitoring Committee

The Data Monitoring Committee (DMC) will be established to oversee the safety and design of the study. The members of the DMC are a small group of three members – two members from the co-investigator team and a third member who would be completely independent of the trial. The rationale not to have a mixed DMC and rather have all independent members is that the ELDER STUDY is a

feasibility trial, and the primary objective is to refine the overall structure and procedure for a definitive trial.

As highlighted in the above session, the DMC takes up an advisory role to the SSC and offers recommendations on all matters relating to patient safety and reporting. Therefore, the committee will take responsibility for reviewing safety data reporting of AEs and line-listings of reported SARs captured throughout the trial and, if the need arises, request further analysis. Furthermore, apart from monitoring for safety signals, the DMC will also be asked to a) advise on whether the data collected is valid by verifying for completeness and accuracy; b) assesses the accumulated data for scientific merit to justify the continuing recruitment of further participants; and finally, c) monitor if clinical equipoise was maintained throughout the duration of the study.

The DMC will be asked to convene at least twice a year and provide advice to the SSC. In case of safety issues, an emergency meeting will be called for. The Coordinating Centre will be in constant communication by emails and telephone with DMC to seek advice on urgent matters, such as when a participant's safety is threatened.

16. Ethical and Regulatory Consideration

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human participants, adopted by the 18th World Medical General Assembly, Helsinki 1964, and its amendments.

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research 2017, the Data Protection Act 2018, and the Guidelines for Good Clinical Practice (GCP). The biological samples collected will be handled, analysed, and disposed of in compliance with Human Tissue Act 2004 Regulations. The protocol and all supporting study documents will be reviewed by the research team at the coordinating centre and then submitted to Health Research Authority via the IRAS portal for a complete ethical review.

17. Confidentiality and Data Protection

The study will be managed in accordance with ICH: GCP guidelines, and all data collected, will be handled, and stored in adherence with the Data Protection Act 2018. The participant's name will not be recorded in any document associated with the study except the consent form and participant contact details. The personal information will be stored in an encrypted Word document, held on CTC's password-protected space on a Teesside University server. Each participant will be allocated a unique trial ID to ensure that all data collected will remain unidentifiable and will be used in any study documents and samples associated with the study. Source documents, including medical and dental records, prescriptions, and laboratory test results holding participant details, will be filed at the study site and anonymised and coded before being sent to the coordinating centre. Participants will always be identified using only their unique study ID on the paper/electronic CRF collected from care homes. All correspondence between the sites, trail staff and coordinating centre will be through a secure study-specific email address separate from the team's official email address. Upon receiving any source documents and paper CRFs, the CTC at the coordinating centre will sign and date stamp each copy and update the tracking log until site close-out. All paper records (ICF and CRFs) will be kept in locked filing cabinets in secure buildings. Furthermore, any hard copies stored at each study site will be managed according to the Standard Operating Procedures (SOPs) of every respective site. All data kept at the coordinating centre will be held securely on password-protected servers and stored in

compliance with Teesside University's SOP for managing research and regulatory data. Apart from the research team members at the coordinating centre, only authorised members of the trial staff as listed on the delegation log will have access to ELDER trial data. The study team seeks to prioritise and maintain participant confidentiality throughout the study period and will ensure to employ only GCP-trained staff to handle trial-specific entries and documentation.

18. Timelines and Milestones

The ELDER trial is a two-year project with rigorous activities planned within the time frame. The timelines, together with key milestones, are as follows:

- Project duration: July 2022 – June 2024
- Recruitment of care homes: Oct/Nov 2022 – Jan/Feb 2023
- Participant recruitment and Baseline Data Collection: Nov 2022 – March 2023
- Follow-up data collection: June 2023 – December 2023
- Study End date: 30/12/23
- Trial site close-out: January 2024
- Study Closure: January 2024
- Data Analysis: June 2023 – January 2024
- Result write-up: January 2023 – March 2024
- Final report and dissemination: April – June 2024

19. Dissemination Plan

The CI and co-investigators are members with a specialist interest in dental science, dental public health and microbiology and hold a track record of publication in their respective fields. A multi-channel dissemination approach will be used to communicate the findings of this study to a wide range of audiences locally, nationally, and internationally.

The study results will be consolidated to be reported first to the trial collaborators, including the funding organisation and the CRN North East North Cumbria network group. To maintain the quality of reporting, the study will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines. The trial team will aim to disseminate the findings in a way it reaches both academic and non-academic audiences, and therefore, the dissemination output will be tailored accordingly. Findings will be disseminated to the scientific community through publication in academic journals and conference presentations. Oral/poster presentations at Funder/Sponsor hosted events, regional council and professional stakeholder conferences and care home forums, and community meetings will be targeted to promote study findings and visibility. The trial team will use their early engagement links with ENRICH network to identify a wider frame of non-academic national audiences across the UK. The findings will be made available to care home staff and residents as newsletter updates and public-friendly summaries presented as infographics which will be featured on the service provider's media page and websites and displayed on their bulletin boards. Enabling the help from the academic members in the trial team and with their links sought media coverage in newspapers, local radio outlets and social media.

20. Outbreak Plan

The coronavirus (CV-19) has significantly impacted research within care homes. Protection of the residents and staff and safe implementation of research has presented a challenge throughout the pandemic. The safety of the residents, as well as the care home staff, is paramount. Therefore, the ELDER trial staff will ensure every protection is taken to minimise the risk of infection. The trial staff visiting a trial site before scheduling a visit will confirm with the care home staff for any incidence of an outbreak within the last 14-days. The trial staff will also declare their covid status and imperative of the national guidelines will wear a face mask and ensure social distancing throughout the visit. If a trial participant tests positive for CV-19, the intervention will immediately stop and follow the AE reporting protocol. After submission of an AE form, a trial staff will get in touch with the care home staff to collect further information about the outbreak. The following information will be collected: the resident's vaccination history and hospital admission report. The information will be recorded in the Outbreak form within the CRF.

Reference

1. Ijaopo E, Ijaopo R. A Review of Oral Health in Older Adults: Key to Improving Nutrition and Quality of Life. OBM Geriatrics. 2018;2(3).
2. Thomson WM. Dental caries experience in older people over time: what can the large cohort studies tell us? Br Dent J. 2004;196(2):89-92; discussion 87.
3. National institute for Health and Care Excellence. Oral health: local authorities and partners (PH 55). NICE; 2014.
4. The James Lind Alliance (JLA) Priority Setting Partnerships (PSPs). Oral and Dental Health Top 10 2019 [Available from: http://www.jla.nihr.ac.uk/priority-setting-partnerships/oral-and-dental-health/top-10-priorities.htm.
5. National Institutes of Health. Diagnosis and management of dental caries throughout life. NIH Consens Statement. 2001;18(1):1-23.
6. Maughan RJ, Watson P, Cordery PAA, Walsh NP, Oliver SJ, Dolci A, et al. A randomized trial to assess the potential of different beverages to affect hydration status: development of a beverage hydration index. Am J Clin Nutr. 2016;103(3):717-23.
7. Yeung CA, Hitchings JL, Macfarlane TV, Threlfall AG, Tickle M, Glenny AM. Fluoridated milk for preventing dental caries. Cochrane Database of Systematic Reviews. 2005(3).
8. ONS. Living longer - Office for National Statistics.; 2018.
9. Fuller E, Steele J, Watt R, Nuttall N. 1: Oral health and function – a report from the Adult Dental Health Survey 2009 London: The Health and Social Care Information Centre; 2011.
10. Royal College of Surgeons. Improving older people's oral health. London: The Faculty of Dental Surgery of the Royal College of Surgeons of England; 2017.
11. Griffin SO, Regnier E, Griffin PM, Huntley V. Effectiveness of fluoride in preventing caries in adults. J Dent Res. 2007;86(5):410-5.
12. Watson F, Tomson M, Morris AJ, Taylor-Weetman K, Wilson KI. West Midlands Care Home Dental Survey 2011: part 1. Results of questionnaire to care home managers. Br Dent J. 2015;219(7):343-6.
13. Care Quality Commission. Smiling matters: oral health care in care homes. 2019 [Available from: https://www.cqc.org.uk/publications/major-report/smiling-matters-oral-health-care-care-homes.
14. Hoben M, Clarke A, Huynh KT, Kobagi N, Kent A, Hu H, et al. Barriers and facilitators in providing oral care to nursing home residents, from the perspective of care aides: A systematic review and meta-analysis. Int J Nurs Stud. 2017;73:34-51.
15. Cagetti MG, Campus G, Milia E, Lingström P. A systematic review on fluoridated food in caries prevention. Acta Odontologica Scandinavica. 2013(0):1-7.
16.Broekaert IJ, Walker WA. Probiotics and chronic disease. J Clin Gastroenterol. 2006;40(3):270-4.
17.Hasslöf P, Stecksén-Blicks C. Probiotic Bacteria and Dental Caries. In: F.V. Z, Duckworth RM, editors. The Impact of Nutrition and Diet on Oral Health. Monographs in Oral Science. 28. Basel: Karger; 2020. p. 99-107.
18. Nase L, Hatakka K, Savilahti E, Saxelin M, Ponka A, Poussa T, et al. Effect of long-term consumption of a probiotic bacterium, Lactobacillus rhamnosus GG, in milk on dental caries and caries risk in children. Caries Research. 2001;35(6):412-20.

19. Rodriguez G, Ruiz B, Faleiros S, Vistoso A, Marro ML, Sanchez J, et al. Probiotic Compared with Standard Milk for High-caries Children: A Cluster Randomized Trial. Journal of Dental Research. 2016;95(4):402-7.
20. Stecksen-Blicks C, Sjostrom I, Twetman S. Effect of Long-Term Consumption of Milk Supplemented with Probiotic Lactobacilli and Fluoride on Dental Caries and General Health in Preschool Children: A Cluster-Randomized Study. Caries Research. 2009;43(5):374-81.
21. Petersson LG, Magnusson K, Hakestam U, Baigi A, Twetman S. Reversal of primary root caries lesions after daily intake of milk supplemented with fluoride and probiotic lactobacilli in older adults. Acta Odontol Scand. 2011;69(6):321- 7.
22. Kraft-Bodi E, Jorgensen MR, Keller MK, Kragelund C, Twetman S. Effect of Probiotic Bacteria on Oral Candida in Frail Elderly. Journal of Dental Research. 2015;94(9):181s-6s.
23. Hao QK, Dong BR, Wu TX. Probiotics for preventing acute upper respiratory tract infections. Cochrane Database of Systematic Reviews. 2015(2).
24. Public Health England. Healthier and more sustainable catering. A toolkit for serving food to older people in residential care London; 2017.
25. Peng YN, West GE, Wang C. Consumer attitudes and acceptance of CLA-enriched dairy products. Can J Agr Econ. 2006;54(4):663-84.
26.Hall S, Longhurst SL, Higginson IJH. Challenges to conducting research with older people living in nursing homes. BMC Geriatr. 2009;**9**:38
27.Luff R, Ferreira Z, Meyer J. Care homes. London: Social Care Research Methods Review 8, NIHR School of Social Care Research; 2012
28.Zermansky AG, Allred DP, Petty DR, Raynor DK. Striving to recruit: the difficulties of conducting clinical research on elderly care home residents. J Royal Soc Med. 2007;**100**:258–261
29. Petersson LG, Hakestam U, Baigi A, Lynch E. Remineralisation of primary root caries lesions using an amine fluoride rinse and dentifrice twice a day. Am J Dent 2007; 20:93-6
30. Baysan A, Prinz JF, Lynch E. Clinical criteria used to detect primary root caries with electrical and mechanical measurements in vitro. Am J Dent. 2004;17(2):94-8
31. Coomarasamy, A., Williams, H., Truchanowicz, E., Seed, P. T., Small, R., Quenby, S., Gupta, P., Dawood, F., Koot, Y. E., Atik, R. B., Bloemenkamp, K. W., Brady, R., Briley, A., Cavallaro, R., Cheong, Y. C., Chu, J., Eapen, A., Essex, H., Ewies, A., ... Rai, R. (2016). PROMISE: first-trimester progesterone therapy in women with a history of unexplained recurrent miscarriages - a randomised, double-blind, placebo-controlled, international multicentre trial and economic evaluation. Health technology assessment (Winchester, England*)*, 20(41), 1-92
32.Chugh P, Dutt R, Sharma A, Bhagat N, Dhar MS. A critical appraisal of the effects of probiotics on oral health. Journal of Functional Foods. 2020;70:103985.
33.Williams NT. Probiotics. American Journal of Health-System Pharmacy. 2010;67(6):449-58.