

Fissure Seal or Fluoride Varnish? A randomised trial of their relative effectiveness.

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ABSTRACT

Background: Fissure sealants (FS) and fluoride varnish (FV) are effective in preventing dental caries when compared with a no treatment control. However, the relative clinical effectiveness of these interventions is uncertain.

Objective: To compare the clinical effectiveness of FS and FV in preventing dental caries in first permanent molars (FPMs) in 6-7 year-olds.

Design: A randomised clinical trial, with two parallel arms.

Setting: A targeted population programme using mobile dental clinics in schools located in areas of high social and economic deprivation in South Wales.

Participants: 1016 children were randomised 1:1 to receive either FS or FV.

Interventions: Resin-based fissure sealants were applied to caries-free FPMs and maintained at six monthly intervals. Fluoride varnish was applied at baseline and at six month intervals for 3 years.

Main outcome measures: The proportion of children developing caries into dentine (D₄₋₆MFT) on any one of up to four treated first permanent molars after 36 months.

Results: At 36 months 835 (82%) children remained, 417 in the FS and 418 in the FV arms respectively. A smaller proportion of children who received FV (73[17.5%]) developed caries into dentine on a least one FPM compared with FS (82 [19.6%]) Odds Ratio (OR) = 0.84 (CI 0.59 to 1.21) p = 0.35, a non-statistically significant difference between FS and FV treatments. The results were similar when the number of newly decayed teeth OR = 0.86 (CI 0.60 to 1.22) and tooth surfaces OR = 0.85 (CI 0.59 to 1.21) were examined.

Conclusions: In a community oral health programme, twice yearly application of fluoride varnish resulted in caries prevention which is not significantly different from that obtained by applying and maintaining fissure sealants after 36 months.

Keywords: dental caries, prevention, clinical trial, dental public health, clinical effectiveness, molar

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INTRODUCTION

Children vary in their susceptibility to dental caries, disease prevalence being closely linked to social and economic disadvantage (Locker, 2000; Watt et al., 2016). Further, teeth differ in their susceptibility to dental caries. The occlusal surface of first permanent molars is particularly prone to dental caries, often within a short period after eruption into the mouth. Decay on this surface accounts for the majority of affected tooth surfaces in adolescents and adults (Carvalho et al., 2001; Chestnutt et al., 1996; Hopcraft and Morgan, 2006; Marthaler, 2004). Management of occlusal caries has proven to be a great challenge to the dental profession (Carvalho, 2014) and preventing dental caries on the occlusal surfaces of first permanent molars in high-risk children is a key objective in preventive dental care.

There are two preventive dental technologies which have the potential to be targeted specifically at occlusal surfaces of first permanent molars; pit and fissure sealants (FS) and fluoride varnish (FV).

A 2013 Cochrane systematic review of sealants for preventing dental decay in the permanent teeth, concluded that in 12 trials where resin-based sealants were compared with no sealant controls, the sealed teeth were significantly less likely to be carious at two years follow-up (OR 0.12 95% CI 0.07-0.19) (Ahovuo-Saloranta et al., 2013). The clinical effectiveness of fluoride varnish has also been the subject of a Cochrane review (Marinho et al., 2013). This identified 13 studies which compared fluoride varnish with a placebo or no treatment and concluded that the pooled D(M)FS prevented fraction was 43% (95% CI 30% to 57%, $p < 0.0001$).

Thus while it is generally accepted that FS and FV are effective in the prevention of dental caries which technology is clinically superior is unknown. Ahovuo-Saloranta and colleagues published a Cochrane systematic review on the relative effectiveness of FS versus FV (Ahovuo-Saloranta et al., 2016). This updates a previous version of the review published in 2010 (Hiiri et al., 2010). The review identified four trials which compared resin-based FS with FV. Two of these studies, involving 358 children suggested that compared with FV, FS prevented more caries in first permanent molars at 2 year follow up. The pooled odds ratio was 0.65 (95% CI 0.50-0.94 $p = 0.02$). The authors stated that the body of evidence was assessed as of low quality. They concluded,

“Scarce and clinically diverse data are available on the comparison of sealants and fluoride varnish application, therefore it is not possible to draw clear conclusions about possible

differences in effectiveness for preventing or controlling dental caries on occlusal surfaces of permanent molars. The conclusion of this updated review remains the same as the last update in 2010” (Ahovuo-Saloranta et al., 2016).

The objective of the trial reported here was to compare the clinical effectiveness of FS and FV in preventing dental caries in first permanent molars (FPM) in 6-7 year-olds. The cost-effectiveness of the interventions and acceptability of these treatments was also examined and will be reported elsewhere.

METHODS

The full trial protocol was published at the commencement of the trial (Chestnutt et al., 2012) and is reported here in summary in line with CONSORT guidelines (Schulz et al., 2010).

Trial Design and setting

The trial design is illustrated in Figure 1. The study comprised a phase IV randomised, two-arm, parallel group trial. Participants were randomised to receive: resin fissure sealants or fluoride varnish. Clinical examinations and treatments were undertaken in schools using mobile dental clinics (MDC) as part of the Designed to Smile, Wales national oral health improvement programme (Welsh Government, 2016). Participants were recruited in two cohorts between October and January in school years 2011/12 and 2012/3. The fluoride level in the local water supply is < 0.1 part per million.

Participants

The target population were children aged 6-7 years attending 66 primary schools in Communities First areas – these localities have been identified as areas of social and economic deprivation by Welsh Government. All children in such schools are deemed at high caries-risk and qualify for FS/FV application (Public Health England, 2014; Scottish Intercollegiate Guidelines Network, 2014). To be included in the study, written consent from the child’s parent or guardian was required and at least one fully-erupted FPM needed to be present at the baseline examination. Children with known sensitivity to colophony (an ingredient in the FV), who had a history of severe allergies or who been hospitalised due to

asthma, or were participating in another Clinical Trial of an Investigational Medicinal Product (CTIMP) were excluded from participation.

Interventions

Clinical examinations

Study participants were examined supine in the MDC, under a standard overhead dental clinical light, using a plane dental mirror and ball-ended probe. The probe was used only to remove debris and to determine surface texture. It was not used to probe for cavitation. Teeth were not dried prior to clinical dental examination. Gross debris was removed using a toothbrush.

Caries status was assessed at baseline and 12, 24 and 36 months by trained and calibrated dentists at the d1/D1- d6/D6 level using ICDAS criteria (International Caries Detection and Assessment System, 2016). In this report caries presence is reported at the ICDAS codes (4-6) into dentine level. The clinical dental examinations were undertaken by experienced community dental officers. A total of six were used across the study with one examiner involved in all years of the project. A training and calibration exercise was undertaken in advance of each round of clinical examinations. As part of the annual caries assessment approximately 5% of study participants were re-examined to determine intra-examiner reproducibility.

Technologies evaluated

The FS used was Delton® Light Curing Opaque Pit & Fissure Sealant (Dentsply Ltd; CE0086). The standard clinical protocol as described by the product manufacturer was used to apply FS to the occlusal surfaces of included FPMs. Initial application of FS occurred within two weeks of the baseline dental examination, performed by a qualified and trained dental hygienist. In the case of partially erupted molars, where sufficient tooth surface was available, sealant was applied. This situation arose particularly in the case of upper molars. The same two dental hygienists provided treatments throughout the trial using two mobile dental clinics. The condition of the FS was re-examined at 6, 12, 18, 24, and 30 months. FS was re-applied if the existing sealant had become detached, or if occlusal coverage was

considered insufficient – either due to further eruption of the tooth or due to part of the sealant becoming lost.

The FV used was Duraphat® 50 mg/ml dental suspension (Colgate-Palmolive (UK) Ltd; PL 00049/0042), equivalent to 22,600ppm fluoride. Dosage per single application did not exceed 0.4 ml. The standard clinical protocol was used to apply the FV to all surfaces of the FPM. FS were applied by a dental hygienist in the MDC within two weeks of the baseline clinical examination and at six monthly intervals for 30 months. The study protocol dictated that reapplication should occur within a 4-week interval either side of the six month anniversary of the previous application.

Caries risk related habits and dental care during the trial

An annual parental questionnaire asked about tooth brushing frequency, if the child brushed on their own or with parental assistance, the type of toothpaste used and the quantity of toothpaste dispensed to the toothbrush. Enquiry was also made of the age at which tooth brushing started. The use of mouthwash, fluoride drops and fluoride tablets was determined, as was previous application of fluoride varnish by the child's own dentist. Attendance at a dentist outside the Designed to Smile programme was ascertained as well as the frequency of dental attendance. Parents were asked about life time residency in South Wales. The annual questionnaire also collected data on dietary habits, with an emphasis on the frequency of the consumption of sugar-rich food and drinks. The questionnaire was sense checked and designed using patient and public representatives from a school not involved in the study prior to trial commencement.

Children attended their usual source of dental care during the trial but their dentist was asked to refrain from providing FS or FV treatments. Children and their parents continued with their usual oral hygiene regime, details of which were gathered via the annual questionnaire.

The occurrence of any serious adverse events (SAEs) or serious adverse reactions (SARs) were ascertained and recorded using the study SAE form.

Outcome measures

The pre-specified clinical outcome measures were:

Primary outcome: The proportion of children developing new caries (D₄₋₆MFT) on any surface of up to four treated FPMs

Secondary caries models at child, tooth and surface levels were as follows:

- The number of FPMs remaining free of caries into dentine per child for those FPMs included in the trial
- The caries status of treated or untreated caries on each surface of each FPM
- The binary outcome of caries occurrence on occlusal vs non-occlusal surfaces of each FPM

Sample size

Data from a previous cohort study of local primary school children were used to derive the caries incidence in children (mean age 6.5yrs) with at least one erupted first permanent molar (Treasure et al., 2005). By the age of 10 years, 40% had caries in one or more of their first permanent molars. Based on recent Cochrane reviews it was estimated that FV would reduce the 3 year incidence from 40% to 30% in this population (Marinho et al., 2013), whereas FS would reduce it further to 20% (Ahovuo-Saloranta et al., 2013). For an individually randomised trial at a power of 80% with a significance level of 5%, at least 313 children per group were required for a comparison of caries incidence of 20% vs 30% at 36 month follow-up.

Randomisation

Randomisation of participants was stratified by school and balanced for gender and primary dentition baseline caries levels using minimisation in a 1:1 ratio for treatments. A random component was added to the minimisation algorithm (Altman and Bland, 2005), such that it was not completely deterministic (Brown et al., 2005).

Sequence generation

Randomisation was carried out by the South East Wales Trials Unit, independently of the recruiting and examining personnel in the MDC, using lists of pupil gender and caries data charts collected at baseline.

Allocation concealment mechanism and implementation

Allocation lists were produced and provided to the MDC staff within a two week window before they returned to the school for the baseline treatments.

Blinding

The physical nature of the technologies under test limited the scope for blinding. Both the participant and the dental hygienist were aware of the treatment provided. The dentist undertaking the clinical dental examinations at baseline, 12, 24 and 36 months was not informed of the arm to which the participant had been randomised. However, the presence or absence of fissure sealants at assessment would obviously indicate the likely treatment received.

Statistical methods

All comparative analyses were carried out on an intention-to-treat (ITT) basis (without imputation). The primary outcome was the proportion of children experiencing caries into dentine at ICDAS level 4-6 on any one of up to four FPMs in the trial at 36 months. The $D_{4-6}MFT$ variable was calculated (and converted to a binary outcome) from the full caries charts of those children attending the 36 months examination and included only those FPMs in the trial. FPMs which were already sealed, carious into dentine, filled or affected by Post Eruptive Breakdown (PEB) at baseline were excluded from the trial.

The primary outcome was analysed using a logistic regression model. The results are presented as unadjusted and adjusted odds ratios (ORs) for the FV arm compared to the FS arm. The intervention was carried out within schools so a two-level logistic model was used to account for clustering by school. If clustering was found to be negligible the primary analysis was taken to be a single level model. Two- and three-level logistic regression models were used for the analysis of tooth and surface level caries outcomes. Ordinal regression was used to analyse the number of FPMs with caries. All models were adjusted for the randomisation balancing variables, gender and baseline caries in the primary dentition. Baseline caries ($d_{4-6}mft$) was categorised as (none, 1-2 primary teeth, 3 or more primary teeth). The number of FPM per child in the trial was also added to the models as a covariate

but removed if non-significant. Other covariates added to the primary analysis model were those from the dental health questionnaire.

Statistical analysis was conducted using SPSS for Windows v.20 (IBM Corp, Armonk, New York) and STATA (StataCorp, Texas).

Approvals

Research ethics approval was granted by the Research Ethics Committee for Wales 3 (Ref 11/MRE09/6). The trial was regulated by the UK Medicines and Healthcare Regulatory Authority (MHRA) as a clinical trial of an investigational medicinal product (CTIMP).

There were no significant changes to the trial methodology after trial commencement.

RESULTS

Participant flow through the trial is illustrated in Figure 2. In total, 1303 children for whom parental consent had been obtained, were screened for participation in the trial. Of these, 1016 were deemed eligible for inclusion, but one participant subsequently withdrew consent to participation and use of any of their data. At screening, 287 children were excluded mainly due to lack of FPM eruption. Children were randomised to receive fissure sealants (514) or fluoride varnish (501).

The baseline characteristics of the study participants are shown in Table 1. In line with the targeted population approach of Designed to Smile, 78.7% of the study population were resident in the second most and most deprived quintiles of deprivation. There were no apparent differences between trial arms in gender or the proportion of children with caries experience in their primary dentition. Within deprivation quintiles, the distribution of children across trial arms was similar and 78.6% of children lived in the bottom two quintiles of deprivation. There were no marked differences in baseline dental caries experience at baseline of the 835 children who completed the trial or of the 180 who either were lost to follow-up or withdrew.

At 36 months, 835 (82.2%) children underwent a final clinical examination, 418 in the FS arm and 417 in the FV. The most common reason for not completing the trial was moving away from the area or to a school that was not participating in the trial, reported as lost to follow-up (Figure 2). Five children withdrew from the FS arm and seven from the FV arm.

Drop-out bias was assessed using baseline data and was not identified, missing data were therefore assumed to be missing completely at random. We also ascertained that drop out was low, mainly due to moving school and was not associated with treatment arm. This all pointed to a conclusion that missing data were missing completely at random.

Trial fidelity was high, 95% received at least 5 of the 6 scheduled treatments and 97.6% of children had their treatment on time or outside the 4 week window only once. Sealant retention was high. At 36 months, in the maxillary FPM 74.5% were intact, 23.3% were partially intact and 0.5% were lost. Corresponding figures for the mandibular FPMs were 91.4%, 5.1% and 0.8%. No adverse effects were reported during or in the 48 hours after treatment in either group. Both inter and intra examiner reproducibility were high with mean kappa scores of 0.82 and 0.89 respectively.

The proportion of children who developed dentine caries ($D_{4-6}MFT$) on at least one FPM at 36 months was broadly similar in both the FS (19.6%) and FV (17.5%) arms (Table 2). Since gender and baseline caries prevalence were used to balance the randomisation an adjusted model was also performed and was taken as the primary analysis. The odds ratio for developing caries in the FV arm was 0.84 (95% CI 0.59 to 1.21) in the adjusted model. The final model (Table 2) shows that there was no significant difference in the proportion of children with dentine caries ($D_{4-6}MFT$) on any FPM in the trial at 36 months whether the children received either FS or FV. Children who had more than three carious primary teeth at baseline were significantly more likely to develop caries into dentine on a FPM at 36 months. There was no difference between the proportion of boys and girls developing caries into dentine on at least one FPM. None of the covariates altered the main effect for arm.

The findings for caries outcome models at tooth, tooth surface, and occlusal vs non-occlusal surfaces are shown in Table 3. No significant differences between the interventions tested were observed, the number of teeth developing caries in both trial arms being very similar.

DISCUSSION

This is the largest ever study to address the question of the clinical and cost effectiveness of FS and FV. The very high standard to which this work was conducted and the excellent Statfidelity obtained, means that the findings here are robust.

Given that the recent systematic review of the effectiveness of the technologies tested suggest that FS may be clinically superior (Ahovuo-Saloranta et al., 2016), the results obtained in this trial are perhaps contrary to what many paediatric and public health dentists would have expected. However the evidence available to inform that review was very weak. There have previously only been four studies which have directly compared FS and FV (Bravo et al., 2005; Liu et al., 2012; Raadal et al., 1984; Salem et al., 2014). Three of these contributed to the Cochrane review. Two studies of two years duration, a split-mouth study at high risk of bias conducted in 1984 (Raadal et al., 1984) and one parallel-group study (Liu et al., 2012) at unclear risk of bias, together provided a total of 358 children to the analysis. The work of Bravo and colleagues (Bravo et al., 2005), reported on a comparison of FS and FV at 4 and 9 years, but the final outcome was based on just 75 children and was deemed by the Cochrane group to be at high risk of bias (Ahovuo-Saloranta et al., 2016).

The Seal or Varnish trial has clearly shown that, while at 36 months fewer than one in five children had developed decay into dentine in their FPM, there was no clinically important difference in the proportion of children developing decay (D₄₋₆MFT) on any FPM whether treated with FS or FV. The effectiveness of fissure sealants when tested against no treatment controls is generally accepted and has been reinforced by the findings of two recent systematic reviews (Ahovuo-Saloranta et al., 2013; Wright et al., 2016b). Both the Department of Health in England (Public Health England, 2014), and the American Dental Association (Wright et al., 2016a) endorse the use of sealants as effective caries preventive agents. However, the current study suggests that six-monthly application of fluoride varnish results in a caries preventive effect that is not significantly different from that obtained by the use of sealants. This may contradict the recent recommendations of the American Dental Association (Wright et al., 2016a) of a preference for FS over FV in preventing occlusal caries.

CONCLUSIONS

The findings of this trial demonstrate that in community oral health programmes targeted at children at high caries risk, the application of fluoride varnish as a caries preventive measure will result in caries prevention that is not significantly different from that obtained by applying and maintaining fissure sealants after 36 months.

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LEGENDS FOR FIGURES

Figure 1 Trial design

Figure 2 Participant flow through the trial

Table 2 The proportion of children with dentine caries (D4-6MFT) on any FPM in the trial, at 36 month follow up by trial arm and the influence of covariates.

	Fissure Sealant Arm N=418	Fluoride Varnish Arm N=417	Total N=835	
No dental caries on any FPM	336 (80.4%)	344 (82.5%)	680 (81.4%)	
Dentine caries on at least one FPM	82 (19.6%)	73 (17.5%)	155 (18.6%)	
	Unadjusted OR (95% CI)	p-value	Adjusted* OR (95% CI)	p-value
Fissure sealant	reference		reference	
Fluoride varnish	0.87 (0.61 to 1.23)	0.433	0.84 (0.59 to 1.21)	0.351
Covariate			Adjusted* OR (95% CI)	p-value
Global Oral Hygiene Regimen	Fissure sealant		reference	
	Fluoride varnish		0.90 (0.55, 1.45)	0.652
Additional Fluoride	Fissure sealant		reference	
	Fluoride varnish		0.93 (0.57, 1.50)	0.753
Cariogenic Global Score	Fissure sealant		reference	
	Fluoride varnish		0.85 (0.53, 1.39)	0.526
Socio-economic group	Fissure sealant		reference	
	Fluoride varnish		0.85 (0.51, 1.41)	0.524
Frequency of brushing	Fissure sealant		reference	
	Fluoride varnish		0.97 (0.59, 1.59)	0.904
Toothpaste type	Fissure sealant		reference	
	Fluoride varnish		0.88 (0.54, 1.44)	0.616
Length of time brushing	Fissure sealant		reference	
	Fluoride varnish		0.99 (0.55, 1.47)	0.666
WIMD child	Fissure sealant		reference	
	Fluoride varnish		0.85 (0.59, 1.22)	0.371

**FV compared FS. Analysis adjusted for baseline caries prevalence and gender*

Table 3 The development of caries into dentine at (a) tooth, (b) tooth surface and (c) occlusal vs non-occlusal surface on first permanent molars (FPM) by intervention arm at 36 months.

(a) The proportion of FPM teeth with dentine caries (D₄₋₆MFT) at 36 months by intervention arm				
	Fissure sealant N=1609	Fluoride varnish N=1596	Total N=3205	
No caries	1489 (92.5%)	1476 (92.5%)	2965 (92.5%)	
Caries on FPM tooth	120 (7.5%)	120 (7.5%)	240 (7.5%)	
	Unadjusted OR (95% CI)	p-value	Adjusted* OR (95% CI)	p-value
Fissure sealant	reference		reference	
Fluoride Varnish	1.03 (0.79 to 1.35)	0.825	0.97 (0.73 to 1.28)	0.830
<i>Intraclass Correlation Coefficient for quadrant = 0.12</i>				
(b) The proportion of FPM surfaces with dentine caries (D₄₋₆MFT) at 36 months by intervention arm				
	Fissure Sealant N=8041	Fluoride Varnish N=7975	Total N=16016	
No caries	7872 (97.9%)	7794 (97.7%)	15666 (97.8%)	
Caries on FPM surface	169 (2.1%)	181 (2.3%)	350 (2.2%)	
	Unadjusted OR (95% CI)	p-value	Adjusted** OR (95% CI)	p-value
Fissure Sealant	reference		reference	
Fluoride Varnish	1.17 (0.93 to 1.46)	0.177	1.06 (0.84 to 1.33)	0.619
<i>Intraclass Correlation Coefficient for quadrant= 0.197, ICC for surface= 0.058</i>				
(c) The proportion of occlusal and non-occlusal surfaces with dentine caries (D₄₋₆MFS) at 36 months by intervention arm				
	Fissure Sealant N=8041	Fluoride Varnish N=7975	Total N=16016	
Caries on non-occlusal surface	64/6432 (1.0%)	81/6380 (1.3%)	145 /12812 (1.1%)	
Caries on occlusal surface	105 /1609 (6.5%)	100 /1595 (6.3%)	205/3204 (6.4%)	
			Adjusted** OR (95% CI)	p-value
Fissure sealant			reference	
Fluoride Varnish			1.25 (0.89 to 1.77)	0.202
<i>Intraclass Correlation Coefficient for quadrant=0.213 ICC for surface=0.075</i>				

*Adjusted for gender and baseline caries risk.

**Adjusted for baseline caries risk group, gender, number of FPMs in the trial.

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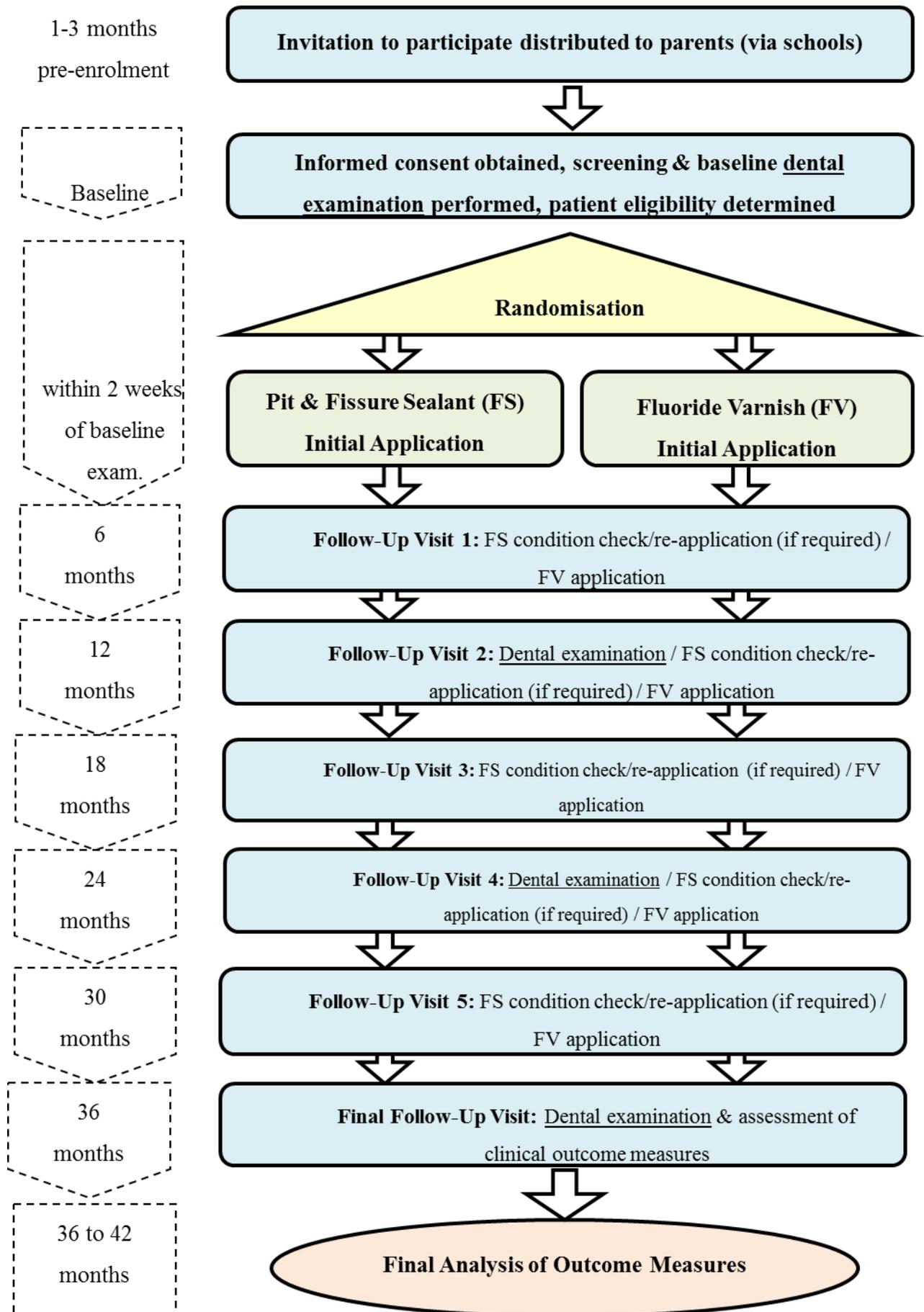
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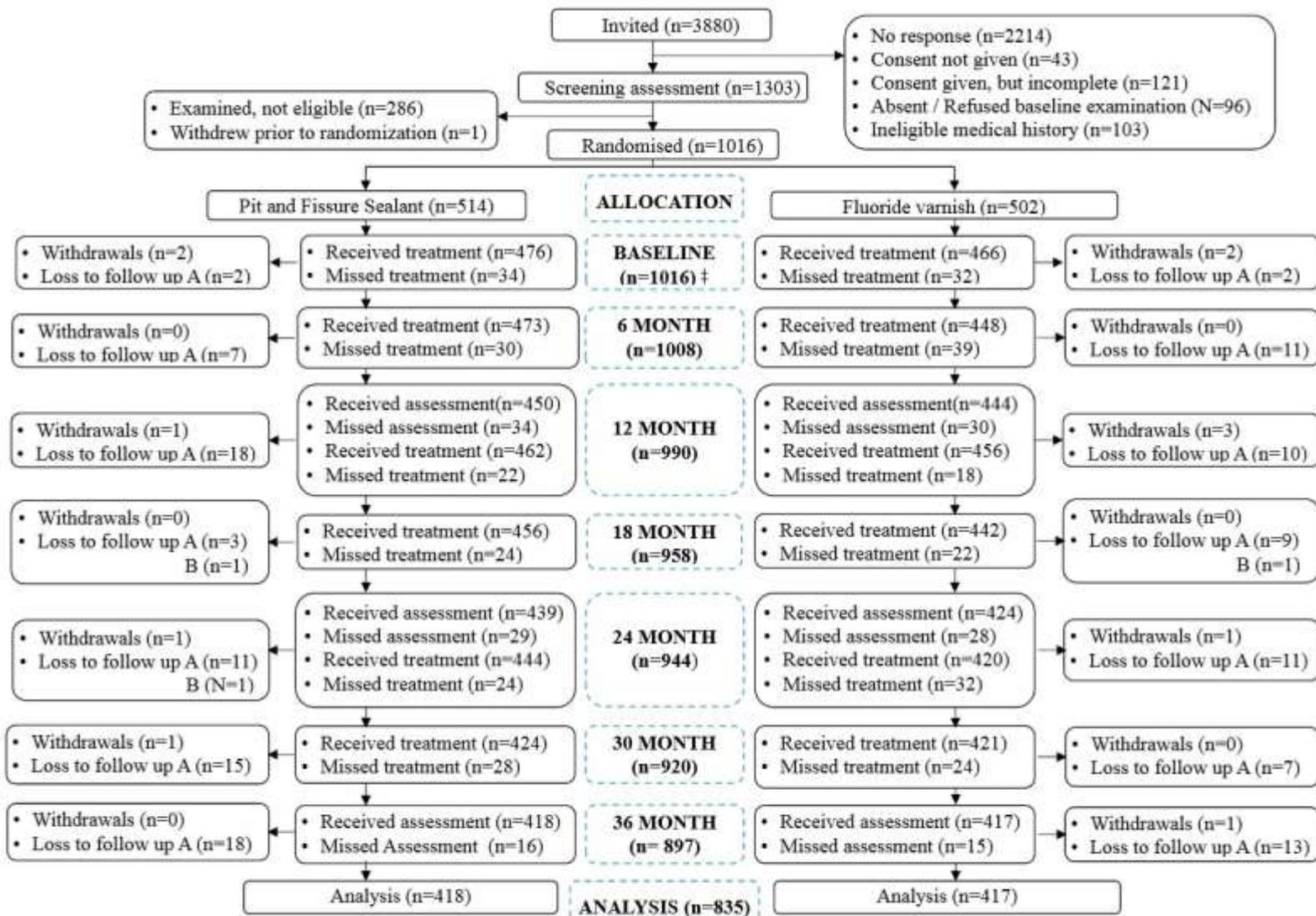
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† - One participant from the Fluoride Varnish arm subsequently withdrew consent to use all data

Loss to follow up: A= moved to a non-participating school, B= change in medical circumstances prevented further participation in the trial.

