



## Clinical trial results:

### Comparison of the caries-protective effect of fluoride varnish (Duraphat®) with treatment as usual in nursery school attenders receiving preventive oral health support through the Childsmile Programme: a Randomised Controlled Trial

#### Summary

EudraCT number	2012-002287-26
Trial protocol	GB
Global end of trial date	31 August 2017

#### Results information

Result version number	v1 (current)
This version publication date	13 February 2019
First version publication date	13 February 2019

#### Trial information

##### Trial identification

Sponsor protocol code	GN12CO201
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01674933
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Greater Glasgow & Clyde Health Board
Sponsor organisation address	Clinical Research & Development, Dalnair Street , Glasgow, United Kingdom, G3 8SW
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Sponsor organisation name	The University of Glasgow
Sponsor organisation address	University Avenue, Glasgow, United Kingdom, G12 8QQ
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**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:

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**Results analysis stage**

Analysis stage	Interim
Date of interim/final analysis	22 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 April 2017
Global end of trial reached?	Yes
Global end of trial date	31 August 2017
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

Main objective of the trial:

Does Duraphat® fluoride varnish applied in addition to usual treatment provide additional protection against dental decay in children attending nursery school? Dental decay is measured by the d3mft score, based on the number of decayed (i.e. decay into the tooth dentine), missing or filled teeth. This score will be compared at baseline and 2 years later.

Protection of trial subjects:

The participants' parents / guardians completed a contraindications checklist prior to each of the study interventions. Children were assessed for obvious temporary infections or injuries by dental nurses immediately before each of the study interventions and any child deemed too unwell or injured were excluded from that intervention, also children who were regarded as too distressed or nervous to undertake an intervention were excluded from that particular intervention. Children who were assessed as too nervous or distressed to undertake the baseline dental inspection were excluded from the trial and participants who were too nervous or distressed to undergo an endpoint dental inspection were excluded from that inspection. All children presented for inspections and study interventions in groups and dentists and dental nurses tried to ensure that the more confident and relaxed children were given the inspection or intervention first in order to provide an example for the others.

Background therapy:

Background therapy is the Childsmile Core (CS) intervention, which is part of the Childsmile child oral health improvement programme. CS Core comprises supervised daily toothbrushing with fluoride toothpaste (circa 1000ppm F) in nursery schools, free dental packs of fluoride toothpaste, toothbrushes and advice. Participants in both arms of the trial receive CS Core as the treatment as usual (TAU).

Evidence for comparator:

No treatment

Actual start date of recruitment	01 November 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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Country: Number of subjects enrolled	United Kingdom: 1284
Worldwide total number of subjects	1284
EEA total number of subjects	1284

Notes:

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**Subjects enrolled per age group**

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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)	1284
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Consent was taken from parents / guardians using both postal and face-to-face recruitment methods. Participants were recruited from the ante pre-school classes in 65 public nursery schools in 13 Local Authorities in Scotland during the school years of 2012-13, 2013-14 and 2014-15. Children has were inspected and randomised in their nursery school

### Pre-assignment

Screening details:

Inclusion criteria: provision of a signed informed consent form from a parent or legal guardian; children in the first year of nursery school; Exclusion criteria: hypersensitivity to colophony and / or any other constituents; a history of bronchial asthma requiring hospitalisation; and history of allergic episodes requiring hospital admission.

### Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor <sup>[1]</sup>

Blinding implementation details:

Assessors in this instance are the dentists conducting the baseline and endpoint dental inspections and they were not made aware of the participants allocation to either study arm. Dental nurses applied the study intervention (fluoride varnish) so were aware. All trial data was recorded on paper case report forms and transferred from the study sites to the central trial management site for checking and transfer to an independent clinical trials unit.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Intervention

Arm description:

Participants in the intervention arm will receive, at each treatment, a total volume of 0.25ml of Duraphat® Dental Suspension. Each 1 ml of Duraphat® Dental Suspension contains 50mg sodium fluoride which is equivalent to 22.6mg of fluoride. The treatments will be applied at approximately six monthly intervals for 18 months i.e. baseline, and at 6 months, 12 months and finally 18 months post-baseline. Participants also received supervised daily toothbrushing with fluoride toothpaste (1000 ppm).

Arm type	Experimental
Investigational medicinal product name	Duraphat dental suspension
Investigational medicinal product code	A01AA
Other name	Duraphat 50/mg/ml Dental Suspension, Colgate Duraphat Varnish 50mg/ml Dental Suspension
Pharmaceutical forms	Dental suspension
Routes of administration	Dental use

Dosage and administration details:

At each treatment, a total volume of 0.25ml of Duraphat® Dental Suspension will be applied by study dental nurses to the teeth of children using an applicator brush. Each 1 ml of Duraphat® Dental Suspension contains 50mg sodium fluoride which is equivalent to 22.6mg of fluoride. Participants will receive 4 applications at approximately 6 monthly intervals over an 18 month period.

<b>Arm title</b>	Treatment as Usual
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Arm description:

All children receive treatment as usual (TAU), namely supervised toothbrushing in their nursery school. TAU is the Childsmile Core intervention comprising supervised daily toothbrushing with fluoride toothpaste (circa 1000ppm F), free dental packs of fluoride toothpaste, toothbrushes and advice. Children in the TAU arm will receive the same series of contacts as those in the intervention arm, including the Childsmile Core intervention, without the application of varnish.

Arm type	No intervention
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## Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: The dentists / assessors who undertook the baseline and the endpoint dental inspections were not made aware which trial arm participants were allocated to. This was undertaken to avoid any potential influence or bias this knowledge might have had during both dental inspections. Dental nurses applied the varnish at the interventions and therefore had to be aware. The participants would also have been aware if fluoride varnish had been applied to their teeth or not.

<b>Number of subjects in period 1</b>	Intervention	Treatment as Usual
Started	643	641
Completed	577	573
Not completed	66	68
Consent withdrawn by subject	8	13
Contraindication	2	1
Missing final inspection case report form	-	5
Final inspection visit not undertaken	1	-
Incomplete data excluded from analyses	1	1
Lost to follow-up	42	35
Incomplete case report form	1	-
Refused final inspection	2	2
Absent final inspection	9	11

## Baseline characteristics

### Reporting groups

Reporting group title	Overall trial
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Reporting group description:

Participants were screened and given a baseline dental inspection prior to randomisation into one of the two trial arms. The number of subjects reported here are those randomised into the trial after screening and baseline inspections had been completed.

Reporting group values	Overall trial	Total	
Number of subjects	1284	1284	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	3.52 ± 0.28	-	
Gender categorical Units: Subjects			
Female	673	673	
Male	611	611	

## End points

### End points reporting groups

Reporting group title	Intervention
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Reporting group description:

Participants in the intervention arm will receive, at each treatment, a total volume of 0.25ml of Duraphat® Dental Suspension. Each 1 ml of Duraphat® Dental Suspension contains 50mg sodium fluoride which is equivalent to 22.6mg of fluoride. The treatments will be applied at approximately six monthly intervals for 18 months i.e. baseline, and at 6 months, 12 months and finally 18 months post-baseline. Participants also received supervised daily toothbrushing with fluoride toothpaste (1000 ppm).

Reporting group title	Treatment as Usual
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Reporting group description:

All children receive treatment as usual (TAU), namely supervised toothbrushing in their nursery school. TAU is the Childsmile Core intervention comprising supervised daily toothbrushing with fluoride toothpaste (circa 1000ppm F), free dental packs of fluoride toothpaste, toothbrushes and advice. Children in the TAU arm will receive the same series of contacts as those in the intervention arm, including the Childsmile Core intervention, without the application of varnish.

### Primary: Occurrence of new caries lesions

End point title	Occurrence of new caries lesions
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End point description:

The primary endpoint for each individual child is whether or not there has been any occurrence of new caries lesions over the two year period, as measured by any increase in d3mft at two years of follow up compared to the d3mft at baseline (d3mft is dental decay as measured by the dmft scale in the dentine).

End point type	Primary
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End point timeframe:

The primary endpoint for each individual child is whether or not there has been any occurrence of new caries lesions over a two year period.

End point values	Intervention	Treatment as Usual		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	643	641		
Units: d3mft scores	577	573		

### Statistical analyses

Statistical analysis title	Analyses - clinical trial with a binary endpoint
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Statistical analysis description:

Binary endpoints will be analysed by Mantel-Haenszel Chi-squared tests and odds-ratios, with the attendant 95% confidence intervals. Changes in d3mft will be analysed by Wilcoxon tests, unless these changes are normally distributed and therefore suitable for analysis by Analysis of Covariance. Compliance will be compared with a chi-squared test. Null hypothesis: dental health of children in the FV arm of study is no better after 18m of varnish application than that of the children in the TAU arm

Comparison groups	Intervention v Treatment as Usual
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Number of subjects included in analysis	1284
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0782 <sup>[1]</sup>
Method	Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.7955
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6166
upper limit	1.0263
Variability estimate	Standard error of the mean

Notes:

[1] - All statistical tests will be two-tailed tests at the 5% significance level.



## Adverse events

### Adverse events information<sup>[1]</sup>

Timeframe for reporting adverse events:

Any adverse reaction is extremely likely to be seen within a maximum of 24 hours post application. Any adverse events reported by parents during that time will be recorded and evaluated by the Childsmile coordinator and the local Principal Investigator.

Adverse event reporting additional description:

Any adverse reactions whether noted by Childsmile staff or reported to Childsmile staff by parents or the staff at the nursery school, will cause either the study dental nurse or dental health support worker to record details in the relevant Case Report Form and to inform the site Principal Investigator.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0 2017

### Reporting groups

Reporting group title	Intervention
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Reporting group description:

Participants in the intervention arm will receive at each treatment, a total volume of 0.25ml of Duraphat® Dental Suspension. Each 1 ml of Duraphat® Dental Suspension contains 50mg sodium fluoride which is equivalent to 22.6mg of fluoride. The treatments will be applied at approximately six monthly intervals for 18 months i.e. baseline, and at 6 months, 12 months and finally 18 months post-baseline. Participants also received supervised daily toothbrushing with fluoride toothpaste (1000 ppm).

Reporting group title	Treatment as Usual
-----------------------	--------------------

Reporting group description:

Treatment as usual (TAU) is the Childsmile Core intervention comprising supervised daily toothbrushing with fluoride toothpaste (circa 1000ppm F), free dental packs of fluoride toothpaste, toothbrushes and advice. Children in the TAU arm will receive the same series of contacts as those in the intervention arm, including the Childsmile Core intervention, without the application of varnish.

Serious adverse events	Intervention	Treatment as Usual	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 643 (0.00%)	0 / 641 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Intervention	Treatment as Usual	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 643 (0.00%)	0 / 641 (0.00%)	

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Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: The reporting period for any adverse events or adverse reactions in this trial was set at 24 hours post-application of the fluoride varnish, which is a relatively short length of time. We did not have any adverse events (non-serious or serious) reported to trial staff, by parents or nursery staff, during this period and nor did any of the trial staff record an adverse event (non-serious or serious) during any of the intervention or inspection visits.

## 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
26 June 2015	<p>On Friday 26th of June 2015, the Chief Investigator notified our co-sponsor (NHS Health Board Greater Glasgow and Clyde) of the suspension of the trial pending clarification of a potential trial medication safety issue. This centered around the possibility that a component of the packaging of the Duraphat® fluoride varnish (the 'O' ring seal) used in the study contained latex, and this could constitute a possible risk of an allergic reaction among children given the product. Following consultation with the manufacturer, the co-sponsor notified the Research Ethics Committee (REC) and the Medicines and Healthcare products Regulatory Agency (MHRA) by a substantial amendment, dated 09/07/2015, of the temporary suspension of recruitment and treatment of study participants.</p> <p>After assessing the potential safety implication of this new information the co-sponsor concluded that overall there is no fundamental change to the risk-benefit assessment of the trial based on the new information. In addition the manufacturer, Colgate Palmolive, considers it unlikely under normal or extraordinary circumstances that a latex sensitivity or reaction could arise through use of the product. Accordingly, the co-sponsor did not consider that the exclusion criteria of the protocol needed to be amended. The current protocol already excluded children with serious allergy. The co-sponsor made an application to the MHRA to restart the trial on the 8th of August 2015, permission was granted to re-start by the Agency on the 3rd of September 2015.</p>	03 September 2015

Notes:

### Limitations and caveats

None reported

### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26681191>