Reflect

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)

Based on protocol version: 1.6

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1 Introduction

1.1 Background and rationale

REFLECT is a two-arm parallel group, pragmatic, open-label randomised controlled trial to evaluate the effectiveness and cost benefit of GDP prescribing 5000 parts per million (ppm) fluoride toothpaste plus usual care compared to usual care only (any advice given by the GDP will be to use standard, off-the-shelf, fluoride toothpaste (1350-1500 ppm)) in individuals 50 years and over attending NHS dental practices with a high-risk of caries.

1.2 Research objectives

To evaluate the effectiveness and cost benefit of GDP prescribing of 5000ppm fluoride toothpaste on treatment for caries compared to usual care in individuals 50 years and over with high-risk of caries.

Primary objectives:

- To compare the effect of prescribing 5000ppm fluoride toothpaste and usual care with usual care alone 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

Secondary objectives:

- To evaluate the effect of prescribing 5000ppm fluoride toothpaste on root and coronal caries (mean Decayed, Missing, Filled Surfaces (DMFS) score increment for each, progression of early caries lesions, bleeding on probing, quality of life (generic and condition specific), costs to the NHS and to individuals and society, oral health behaviour and episodes of pain.
- To explore the attitudes of clinicians and patients to the prescribing and use of high fluoride toothpaste.

1.3 Design

Two-arm parallel group, pragmatic, open-label individually Randomised Controlled Trial (RCT) with internal pilot comparing the clinical effectiveness and net benefit of GDP prescribing of high concentration fluoride toothpaste compared to standard care.

1.4 Interventions

1.4.1 Prescription of 5000ppm Fl toothpaste

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

1.4.2 Usual care only

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

2 Statistical principles

2.1 Randomisation and blinding

This is a two-arm parallel trial where participants are randomised to receive either the intervention or usual care. Blinding of outcome assessment using the primary outcome will not be possible, as the participants' dentist will collect primary outcome data. A more detailed clinical examination undertaken by independent (external to the trial dental practices) and blinded trained clinical examiners will be used to collect secondary outcomes (caries increment and bleeding on probing) in the Scottish practices only.

2.2 Sample size and power calculation

The sample size calculation is based on a meaningful absolute target difference of 10% (75% vs 65%) in the primary outcome measure. This difference is considered to be both a realistic and important from discussion with dentists, PPI groups and from published estimates. The value for the comparator group (75% of individuals allocated to standard care who have restoration(s) or extraction(s) due to caries during the 36 months of follow up) is based on published data and Scottish treatment data. For the proposed target difference between a proportion of 0.75 and a proportion of 0.65 (odds ratio of 0.62), a two-sided 5% significance level, and 90% power, 440 participants (880 in total) will be required to provide data for the primary outcome at 36 months. Based on our previous and current HTA trials, we are assuming 25% attrition, and so 587 participants per group are required (1174 in total) in 60 practices (each practice recruiting an average of 20 participants). Based on an estimated consent rate of 50% (data from IQuaD), 2348 eligible patients will be invited to participate.

An important secondary outcome within our proposed trial is caries increment, measured using the number of Decayed Missing and Filled tooth Surfaces (DMFS). Using the mean number of Decayed Missing and Filled tooth Surfaces (DMFS), the caries increments for an older population in the published literature vary, but there seems to be consensus around one surface per year. Given the fact that the standard deviations approximate the means in terms of caries increment, a reduction in caries increment from 3 to 2 surfaces with the intervention would produce a 30% reduction in caries increment with the intervention over three years. The numbers needed to adequately power this secondary outcome are relatively small compared with the primary out- come measure: For secondary caries outcomes, group sample sizes of 200 and 200 achieve 97.5% power to reject the null hypothesis of equal means when the population mean difference DMFS increment is $\mu 1 - \mu 2 = 2 - 3 = -1.0$ with standard deviations of 2 for group 1 (intervention) and 3 for group 2 (control), and with a significance level (alpha) of 0.05 using a two-sided two sample t-test allowing for unequal variances. Assuming 25% attrition, 267 participants per group are required (534) in total in 28 practices. Based on an estimated consent rate of 50% 1068 eligible patients will be invited to participate.

2.3 Post-randomisation exclusions

Post-randomisation exclusions are those cases where randomisation was made in error.

2.4 Interim analysis

No interim analyses are planned during the course of the trial.

2.5 Time points of outcome collection

Details on outcome collection are specified in the published protocol (Tickle *et al.*, 2019).

3 Study population

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.

3.1 Eligibility

Inclusion criteria

Inclusion criteria have been defined to ensure the participants in the trial are similar to those who would receive this intervention if it were part of usual care. We will focus on older patients with an increased risk of caries, more specifically people:

• aged 50 years or older

• with a diagnosis of active coronal caries (into dentine) in the last 12 months which may\may not have been treated, or any root caries; and\or other risk factors as determined by their GDP.

• receive their dental care in part or fully as an NHS patient

• living in any residential setting, and

• for whom their GDP decides prescription of high concentration fluoride toothpaste is appropriate for the patient

Exclusion criteria

People who:

• are currently prescribed (by GDP or GP) high concentration fluoride toothpaste (for GDPs prescription must have been issued at last examination visit)

• hypersensitivity for Sodium Fluoride and\or other ingredients used in 5000ppm toothpaste

• are living in the same household as someone already recruited to Reflect, or someone who is routinely using a high concentration fluoride toothpaste

• are unable to provide informed consent

4 Analysis

4.1 Statistical methods

4.1.1 Outcomes

Primary outcome measures

- *Definition*: Number and proportion of participants requiring restoration or endodontics or extraction of one or more teeth due to caries
- *Operationalisation*: Number expressed as proportion of individuals requiring any dental treatment due to caries including restorations, endodontics or extraction up to 36 -3/+6 months post-randomisation. This will include any new fillings identified via dental charting.

Secondary outcome measures

Clinical (Scotland only):

- Caries increment (mean DMFS coronal and DFS root caries) at 36 months
- Progression of early caries lesions at 36 months - initial stage caries progressing to moderate or extensive stage caries using the International Caries Detection and Assessment System (ICDAS)
- Bleeding on Probing (BoP) at 36 months

These clinical outcomes will be measured by a dedicated team of calibrated and trained dental examiners, in a subgroup of the included participants from the Scottish practices.

Patient reported:

Oral health-related QoL (OHIP-14), health-related QoL (EQ5D-5L), oral health behaviour (including tooth brushing frequency, duration and behaviour after toothbrushing), experience of episodes of pain (any self-reported episodes of pain during follow-up versus none).

Economic:

NHS and patient perspective costs, willingness to pay, net benefit, long-term cost-effectiveness

4.1.2 Additional measures

Self-reported data on **exposure to fluoride sources** was collected yearly in patient reported questionnaires. Questions will be presented separately with selected questions being combined to facilitate interpretation. Combined questions will include: dose of toothpaste (irrespective of the size of the toothbrush, using full coverage, which is the recommended dose, vs smear or pea sized); use of fluoride mouthwash daily vs any other option (i.e., no mouthwash, mouthwash without fluoride, or mouthwash with fluoride less frequently). More details about presentation of these measures are available in the dummy tables.

Self-reported data on **exposure to sugar intake** was also collected yearly in patient reported questionnaires and it will be combined to facilitate interpretation. Three questions covered frequency of consumption of sugary items (i.e. cakes, sweets, fizzy drinks) using five frequency categories as possible answers. We will calculate a score of exposure to sugar

intake by coding the replies to each question as follows: we will attribute 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. A final question focuses on the addition of sugar to hot drinks (yes, no, do not consume hot drinks). If participants report to have sugar in hot drinks, we will give them the maximum exposure score (4), versus no consumption (0). The final exposure to sugar intake score will vary from 0 (no exposure to sugar intake) to 16 (very frequent exposure to sugar intake).

4.2 Caries related measures and outcome calculations

4.2.1 Measurement

- **DMFS/T Coronal and DFS/T Root**

Caries indices including coronal decayed, missing, filled surfaces/teeth (DMFS/T), the prevalence of coronal caries experience (cavitation into dentine, DMF>0), number of teeth with decayed root surfaces (DRT), and prevalence of recession with caries cavitated into dentine for root surfaces (DR>0) will be calculated from baseline charts completed by participating General Dental Practitioners for the whole trial sample.

For the subset of individuals from participating Scottish practices an extended clinical charting will be undertaken by trained REFLECT assessors. At baseline and follow-up the following measures will be calculated: DMFS/T coronal, DFS/T root, the prevalence of coronal caries experience (cavitation into dentine, DMF>0), the prevalence of recessed decayed or filled root surfaces caries (DFR>0), DFRS Root (the sum of roots with caries, filled or filled with caries), and DFRT Root (the sum of the teeth with caries or filled).

The scores will be calculated excluding third molars to enhance comparability of our findings with wider caries research. The missing component of the score for DMFS/T Coronal will be calculated as any missing teeth recorded in the patient's mouth. This assumes that missing teeth are missing due to caries. Given the age group in REFLECT, and the randomised nature of the trial, we would expect any other reasons for teeth missingness (i.e., accidents, periodontal disease) to be rare, and equally distributed between randomised groups.

- **ICDAS**

A detailed caries measurement will be made using the validated International Caries Detection and Assessment System (ICDAS) for the classification of coronal caries for the subset of participants from participating Scottish practices only. The ICDAS model categorises both early and more advanced stages of caries. For early caries, ICDAS measures the surface changes and potential histological depth of carious lesions by relying on surface characteristics related to the optical properties of sound and demineralised enamel prior to cavitation. The primary requirement for applying the ICDAS system is the examination of clean and dry teeth aided by a ball-ended explorer that is used to remove any remaining plaque and debris and to check for surface contour, minor cavitation or sealants. In this trial the ICCMS Caries Merged categories will be used to determine the progression of caries lesions. All coronal surfaces of all teeth will be examined, and the caries status categorised from sound surfaces (ICDAS 0), through initial stage caries (ICDAS 1 and 2), moderate stage caries (ICDAS 3 and 4) to

extensive stage caries (ICDAS 5 and 6).

4.2.2 Data quality

A process to ensure data quality was carried out in which training and discussion of clinical assessment for ICDAS was done and used to refine practice. The training involved presentation of case studies to the trainees (trial clinical examiners) including different ICDAS scores, whereas the discussion involved trainees scoring their own case studies and then discussing as a group until consensus on a specific ICDAS score was reached.

4.2.3 Outcomes

- **DMFS increment and DFS Root increment**

The increment outcomes will be calculated as disease incidence (cavitation level) including the dentist replacement restorations for caries i.e. where disease incidence is recorded either from the dental charts or the Care Report Form (CRF). The information from the dental charting will be supplemented by information from the CRF regarding the filled component as appropriate (i.e. if a tooth remains filled from baseline to follow-up, we will supplement the dental chart information with whether treatment for caries was undertaken from the treatment CRF).

- **Progression of early coronal caries according to ICDAS**

The outcome will be calculated for each participant as the proportion of surfaces with initial (untreated) caries lesions (ICDAS 1 or 2) at baseline that have progressed to (untreated) moderate or extensive caries lesions (ICDAS 3 to 6 score) or restored (filled) at follow-up. Alternatives to this calculation will be considered if appropriate, specifically categorising ICDAS scores into three groups: 0, 1-3, and 4-6.

- **Bleeding on probing**

Bleeding on probing is measured as a yes/no at each site (2xtooth). We will calculate the proportion of sites with bleeding on probing per participant.

4.3 Analysis method

There will be a single analysis at study end. This will follow the intention-to-treat principle applied to all outcomes (i.e. participants will be analysed as randomised).

4.3.1 Primary outcome

The primary outcome measure, requirement for any dental treatment due to caries including restorations, endodontics or extraction, will be analysed using a generalised linear model with adjustment for minimisation variables (recruitment site, residential setting (own home/care home), exemption (including partial exemption) from dental treatment charges (yes/no) and age band (50-65; >65). Statistical significance will be at the 2-sided 5% level with corresponding confidence intervals derived. A binary logistic regression model will be fitted to the primary outcome, requiring dental treatment due to caries, with minimization variables as covariates.

Table 1 describes the estimand framework for REFLECT's primary analysis. The primary analysis aims to address a treatment policy estimand (i.e. what is the treatment effect of offering a policy of fluoride toothpaste vs not offering it) as stipulated in the trial's protocol. For

that reason, any intercurrent events (i.e. non-adherence to treatment) will be ignored in the primary analysis.

Table 1 – Estimand framework for REFLECT's primary analysis

Component	Definition
Treatment conditions	Prescribing of high-fluoride toothpaste + usual care vs usual care
Population	Adults over the age of 50 with high-risk of caries
Outcome	Proportion of participants requiring treatment for caries up to 36-months post-randomisation (acceptable window to confirm information: 3 months before, and 6 months after 36-month time point)
Population level measure	Mean difference in proportion
Intercurrent events	All intercurrent events related to treatment non-adherence or related to use of non-trial treatments will be handled using a treatment policy strategy

4.3.2 Secondary outcomes

Secondary outcomes will be analysed using generalised linear models with adjustment for minimisation and baseline variables when available.

4.4 **Missing data**

4.4.1 Missing primary outcome data

Missing primary outcome data will be minimised by collecting a final CRF at 36 months requesting information about the final status of each trial participant (i.e. needed further treatment; received further treatment; did not need further treatment; or lost to follow-up). Participants lost to follow-up will be deemed missing in the main analysis. We will investigate the mechanism of missingness using regression models incorporating baseline covariates which will inform a sensitivity analysis using multiple imputation and assuming a missing at random mechanism.

4.4.2 Missing outcome baseline data

When analysing follow-up data, imputation of missing baseline data (collected prior to randomisation) will be undertaken to reduce bias. Following published recommendations, this will be done using the centre mean or adding a missing category, depending on the type of

variable (White and Thompson, 2005). Imputation of instruments will be undertaken according to the rules of the specific instrument.

4.4.3 Missing item data

Where validated scales are used, missing item data will be dealt with according to the original publication's criteria (i.e. EQ5-D, OHIP). If no indication on handling of missing item data is given, then a complete case approach will be used (i.e. only participants that provided all items will be included).

4.5 COVID-19 related considerations

To explore the impact of COVID-19 related restrictions in participants' follow-up, we used the Chief Dental Office England/Scotland timelines for stopping and resuming treatments at dental practices, as follows:

- Pre-restrictions: regular treatment was provided until the 22nd March 2020
- Restrictions in dental treatments provided: between the 23rd of March and 31st of October 2020 (English and Scottish practices re-opened for face-to-face care in June, but were very limited in their ability to provide treatments)
- Post-restrictions: from the 1st of November 2020 onwards, both nations resumed regular care (i.e. return to provision of full range of treatments) despite significant delays in service provision due to wait lists

COVID-19 dental services related restrictions did not affect REFLECT's recruitment: all participants had been recruited by the time the pandemic started varying their time of follow-up between less than a month and 23 months post-randomisation. This means no REFLECT participant initial treatment prescription would have been affected by the pandemic.

The primary outcome for REFLECT is measured up to 36 months post-randomisation, which means no participant had full follow-up by the time the pandemic started and, therefore, it is impossible to estimate "pandemic-free" treatment effect (Cro *et al.*, 2020). Participants that were noted as requiring treatment for caries will be included in our main and sensitivity analyses as requiring treatment independent of when this happened. Participants that did not require treatment will be included as such in the analysis if we have confirmation of that information within an acceptable window between 3 months prior and 6 months after final follow-up at 36 months post-randomisation. This means information confirming no treatment was needed in REFLECT participants will be collected post-restrictions to provision of full treatment in dental services. We will perform a sensitivity analysis including all patients that provided primary outcome data outside of the acceptable window (i.e. any time after randomisation for those that received or were planned to receive treatment, or confirmation of no treatment received up to 6 months prior to their 36-month appointment, and with no upper limit after the 36 month appointment).

For the reasons outlined above, we do not anticipate any changes to the main or sensitivity analyses as described in the SAP of REFLECT related to pandemic restrictions. We will, however, explore patterns of appointments, including primary outcome collection, and patient reported data collection based on the three periods outlined above. The exploration of the pandemic's impact on dose of treatment received is discussed in section 4.8.

4.6 Subgroup analysis

Planned subgroup analyses on the primary outcome will explore the possible modification of treatment effect by clinically important factors: gender, age and NHS dental charges exemption status. This will be done by including treatment-by-factor interactions in the model and they will be classified as exploratory analyses. These analyses will be evaluated using stricter levels of statistical significance ($p<0.001$).

4.7 Comparisons

A single comparison of prescription of 5000ppm fluoride toothpaste versus usual care

4.8 Non-compliance with allocated treatment

We will classify patients as compliant with allocated treatment if they were prescribed fluoride toothpaste up to 3 months from their initial treatment visit in the intervention group; and if they were not prescribed fluoride toothpaste up to 3 months from their initial treatment visit in the control group. This is in line with REFLECT's pragmatic approach to defining the trial's intervention where frequency of prescription and duration of the regimen were determined by the patient's GDPs after assessing each patient's risk.

Patient's risk assessment is collected at each appointment; descriptive statistics will be prepared exploring number of prescriptions in each appointment, and how that relates to patient's risk status according to their dentist.

Since all participants were randomised prior to the COVID-19 pandemic, compliance data will be presented as whole and, if deemed necessary, a CACE analysis will be undertaken (considering compliance as a binary variable).

However, number of prescriptions during follow-up might have been influenced by the pandemic. Therefore, we will present the number of prescriptions per randomised arm and period (pre-restrictions, during and post) where available.

5 References

Cro, S. *et al.* (2020) 'A four-step strategy for handling missing outcome data in randomised trials affected by a pandemic', *BMC Medical Research Methodology*, 20(1), pp. 1–12. doi: 10.1186/s12874-020-01089-6.

Tickle, M. *et al.* (2019) 'Protocol for 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)', *BMC Oral Health*, 19(1), pp. 1–13. doi: 10.1186/s12903-019-0749-x.

White, I. and Thompson, S. (2005) 'Adjusting for partially missing baseline measurements in randomized trials', *Stat Med*, 24(7), pp. 993–1007.

6 Appendices

6.1 Draft dummy tables

The following tables are draft dummy tables for REFLECT's reporting. When presenting descriptive statistics, mean and standard deviations will be presented for continuous variables, frequency and percentage will be used for binary and categorical variables.

Table 1: Baseline characteristics (whole sample)

	High-dose fluoride toothpaste	Usual care	Form
General demographics			
Age (mean, sd)			Participant details form
Age band (minimisation) n (%) 50 to 65 years >65 years			Participant details form
Sex (n, % Male Female)			Participant details form
Exemption from NHS charges, including partial exemption (minimisation) n (%)			Participant details form
Recruitment site (minimisation) n (%) Scotland England Northern Ireland			
Residential setting (minimisation) n (%) Own home Care home			Participant details form
Clinical measures			
DMFT Coronal (mean, sd)			Clinical baseline form (general)

DMFS Coronal (mean, sd)			Clinical baseline form (general)
Prevalence of coronal caries experience (DMF > 0) n(%)			Clinical baseline form (general)
DRT (mean, sd)			Clinical baseline form (general)
Prevalence of recession with caries on root surfaces (DR>0) n(%)			Clinical baseline form (general)
No of present teeth (mean, sd)			Clinical baseline form (general)
Reason for caries high risk status n (%) (categories are not mutually exclusive) Caries experience present Diet/Lifestyle Poor oral hygiene Unexplained Dry mouth - Medication Dry mouth - Radiotherapy Dry mouth - Sjorgren syndrome			Clinical baseline form (general)
Self-reported measures			
EQ-5D-5L (mean, SD)			Patient baseline questionnaire (PBQ), section 1
OHIP-14 (mean, SD)			PBQ, section 2

Toothache in previous 12 months?			PQB, section 3, Q14
Oral health behaviour			
Best practice frequency brushing n(%) (2x per day)			PBQ, section 3, Q1
Best practice duration brushing n(%) (2 minutes)			PBQ, section 3, Q2
Best practice post-brushing behaviour, i.e. spit but not rinse n(%)			PBQ, section 3, Q3
Type of toothbrush n (%) Manual Power			PBQ, section 3, Q4
Dose of toothpaste – full coverage n (%)			PBQ, section 3, Q6,7
Applies toothpaste more than once n (%)			PBQ, section 3, Q8
Daily mouthwash contains fluoride n (%)			PBQ, section 3, Q9
Sugar intake - mean (SD), n			PBQ, section 3, Q10-13

Table 2: Clinical baseline data (participants from Scottish practices only)

Additional information for Scottish assessment

Measure	High-dose fluoride toothpaste (N=)	Usual care (N=)	Form
Decayed, Missing, Filled, Surfaces (DMFS) Coronal into dentine – mean(SD), count Decayed, Missing, Filled Teeth (DMFT) Coronal into dentine - mean(SD), count			All measures come from Scotland's

Prevalence of coronal caries experience (cavitation into dentine DMF >0) n(%) Decayed, Filled, Root Surfaces (DFRS) Mean(SD), count Decayed, Filled, Root Tooth (DFRT) Mean(SD), count Prevalence of recessed decayed or filled root surfaces caries (DFR>0) n(%) Prevalence of initial coronal caries (ICDAS 1 or 2) n (%) Bleeding on probing – proportion of sites, mean(SD), count			clinical form

Table 3: Treatment received at baseline

This section summarizes treatment received per randomised allocation.

Measure	High-dose fluoride toothpaste (N=)	Usual care (N=)	Forms
Compliance with allocated treatment: 5000ppm Fluoride toothpaste prescribed at initial visit - n (%)			(Extra Q to all practices referring to baseline)
Number of tubes prescribed at baseline – mean (SD), count			(Extra Q to all practices referring to baseline)

Follow-up

Table 4: Clinical attendance and questionnaire completion rates – n(% out of randomised)

Measure	High-dose fluoride toothpaste (N=)	Usual care (N=)

Clinical assessment at 36-months (y/n) [Scotland only] Annual questionnaires Year 1 Year 2 Year 3		

Table 5: Treatment received during follow-up

Overall	High-dose fluoride toothpaste (N=)	Usual care (N=)	Questions from
Number of tubes prescribed per month - mean (SD), count			(Q9 Follow-up CRF)
Reason for not prescribing (post-baseline) – n (% out of appointments?)			(Q9 if no, Follow-up CRF)
Patient declined Caries risk reduced Oversight by the practice			
Was fluoride varnish applied at least once to the patient's teeth for caries prevention? (Y/N) – n(%)			
If fluoride varnish was applied at least once, what proportion of appointments included its			

application?			

Table 6: Treatment effect of high-dose fluoride toothpaste vs usual care (Primary analysis)

Measure	High-dose fluoride toothpaste (N=)	Usual care (N=)	Treatment effect 95% CI, p-value
Proportion of patients requiring caries treatment – n/N* (% out of those that provided data)	X%	Y%	

*we will employ a complete case analysis for the primary outcome, therefore Ns include participants that provided data on their primary outcome according to our pre-stipulated rules (see Section 4,1,1)

Table 7: Treatment effects for clinical outcomes (Scotland only) (Secondary outcomes)

Measure	High-dose fluoride toothpaste (N=)	Usual care (N=)	Treatment effect 95% CI, p-value
DMFS coronal increment including GDP replacement of restorations for caries (mean, SD, count) DFRS Root increment (mean, SD, count) Progression of early caries by ICDAS (yes (all surfaces progressed to more serious caries or filling) vs no (not all surfaces progressed, i.e. all stayed the same or reversed), % that progressed)			

Bleeding on probing (mean, SD, count)			

Table 8: Treatment effects for patient reported outcomes (Secondary outcomes)

Measure	High-dose fluoride toothpaste (N=)	Usual care (N=)	Treatment effect at 36 months, 95% CI, p-value
OHIP-14 (mean, SD, count) Toothbrush duration (% of correct answer out of those with data) Toothbrush frequency (% with correct answer out of those with data) After brushing behaviour (% with correct answer out of those with data) Experienced episodes of pain (% of participants with any episodes of pain out of those with complete follow-up)			

Table 9: Adverse reactions

Measure	High-dose fluoride toothpaste (N=)	Usual care (N=)
Reported symptoms or reactions related to toothpaste? (y/n, at least once) n/N (% out of participants randomised)		

Serious adverse reaction (y/n) n/N (% out of participants with reported symptoms)		
Adverse (but not serious) symptoms		
Causality of adverse symptom related to toothpaste		
Definitely – n(% out of those that reported symptoms)		
Probably - n(% out of those that reported symptoms)		
Symptoms described		
Symptom 1 – n(% out of those that reported symptoms)		

Table 10: Descriptive statistics to explore the impact of COVID-19

	High-dose fluoride toothpaste (N=)	Usual care (N=)	
Proportion of time spent in the study Pre-restrictions in dental services During restrictions in dental services Post-restrictions in dental services			
Pre-restrictions in dental services provision			
Average number of appointments/CRFs per year – mean (SD), count			
Number of tubes per month mean (SD), count			
During restrictions in dental services provision			
Average number of appointments/CRFs per year –			

mean (SD), count			
Number of tubes per month mean (SD), count			
Post-restrictions in dental services provision			
Average number of appointments/CRFs per year – mean (SD), count			
Number of tubes per month mean (SD), count			

Table 11: Subgroup analyses (may be presented as a figure instead of table)

Subgroup	Effect size[a], 95% confidence interval, p-value
Gender (male, female)	
Age (50 to 65 years, >65 years)	
NHS dental charges exemption status (exempt, not exempt)	

a- Calculated by including treatment-by-factor interactions in the model

REFLECT_SAP version 1

Final Audit Report 2023-10-06

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