



Clinical trial results:

A Randomised controlled trial to Evaluate the effectiveness and cost benefit of prescribing high dose FLuoride toothpaste in preventing and treating dEntal Caries in high-risk older adults (REFLECT trial)

Summary

EudraCT number	2017-002402-13
Trial protocol	GB
Global end of trial date	21 December 2023

Results information

Result version number	v1 (current)
This version publication date	13 August 2026
First version publication date	13 August 2026

Trial information

Trial identification

Sponsor protocol code	R04684
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Additional study identifiers

ISRCTN number	ISRCTN11992428
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Manchester University NHS Foundation Trust
Sponsor organisation address	Oxford Road, Manchester, United Kingdom, M13 9WL
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 March 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 December 2023
Global end of trial reached?	Yes
Global end of trial date	21 December 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effect of prescribing 5000ppm fluoride toothpaste with usual care on treatment for caries, including coronal/root restorations, endodontics or extractions

To compare the costs and benefits, within a net benefit framework of prescribing 5000ppm fluoride toothpaste with usual care

Protection of trial subjects:

Fluoride 5000ppm toothpaste is indicated in adults and adolescents aged 16 years and over for the prevention of dental caries, particularly amongst those at risk for multiple caries. The toothpaste was used within its licence within the REFLECT trial.

Because of the high fluoride content, the SmPC recommends that the opinion of a dental specialist must be sought before the product used. Within REFLECT, all participants were assessed to be eligible by a general dental practitioner (GDP), and those randomised to the fluoride 5000ppm toothpaste had this prescribed to them by the GDP and dispensed by community pharmacists. The toothpaste is topically administered and known side effects are rare and minor.

The CI and sponsor carried out a risk assessment and concluded this is a low-risk trial.

At each routine follow-up appointment, dentists were asked to record any possible adverse reactions (serious or non-serious) to the toothpaste. In addition, all deaths were recorded. The study team monitored accruing safety data.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 January 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 1156
Worldwide total number of subjects	1156
EEA total number of subjects	0

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	660
From 65 to 84 years	479
85 years and over	17

Subject disposition

Recruitment

Recruitment details:

The clinical setting for the trial was general dental practices (primary care) in the UK (excluding N Ireland) providing NHS care. NHS patients 50 years or older, with active coronal caries in the last 12 months or any root caries; and/or other risk factors and for whom the dental practitioner decided were appropriate were invited to participate.

Pre-assignment

Screening details:

See published protocol (Tickle et al., 2019) for specific screening details and inclusion/exclusion criteria.

Pre-assignment period milestones

Number of subjects started	1625 ^[1]
Number of subjects completed	1156

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Declined: Not want to participate in study: 346
Reason: Number of subjects	Ineligible: Already prescribed Fluoride toothpaste: 19
Reason: Number of subjects	Ineligible: Sodium fluoride hypersensitivity: 2
Reason: Number of subjects	Ineligible: Sharing abode with someone in trial: 6
Reason: Number of subjects	Ineligible: Unable to complete questionnaires: 4
Reason: Number of subjects	Ineligible: Unable to give informed consent: 8
Reason: Number of subjects	Other reason given: 81
Reason: Number of subjects	Post Randomisation Exclusions: 3

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 1625 were the number screened for eligibility, 469 declined or were ineligible/post-randomisation exclusions, and 1156 is the final number randomised to the trial.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Trial was open label so neither subject nor dentist were blinded. The trial statistician and the study team were blinded to the allocation during all analyses. Blinding to primary outcome was not possible but a more detailed clinical examination undertaken by independent (external to the trial dental practices) and blinded trained clinical examiners was conducted to collect secondary clinical outcomes in the Scottish practices only.

Arms

Are arms mutually exclusive?	Yes
Arm title	High-dose fluoride plus usual care
Arm description:	
GDP prescription of 5000 parts per million (ppm) fluoride toothpaste, used as advised by the participant's dentist, plus usual care	
Arm type	Experimental

Investigational medicinal product name	5000ppm fluoride toothpaste
Investigational medicinal product code	A01AA01
Other name	
Pharmaceutical forms	Toothpaste
Routes of administration	Dental use
Dosage and administration details:	
GDP prescription of 5000 parts per million (ppm) fluoride toothpaste, used as advised by the participant's dentist (twice a day), plus usual care	
Arm title	Usual care only
Arm description:	
Any advice given by the GDP will be to use standard, off-the-shelf, fluoride toothpaste (1350-1500 ppm).	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	High-dose fluoride plus usual care	Usual care only
Started	579	577
Completed	579	577

Period 2	
Period 2 title	Trial follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded
Arms	
Are arms mutually exclusive?	Yes
Arm title	High-dose fluoride plus usual care
Arm description:	
GDP prescription of 5000 parts per million (ppm) fluoride toothpaste, used as advised by the participant's dentist, plus usual care	
Arm type	Experimental
Investigational medicinal product name	5000ppm fluoride toothpaste
Investigational medicinal product code	A01AA01
Other name	
Pharmaceutical forms	Toothpaste
Routes of administration	Dental use
Dosage and administration details:	
GDP prescription of 5000 parts per million (ppm) fluoride toothpaste, used as advised by the participant's dentist (twice a day), plus usual care	
Arm title	Usual care only
Arm description:	
Any advice given by the GDP will be to use standard, off-the-shelf, fluoride toothpaste (1350-1500	

ppm).

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	High-dose fluoride plus usual care	Usual care only
Started	579	577
Completed	420	427
Not completed	159	150
Lost to follow-up	159	150

Baseline characteristics

Reporting groups

Reporting group title	High-dose fluoride plus usual care
Reporting group description: GDP prescription of 5000 parts per million (ppm) fluoride toothpaste, used as advised by the participant's dentist, plus usual care	
Reporting group title	Usual care only
Reporting group description: Any advice given by the GDP will be to use standard, off-the-shelf, fluoride toothpaste (1350-1500 ppm).	

Reporting group values	High-dose fluoride plus usual care	Usual care only	Total
Number of subjects	579	577	1156
Age categorical			
NHS dental patients, 50 years of age or older, attending a GDP who are considered by their dentist to be at high risk of developing caries.			
Units: Subjects			
50-65	359	354	713
>65	220	223	443
Age continuous			
NHS dental patients, 50 years of age or older, attending a GDP who are considered by their dentist to be at high risk of developing caries.			
Units: years			
arithmetic mean	63.4	63.3	
standard deviation	± 8.9	± 8.6	-
Gender categorical			
Units: Subjects			
Female	282	286	568
Male	297	291	588
Exemption from NHS charges			
Exempt from paying NHS dental treatment charges (minimisation variable).			
Units: Subjects			
Yes	161	162	323
No	418	415	833
Recruitment site			
Recruitment site split by geographic region			
Units: Subjects			
Scotland	298	296	594
Northern Ireland	175	172	347
England	106	109	215
Residential Setting			
Minimisation variable.			
Units: Subjects			
Own Home	577	576	1153
Care Home	2	1	3
Prevalence of coronal caries experience			
Cavitation into dentine			
Units: Subjects			
Yes	578	577	1155

No	1	0	1
Prevalence of recession with caries on root surfaces Units: Subjects			
No	457	459	916
Yes	120	115	235
Missing	2	3	5
Prevalence of active or untreated decay Units: Subjects			
No	374	370	744
Yes	205	206	411
Missing	0	1	1
Toothache in the previous 12 months Units: Subjects			
Yes	188	182	370
No	366	375	741
Missing	25	20	45
Best practice frequency brushing (Twice a day)			
Those following best practice in terms of brushing frequency (twice a day vs all other options)			
Units: Subjects			
Best practice	390	355	745
Not best practice	168	199	367
Missing	21	23	44
Best practice duration brushing (2 minutes)			
Those following best practice for brushing duration (2 minutes vs all other options)			
Units: Subjects			
Best practice	193	211	404
Not best practice	363	340	703
Missing	23	26	49
Best practice post-brushing behaviour (spit but not rinse)			
Those following best practice for post-brushing behaviour (spit, but not rinse vs all other options)			
Units: Subjects			
Best practice	166	171	337
Not best practice	379	375	754
Missing	34	31	65
Type of toothbrush Units: Subjects			
Power	230	207	437
Manual	309	329	638
Both	14	11	25
Missing	26	30	56
Dose of toothpaste on larger head Units: Subjects			
Full coverage of toothbrush head	187	179	366
Not full coverage	196	211	407
Missing	196	187	383
Dose of toothpaste on smaller head Units: Subjects			
Full coverage of toothbrush head	242	216	458

Not full coverage	47	54	101
Missing	290	307	597
Applies toothpaste more than once when brushing teeth			
Units: Subjects			
Yes	51	48	99
No	503	504	1007
Missing	25	25	50
Daily mouthwash contains fluoride			
Units: Subjects			
Yes	83	77	160
No	19	23	42
Don't know	124	127	251
Missing	353	350	703
DMFT Coronal			
Decayed, Missing or Filled coronal Teeth (DMFT) excluding wisdoms			
Units: Teeth			
arithmetic mean	19.2	18.8	
standard deviation	± 4.9	± 4.9	-
DMFS Coronal			
Decayed, Missing or Filled coronal Surfaces (DMFS) excluding wisdoms			
Units: Surfaces			
arithmetic mean	67.4	65.9	
standard deviation	± 23.4	± 23.6	-
DRT			
Root Decayed Teeth			
Units: Teeth			
arithmetic mean	0.5	0.4	
standard deviation	± 1.5	± 1.2	-
Missing teeth			
Units: Teeth			
arithmetic mean	7.6	7.3	
standard deviation	± 5.5	± 5.5	-
EQ-5D-5L			
Units: Utility value			
arithmetic mean	0.832	0.827	
standard deviation	± 0.227	± 0.220	-
EQ-5D-5L-VAS			
Visual Analog Scale (VAS)			
Units: Utility Score			
arithmetic mean	79.595	79.017	
standard deviation	± 20.504	± 20.448	-
OHIP-14			
Oral Health Impact Profile-14			
Units: Utility Score			
arithmetic mean	5.7	5.7	
standard deviation	± 7.9	± 7.3	-
Sugar Intake			
Three questions covered frequency of consumption of sugary items (cakes, sweets, fizzy drinks) using five frequency categories. We calculated a score of exposure to sugar intake by coding the replies to each question as follows: we attributed a four to the maximum frequency of consumption (6 or more times a week) and three to the following category (3-5 times a week) and so on until the last category (rarely or never) which will be coded as zero. Final question asks sugar in hot drinks, if yes, coded as 0.			

Final score ranges from 0 (no exposure) to 16 (very frequent exposure to sugar intake)			
Units: Exposure score			
arithmetic mean	7.4	7.4	
standard deviation	± 3.7	± 3.5	-

End points

End points reporting groups

Reporting group title	High-dose fluoride plus usual care
Reporting group description: GDP prescription of 5000 parts per million (ppm) fluoride toothpaste, used as advised by the participant's dentist, plus usual care	
Reporting group title	Usual care only
Reporting group description: Any advice given by the GDP will be to use standard, off-the-shelf, fluoride toothpaste (1350-1500 ppm).	
Reporting group title	High-dose fluoride plus usual care
Reporting group description: GDP prescription of 5000 parts per million (ppm) fluoride toothpaste, used as advised by the participant's dentist, plus usual care	
Reporting group title	Usual care only
Reporting group description: Any advice given by the GDP will be to use standard, off-the-shelf, fluoride toothpaste (1350-1500 ppm).	

Primary: Number of participants requiring dental treatment of one or more teeth due to caries

End point title	Number of participants requiring dental treatment of one or more teeth due to caries
End point description: The primary outcome measure, requirement for any dental treatment due to caries including restorations, endodontics or extraction, was analysed using a multilevel mixed-effects generalised linear model adjusting for minimisation variables and including a random effect intercept for centre (residential setting (own home/care home), exemption (including partial exemption) from dental treatment charges (yes/no) and age band (50-65; >65)). Analysis followed the intention-to-treat framework in accordance with the approved, pre-specified statistical plan.	
End point type	Primary
End point timeframe: Up to 36 months post randomisation (with a 33-42 month acceptable follow-up window)	

End point values	High-dose fluoride plus usual care	Usual care only		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	420	427		
Units: Participants				
Yes	279	302		
No	141	125		

Statistical analyses

Statistical analysis title	Generalised linear model
Statistical analysis description: A multilevel mixed-effects generalised linear model adjusting for minimisation variables and including a random effect intercept for centre was used to analyse the primary outcome.	
Comparison groups	High-dose fluoride plus usual care v Usual care only
Number of subjects included in analysis	847
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.09
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.04
Variability estimate	Standard error of the mean
Dispersion value	0.12

Secondary: Difference in the OHIP-14 measure

End point title	Difference in the OHIP-14 measure
End point description:	
End point type	Secondary
End point timeframe: Oral health status using OHIP14, a measure of oral health-related Quality of Life (QoL), collected at baseline and annual follow up through patient administered questionnaires. The end point of interest is the 3 year follow up.	

End point values	High-dose fluoride plus usual care	Usual care only		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	396	394		
Units: Score				
arithmetic mean (standard deviation)	6.94 (± 9.89)	7.13 (± 9.23)		

Statistical analyses

Statistical analysis title	Linear mixed model
Statistical analysis description: Linear mixed model used to analyse the repeated measures of the OHIP-14 outcome adjusted for the minimisation variables; residential setting, age band, exemption from NHS dental charges, and centre (the latter via a random effect). Treatment effects at each time were derived from the interaction term for time by treatment.	

Comparison groups	High-dose fluoride plus usual care v Usual care only
Number of subjects included in analysis	790
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.235
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.53
upper limit	0.38
Variability estimate	Standard error of the mean
Dispersion value	0.49

Secondary: Difference in the EQ-5D-5L utility score

End point title	Difference in the EQ-5D-5L utility score
End point description:	
End point type	Secondary
End point timeframe:	Collected at baseline and annual patient reported questionnaires during the 3 year follow up. The endpoint of interest is analysed at 3 years post randomisation.

End point values	High-dose fluoride plus usual care	Usual care only		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	396	397		
Units: Score				
arithmetic mean (standard deviation)	0.743 (± 0.287)	0.747 (± 0.287)		

Statistical analyses

Statistical analysis title	Linear mixed model
Statistical analysis description:	Linear mixed model used to analyse the repeated measures of the OHIP-14 outcome adjusted for the minimisation variables; residential setting, age band, exemption from NHS dental charges, and centre (the latter via a random effect). Treatment effects at each time were derived from the interaction term for time by treatment.
Comparison groups	High-dose fluoride plus usual care v Usual care only

Number of subjects included in analysis	793
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.986
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.026
upper limit	0.025
Variability estimate	Standard error of the mean
Dispersion value	0.013

Secondary: Difference in the EQ-5D visual analog score (VAS)

End point title	Difference in the EQ-5D visual analog score (VAS)
End point description:	
End point type	Secondary
End point timeframe:	
Collected at baseline & each annual questionnaire during the 3 year trial follow up period. The endpoint of interest is analysed at 3 years post randomisation.	

End point values	High-dose fluoride plus usual care	Usual care only		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	397	403		
Units: Score				
arithmetic mean (standard deviation)	76.270 ($\pm$ 20.386)	75.955 ($\pm$ 19.510)		

Statistical analyses

Statistical analysis title	Linear mixed model
Statistical analysis description:	
Linear mixed model used to analyse the repeated measures of the OHIP-14 outcome adjusted for the minimisation variables; residential setting, age band, exemption from NHS dental charges, and centre (the latter via a random effect). Treatment effects at each time were derived from the interaction term for time by treatment.	
Comparison groups	High-dose fluoride plus usual care v Usual care only

Number of subjects included in analysis	800
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.795
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.294
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.921
upper limit	2.509
Variability estimate	Standard error of the mean
Dispersion value	1.13

Secondary: Number of participants following best dental practice: Toothbrush duration (2 minutes)

End point title	Number of participants following best dental practice: Toothbrush duration (2 minutes)
End point description:	
End point type	Secondary
End point timeframe:	Recorded at baseline and annual patient questionnaire during the trial follow up period. The endpoint of interest is analysed at 3 years post randomisation.

End point values	High-dose fluoride plus usual care	Usual care only		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	408	414		
Units: Participants				
Best practice	162	142		
Not best practice	246	272		

Statistical analyses

Statistical analysis title	Generalised linear model
Statistical analysis description:	Generalised linear model - following a binary distribution - used to analyse the toothbrush duration best practice outcome at 3 years adjusted for toothbrush duration best practice at baseline and the minimisation variables; residential setting, age band, exemption from NHS dental charges, and centre (the latter via a random effect).
Comparison groups	High-dose fluoride plus usual care v Usual care only

Number of subjects included in analysis	822
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.112
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	1.7
Variability estimate	Standard error of the mean
Dispersion value	0.19

Secondary: Number of participants following best dental practice: Toothbrush frequency (twice a day)

End point title	Number of participants following best dental practice: Toothbrush frequency (twice a day)
End point description:	
End point type	Secondary
End point timeframe:	Recorded at baseline and annual patient questionnaire during the trial follow up period. The endpoint of interest is analysed at 3 years post randomisation.

End point values	High-dose fluoride plus usual care	Usual care only		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	408	414		
Units: Participants				
Best practice	269	266		
Not best practice	139	148		

Statistical analyses

Statistical analysis title	Generalised linear model
Statistical analysis description:	Generalised linear model - following a binary distribution - used to analyse the toothbrush frequency best practice outcome at 3 years adjusted for toothbrush frequency best practice at baseline and the minimisation variables; residential setting, age band, exemption from NHS dental charges, and centre (the latter via a random effect).
Comparison groups	High-dose fluoride plus usual care v Usual care only

Number of subjects included in analysis	822
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.932
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.44
Variability estimate	Standard error of the mean
Dispersion value	0.18

Secondary: Number of participants following best dental practice: Post-brushing (Spit, but no rinse)

End point title	Number of participants following best dental practice: Post-brushing (Spit, but no rinse)
End point description:	
End point type	Secondary
End point timeframe:	Recorded at baseline and annual patient questionnaire during the trial follow up period. The endpoint of interest is analysed at 3 years post randomisation.

End point values	High-dose fluoride plus usual care	Usual care only		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	408	412		
Units: Participants				
Best practice	202	163		
Not best practice	206	249		

Statistical analyses

Statistical analysis title	Generalised linear model
Statistical analysis description:	Generalised linear model - following a binary distribution - used to analyse the post-brushing best practice outcome at 3 years adjusted for post-brushing best practice at baseline and the minimisation variables; residential setting, age band, exemption from NHS dental charges, and centre (the latter via a random effect).
Comparison groups	High-dose fluoride plus usual care v Usual care only

Number of subjects included in analysis	820
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	1.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.15
upper limit	2.07
Variability estimate	Standard error of the mean
Dispersion value	0.23

Secondary: Number of participants experiencing episodes of toothache (Recorded at least once during follow up)

End point title	Number of participants experiencing episodes of toothache (Recorded at least once during follow up)
End point description:	
End point type	Secondary
End point timeframe:	Recorded at baseline and annual patient questionnaire during the trial follow up period. The endpoint of interest is analysed at 3 years post randomisation.

End point values	High-dose fluoride plus usual care	Usual care only		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	418	430		
Units: Participants				
Yes	214	250		
No	204	180		

Statistical analyses

Statistical analysis title	Generalised linear model
Statistical analysis description:	Generalised linear model - following a binary distribution - used to analyse the episodes of toothache outcome at 3 years adjusted for prior episodes of toothache at baseline and the minimisation variables; residential setting, age band, exemption from NHS dental charges, and centre (the latter via a random effect).
Comparison groups	High-dose fluoride plus usual care v Usual care only

Number of subjects included in analysis	848
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	0.93
Variability estimate	Standard error of the mean
Dispersion value	0.09

Secondary: Difference in Decayed, Missing or Filled Surfaces coronal increment cavitation level (Scottish subset)

End point title	Difference in Decayed, Missing or Filled Surfaces coronal increment cavitation level (Scottish subset)
End point description:	
The increment score was calculated as the difference at follow up from baseline in the number of cavitated tooth surfaces calculated at the patient level. This increment was then supplemented by CRF information to account for coronal restorations due to caries (Filling, crown, extraction, veneer).	
End point type	Secondary
End point timeframe:	
Recorded at baseline and 3 years post randomisation.	

End point values	High-dose fluoride plus usual care	Usual care only		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	103		
Units: Surfaces				
arithmetic mean (standard deviation)	2.26 (± 4.99)	3.20 (± 5.58)		

Statistical analyses

Statistical analysis title	Generalised linear model
Statistical analysis description:	
Generalised mixed model used to analyse the DMFS increment outcome adjusted for the minimisation variables; residential setting, age band, exemption from NHS dental charges, and centre (the latter via a random effect).	
Comparison groups	High-dose fluoride plus usual care v Usual care only

Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.187
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.16
upper limit	0.42
Variability estimate	Standard error of the mean
Dispersion value	0.66

Secondary: Difference in Decayed, Filled Surface root increment cavitation level (Scottish subset)

End point title	Difference in Decayed, Filled Surface root increment cavitation level (Scottish subset)
End point description:	
The increment score was calculated as the difference at follow up from baseline in the number of cavitated root surfaces at the patient level. This increment was then supplemented by CRF information to account for root restorations & root canal treatment due to caries.	
End point type	Secondary
End point timeframe:	
Recorded at baseline and 3 years post randomisation.	

End point values	High-dose fluoride plus usual care	Usual care only		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	103		
Units: Surfaces				
arithmetic mean (standard deviation)	0.82 (± 1.32)	0.74 (± 1.41)		

Statistical analyses

Statistical analysis title	Generalised linear model
Statistical analysis description:	
Generalised mixed model used to analyse the DFS root increment outcome adjusted for the minimisation variables; residential setting, age band, exemption from NHS dental charges, and centre (the latter via a random effect).	
Comparison groups	High-dose fluoride plus usual care v Usual care only

Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.182
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.44
Variability estimate	Standard error of the mean
Dispersion value	0.13

Secondary: Difference in progression of early caries surfaces by ICDAS (Scottish subset)

End point title	Difference in progression of early caries surfaces by ICDAS (Scottish subset)
End point description:	Progression of early caries from baseline to 36 months. Those surfaces progressing from Tooth Surface Code = Caries & ICDAS code = First change in enamel/distinct visual change in enamel at baseline to more severe decay at 36 months. The analysis accounts for number of early caries at baseline since everyone has a different starting point.
End point type	Secondary
End point timeframe:	Recorded at baseline and 3 years post randomisation.

End point values	High-dose fluoride plus usual care	Usual care only		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	97		
Units: Surfaces				
arithmetic mean (standard deviation)	0.96 ($\pm$ 1.03)	1.04 ($\pm$ 1.17)		

Statistical analyses

Statistical analysis title	Generalised linear model
Statistical analysis description:	Generalised mixed model used to analyse the progression of early caries outcome adjusted for the minimisation variables; residential setting, age band, exemption from NHS dental charges, and centre (the latter via a random effect).
Comparison groups	High-dose fluoride plus usual care v Usual care only

Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.099
Method	Mixed models analysis
Parameter estimate	Incidence Rate Ratio
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.05
Variability estimate	Standard error of the mean
Dispersion value	0.13

Secondary: Difference in bleeding on probing surfaces (Scottish subset)

End point title	Difference in bleeding on probing surfaces (Scottish subset)
End point description:	
The number of surfaces with bleeding on probing at 36 months, analysis accounts for differences in number of surfaces measured for BOP at 36 months, and the analysis model includes the number of bleeding surfaces at baseline as a predictor variable.	
End point type	Secondary
End point timeframe:	
Recorded at baseline and 3 years post randomisation.	

End point values	High-dose fluoride plus usual care	Usual care only		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	103		
Units: Surfaces				
arithmetic mean (standard deviation)	2.40 (± 4.42)	1.97 (± 3.60)		

Statistical analyses

Statistical analysis title	Generalised linear model
Statistical analysis description:	
Generalised mixed model used to analyse the bleeding surfaces outcome adjusted for total surfaces bleeding at baseline and the minimisation variables; residential setting, age band, exemption from NHS dental charges, and centre (the latter via a random effect).	
Comparison groups	High-dose fluoride plus usual care v Usual care only

Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.263
Method	Mixed models analysis
Parameter estimate	Incidence Rate Ratio
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	2.04
Variability estimate	Standard error of the mean
Dispersion value	0.3

Other pre-specified: Sensitivity analysis: Number of participants requiring dental treatment on one or more teeth due to caries

End point title	Sensitivity analysis: Number of participants requiring dental treatment on one or more teeth due to caries
End point description:	A sensitivity analysis of the primary outcome up to 36 months post randomisation, using the same analysis as the primary outcome, where participants that did not require treatment will be included as such in the extended acceptable window of 30-48 months post randomisation.
End point type	Other pre-specified
End point timeframe:	Up to 36 months post randomisation with an extended acceptable window of 30-48 months post randomisation.

End point values	High-dose fluoride plus usual care	Usual care only		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	432	442		
Units: Participants				
Yes	282	305		
No	150	137		

Statistical analyses

Statistical analysis title	Generalised linear model
Comparison groups	High-dose fluoride plus usual care v Usual care only

Number of subjects included in analysis	874
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.159
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	1.09
Variability estimate	Standard error of the mean
Dispersion value	0.13

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomisation to end of trial follow up period.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	27.0
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Reporting groups

Reporting group title	High-dose fluoride plus usual care
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Reporting group description:

GDP prescription of 5000 parts per million (ppm) fluoride toothpaste, used as advised by the participant's dentist, plus usual care

Reporting group title	Usual care only
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Reporting group description:

Any advice given by the GDP will be to use standard, off-the-shelf, fluoride toothpaste (1350-1500 ppm).

Serious adverse events	High-dose fluoride plus usual care	Usual care only	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 579 (0.00%)	0 / 577 (0.00%)	
number of deaths (all causes)	13	13	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	High-dose fluoride plus usual care	Usual care only	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 579 (1.55%)	0 / 577 (0.00%)	
Gastrointestinal disorders			
Oral mucosal erythema	Additional description: Symptom described on form as: "redness"		
subjects affected / exposed	1 / 579 (0.17%)	0 / 577 (0.00%)	
occurrences (all)	1	0	
Oral discomfort			
subjects affected / exposed	1 / 579 (0.17%)	0 / 577 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			

subjects affected / exposed	1 / 579 (0.17%)	0 / 577 (0.00%)
occurrences (all)	1	0
Hyperaesthesia teeth		
subjects affected / exposed	4 / 579 (0.69%)	0 / 577 (0.00%)
occurrences (all)	5	0
Oropharyngeal plaque		
subjects affected / exposed	1 / 579 (0.17%)	0 / 577 (0.00%)
occurrences (all)	1	0
Tongue exfoliation		
subjects affected / exposed	1 / 579 (0.17%)	0 / 577 (0.00%)
occurrences (all)	1	0
Gingival pain		
subjects affected / exposed	1 / 579 (0.17%)	0 / 577 (0.00%)
occurrences (all)	1	0
Gingival bleeding		
subjects affected / exposed	1 / 579 (0.17%)	0 / 577 (0.00%)
occurrences (all)	1	0
Abdominal discomfort		
subjects affected / exposed	1 / 579 (0.17%)	0 / 577 (0.00%)
occurrences (all)	1	0
Lip swelling		
subjects affected / exposed	1 / 579 (0.17%)	0 / 577 (0.00%)
occurrences (all)	1	0
Dysgeusia		
subjects affected / exposed	1 / 579 (0.17%)	0 / 577 (0.00%)
occurrences (all)	1	0
Dry mouth		
subjects affected / exposed	1 / 579 (0.17%)	0 / 577 (0.00%)
occurrences (all)	2	0
Paraesthesia oral		
subjects affected / exposed	1 / 579 (0.17%)	0 / 577 (0.00%)
occurrences (all)	2	0
Chapped lips		
subjects affected / exposed	1 / 579 (0.17%)	0 / 577 (0.00%)
occurrences (all)	1	0
Tooth discolouration		

subjects affected / exposed occurrences (all)	1 / 579 (0.17%) 1	0 / 577 (0.00%) 0	
Infections and infestations Oral candidiasis subjects affected / exposed occurrences (all)	1 / 579 (0.17%) 1	0 / 577 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
22 March 2020	Onset of the COVID-19 pandemic and subsequent social restrictions. Time periods are as follows: Pre-restrictions (Randomisation - 22March2020), During-restrictions (23March2020 - 31October2020), Post-restrictions (1November2020 - 42 months post randomisation)	-

Notes:

Limitations and caveats

None reported