FICTION 07/44/03: STATISTICAL ANALYSIS PLAN (SAP)

FiCTION Trial

Filling Children's Teeth: Indicated or Not?

SAP Version number: V1.0

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1. INTRODUCTION

This statistical analysis plan provides guidelines for the analysis, and the presentation of the analysis, of the FiCTION trial data. This plan should be read in conjunction with the current study Protocol and Data Management Plan. This plan, along with all other documents relating to the analysis of this trial, will be stored in the 'Statistical Trial Master File'.

1.1 Trial design

The FiCTION Trial is a multi-centre, three-arm, parallel group, patient randomised controlled trial.

The aim of the FiCTION trial is to compare the relative clinical and cost-effectiveness of the following three treatment strategies in 3-7 year-old children with caries in primary teeth:

1. Conventional management of caries (local anaesthetic, removal of decay and placement of a filling), with best practice prevention.
2. Biological management of caries (sealing in decay with crowns, partial caries removal and fissure sealants), with best practice prevention.
3. Best practice prevention alone.

The trial setting is Primary Care General Dental practices, recruited from one of five centres:

1. Scotland

2. North East/Cumbria

3. Yorkshire/Manchester and Liverpool

4. Wales

5. London

1.1.2 Trial objectives

The primary objective of this trial is to compare the three treatment strategies, when applied over a period of up to three years to 3-7 year old children with caries in primary teeth, with respect to the clinical outcome of incidence of dental pain (i.e. due to caries) and/or dental sepsis.

The secondary objectives are to compare the three treatment strategies with respect to:

a. incidence of caries in primary and permanent teeth
b. patient quality of life;
c. cost-effectiveness over the period of the study
d. acceptability and associated experiences for patients and parents; and
e. dentists' preferences

1.2 Randomisation

This is an open randomised trial; the management strategies being used mean that it is not possible to blind the parents, children, or dentists as to which arm the child is participating in. The unit of randomisation is the child.

Participants are randomised into the three caries management strategies (Conventional with best practice prevention, Biological with best practice prevention and Best practice prevention alone) in a 1:1:1 ratio.

Randomisation is stratified by site (dental practice) using variable length random permuted blocks to ensure concealment of allocation.

Randomisation is through a secure password protected web-based system administered centrally by the Newcastle Clinical Trials Unit (NCTU).

1.3 Sample size

1.3.1 Original sample size

Assumptions:

- Rate of pain and/or sepsis in the three groups at 3 year follow-up is: 20%, 10%, 3%
- Type 1 error rate = 2.5% (to allow for multiple comparisons)
- Attrition rate/ loss to follow-up is 25%
- Allowance for adjustment for strata: sample size increased by 9%
- Power – looking at impact of reducing power requirement from 90% to 80%

The target sample size required to detect the hypothesised effect sizes at specified levels of power are given in the following table:

Power	**Number per group at end of follow-up[a]**	**Number required to allow for 25% attrition[b]**	**Inflated by 9% to allow for adjustment for strata [b]**
90	334	1338	1461
85	293	1173	1281
80	263	1053	1149

[a] Numbers based on Fleiss's method for a difference in proportions incorporating a continuity correction (as implemented in the sampsi procedure in stata v11); the number given is the maximum needed either for 20% v 10% or 10% v 3 %.

[b] figures rounded up to a multiple of 3

An explanation (from Nick Steen) of why an adjustment for strata was included in the original sample size calculation. When designing the study the sample size was inflated by a factor of 1.09 to allow for adjustment of estimates of effect size taking into account differences between the randomisation strata, i.e. differences between dental practices. At the time of the original sample size calculation it was deemed desirable to include an adjustment, but in practice such adjustments are very rarely included in sample size calculations mainly because it is almost impossible to predict in advance what the inclusion of additional terms is going to have on the standard error of the estimates of effect size. It is entirely possible that inclusion of strata as covariates will reduce the standard error and thus may actually suggest that a smaller sample size is required. The actual inflation factor of 9% was entirely arbitrary.

1.3.2 Modified sample size approved by HTA in October 2014

A contract variation request was submitted to the HTA in August 2014 explaining that based on the recruitment trajectory at the time, with recruitment anticipated to continue until December 31st 2014 and follow-up until 30th June 2016, the study would only recruit 1113 children. This would correspond to an effective sample size (after allowing for 25% loss to follow-up) of three groups of 278 children with a mean length of follow-up of 24.6 months, which (assuming a linear incidence of pain or sepsis over the follow-up period) would result in only 61% power to detect the hypothesised effect sizes (13.7% v 6.8%; and 6.8% v 2.05%) assuming a type 1 error rate of 2.5%.

Hence, using a data snapshot of 1012 participants on 31st July 2014, three possible alternative 'Scenarios' were put forward by the FiCTION team to the HTA who approved Scenario 1, detailed below:

Extension to study in months		12
End of Recruitment		31.12.14
End of follow-up		30.06.17
End of trial		31.12.17
New Practices		No
Target recruitment		1113
Mean length of follow-up in months		35.5
Power depending on whether adjustment for strata is necessary	No	82%
	Yes	77.4%

In this Scenario the end of recruitment is still the end of December 2014, with a 12 month extension to the follow-up period to the end of June 2017. As such it was estimated that the trial would recruit 1113 children, but now with an average length of follow-up of 35.5 months. Thus, allowing for 25% loss to follow-up, the effective sample size would be three groups of 278 children followed up for on average 35.5 months. Assuming a linear incidence of pain or sepsis over the period of follow-up we would then have 82.0% power to detect the hypothesised effect sizes (19.72% v 9.86%; and 9.86% v 2.96%) assuming a type 1 error rate of 2.5%

It was subsequently agreed with the HTA (in November 2014) that due to the already variable follow-up and in order to maximise the chances of reaching the desired power, recruitment

could continue until 30th June 2015 and that new sites could be added to facilitate this recruitment on the understanding that any costs this may incur were to be absorbed by the current budget.

Analysis populations

It is important to define the analysis sets before June 2017 so as to minimise any potential bias in the selection of data to be included or excluded from analyses.

Table 1: Analysis sets

Analysis set	n	Definition:
All randomised		All randomised children, retaining participants in their randomised treatment groups.
Intention-to-treat (ITT)		All randomised children with at least one CRF in macro [i.e. at least one clinical assessment of the primary outcome], retaining participants in their randomised treatment groups. Primary outcome data is from completed CRFs
Imputed ITT		The same participants as in the ITT analysis set, but with the addition of an imputed measure of pain for participants where there is an 18m or final visit adult non-attendance questionnaire. Primary outcome data is from completed CRFs and completed adult non-attendance questionnaires. This analysis will only be carried out if ≥ 80% of non-attendance questionnaires are completed and returned.
Per protocol (PP)		The per protocol analysis set will exclude participants from the ITT analysis set who were: • deemed likely to have had dental pain and/or dental sepsis at consent • 'non-compliant' with the operative treatment protocol of their randomised treatment arm (i.e. defined as having a TDF involving a 'major' deviation from the randomised treatment arm operative treatment protocol at every study visit).

TIMING AND REPORTING OF FINAL ANALYSIS

Recruitment to be completed by 30th June 2015

Follow-up to be completed by 31st May 2017 to allow data returns

Cut-off for data returns mid-June 2017

Cut-off for data entry 30th June 2017

Interim data download to carry out data cleaning mid-July 2017

Database lock mid-August 2017

Main analysis to be undertaken mid-August to October 2017

Final report to be submitted to HTA in January 2018

3. DATA QUALITY

3.1 Data sources and data returns

The outcome data collection sources and how each item of each data collection tool maps on to which outcome are documented in the FiCTION Outcomes document.

All data sources, their mode of entry, the number of forms returned (or number of rows of data) and the format in which they will be provided to the statistics team is documented in Table 2 below.

Table 2: Data sources and data returns

Data source	Route	Data entry	Data entered	Format provided to statisticians	Notes
Randomisation log	From live randomisation log	Entered directly on to randomisation website	n= 1149	FictionRandLog20160210.csv	This includes the 5 entries where a participant didn't exist – 'administration errors'. n=1144 – children randomised
CRFs	Posted to NCTU monthly by sites	Entered in to MACRO by time of data snapshot.	n=	MACRO will be downloaded to STATA by eform	Stats will remove any blank rows (that is rows with only an ID and a date, blank otherwise) and will program implied yeses and nos where necessary
TDFs	Posted by sites attached to relevant CRF	Entered in to MACRO, but then verified by clinical research fellow	n=	MACRO TDF eform will be downloaded to STATA	
Withdrawal forms	Faxed to NCTU	Entered in to MACRO by time of data snapshot.	n=	MACRO Withdrawal eform will be downloaded to STATA	
Child Questionnaires "Questions about your teeth"	Posted to NCTU monthly by sites	Received by NCTU and entered in to SPSS by time of data snapshot.	n=	SPSS dataset	

Data source	Route	Data entry	Data entered	Format provided to statisticians	Notes
Baseline appointment Adult Questionnaire "About your child's teeth"	Posted to NCTU monthly by sites	Received by NCTU and entered in to SPSS by time of data snapshot.	n=	SPSS dataset	
Scheduled/recall Emergency/unscheduled appointment Adult Questionnaire	Posted to NCTU monthly by sites	Received by NCTU and entered in to SPSS by time of data snapshot.	n=	SPSS dataset	
Final assessment Adult Questionnaire	Posted to NCTU monthly by sites	Received by NCTU and entered in to SPSS by time of data snapshot.	n=	SPSS dataset	
Subsequent non-attendance Adult Questionnaire	Posted directly by participant to NCTU	Received by NCTU and entered in to SPSS by time of data snapshot.	n=	SPSS dataset	
Final non-attendance Adult Questionnaire	Posted directly by participant to NCTU	Received by NCTU and entered in to SPSS by time of data snapshot.	n=	SPSS dataset	

Data source	Route	Data entry	Data entered	Format provided to statisticians	Notes
First treatment visit ICDAS Recording Sheet	Posted to NCTU monthly by sites	Received by NCTU and entered on to ICDAS website by time of data snapshot.	n=	Downloaded from ICDAS website as a text file and read into SPSS and cleaned according to the rules documented in the DMP.	These data will be forwarded to Professor William J. Montelpare who will be analysing the data according to the ICDAS SAP.
Final treatment visit ICDAS Recording Sheet	Posted to NCTU monthly by sites	Received by NCTU and entered on to ICDAS website by time of data snapshot.	n=	Downloaded from ICDAS website as a text file and read into SPSS and cleaned according to the rules documented in the DMP.	These data will be forwarded to Professor William J. Montelpare who will be analysing the data according to the ICDAS SAP.
Consent dates	Extracted from screening logs received by NCTU			Excel spreadsheet from TM	Only required to check eligibility for participants with pain at first visit where first visit was ≤7 days since randomisation. And also to check age, where <3 years at randomisation or ≥8 years.
Referral data	CRFs and also notification from Clinical Lead secretaries	Clinical research fellow	Number of referrals=	Excel spreadsheet from clinical research fellow	Referrals are identified via the CRF and via Clinical Leads secretaries and followed up by the clinical research fellow with sites for additional information

Data source	Route	Data entry	Data entered	Format provided to statisticians	Notes
Practice fluoridation status data	Analysed in Newcastle Dental School	Coordinated by Professor Anne Maguire	Number of practices=	Excel spreadsheet from clinical research fellow	
Practice 'index of deprivation'	Extracted from relevant data source by clinical research fellow.	Clinical research fellow	Number of practices=	Excel spreadsheet from clinical research fellow	

3.2 Data Validation

Any data cleaning performed by the data manager up to the point of the statistician receiving the data will be documented in Appendix 1 of the DMP (Data Processing Rules) with documented evidence of validation and checking.

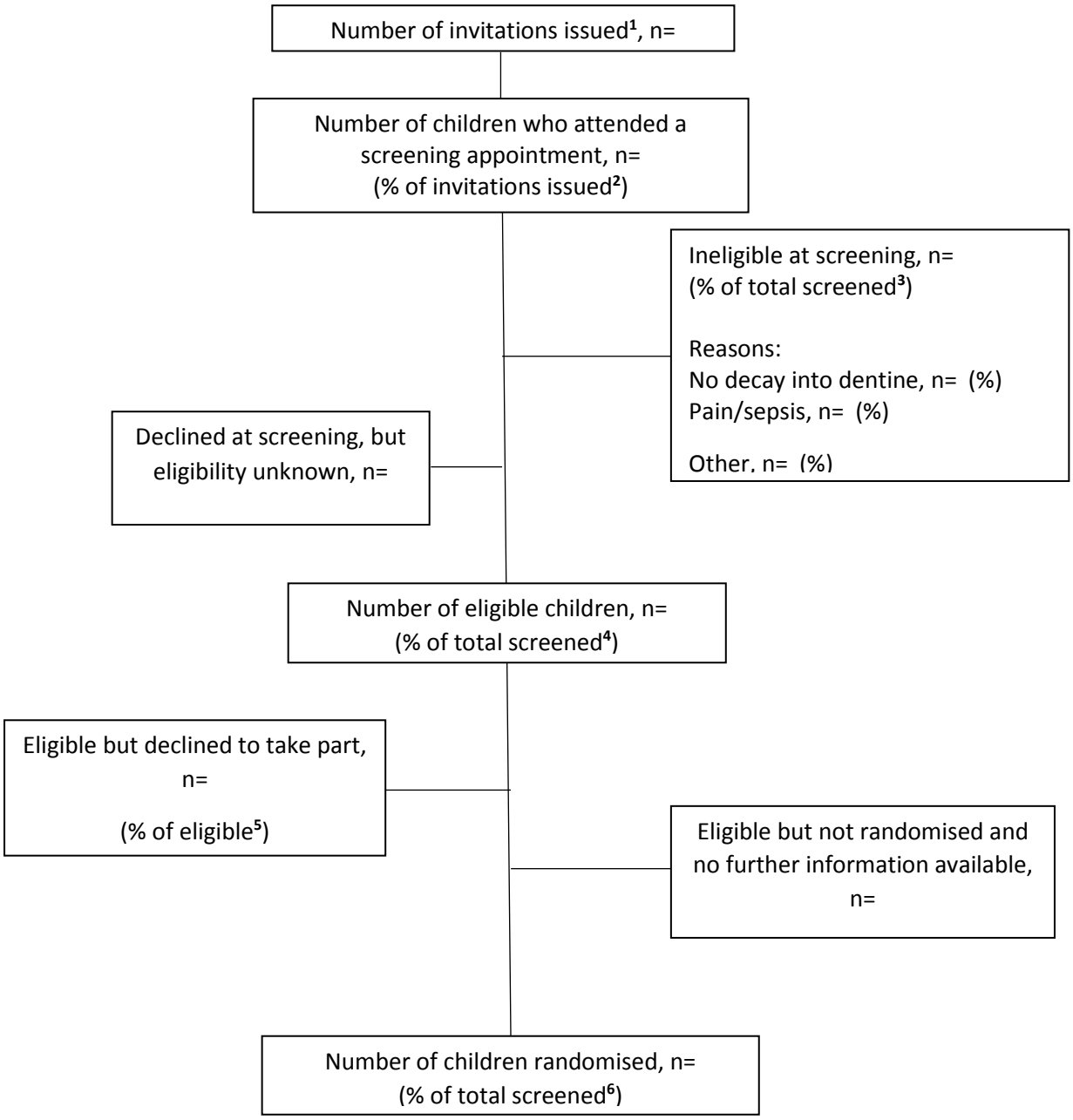
4. STUDY POPULATION

4.1 Recruitment

Recruitment opened on 1st October 2012; the first child was randomised on 12th October 2012.

The trial closed to recruitment on 30th June 2015; the last child to enter the study was randomised on 18th June 2015.

Figure 1: Recruitment summary



[1] Prior to the start of the study, it was estimated that 18717 children would be invited

[2] Prior to the start of the study, it was estimated that 65% of children invited would attend a screening appointment

[3] Prior to the start of the study, it was estimated that 85% of children screened would be ineligible

[4] Prior to the start of the study, it was estimated that 15% of children screened would be eligible.

[5] Prior to the start of the study, it was estimated that 20% of children screened and found eligible would decline to take part in the trial.

[6] Prior to the start of the study it was estimated that 12% of children screened would be randomised.

4.1.1: Randomisations by month

Figure 2: Cumulative number of children randomised by month [All randomised analysis set, n=xxxx]

4.1.2: Practice recruitment phases

The original target was to recruit fifty practices; approximately ten from each of the five Centres: Dundee/Glasgow, Newcastle, Sheffield/Leeds, Cardiff and London. The number of practices was subsequently increased to a target of 70 sites in light of conversations with the TSC, IDMC and HTA. The Centres were also expanded and are now defined as:
Scotland, North East England/Cumbria, Yorkshire/Manchester+Liverpool, Wales, London.

Table 3: Practice recruitment by phase and by Centre [All randomised analysis set, n=xxxx]

Centre	Phase[a]	No. of Initiated Sites [b]	No. of Sites that randomised at least one participant	No. of Sites that withdrew or were withdrawn (having randomised at least one participant)	Participants Randomised
Scotland	1				
	2				
	3				
	4				
Scotland Totals					
North East/ Cumbria	1				
	2				
	3				
	4				
North East Totals					
Yorkshire/ Manchester + Liverpool	1				
	3				
	4				
	5				
Yorkshire Totals					
Wales	1				
Wales Totals					
London	1				
	4				
London Totals					
Totals					

[a] *Phase 1 included those practices that had randomised at least one child into the study prior to the end of July 2013. Phase 2 was the recruitment of practices which hadn't been included in Phase 1 and was from July 2013, Phase 3 was from August 2013 and Phase 4 from December 2013. Phase 5 was from January 2015 and only includes sites in the Manchester/Liverpool Centre*

[b] *Site received site initiation visit and site approval*

4.1.3: Recruitment by randomisation strata

Randomisation was through a secure password protected web-based system administered centrally by the Newcastle Clinical Trials Unit (NCTU). Randomisation was stratified by site (dental practice) using variable length random permuted blocks to ensure concealment of allocation. xx sites had randomised at least one child by 30th June 2015. Summaries are presented across treatment arms by Centre and by site.

Table 4: Distribution of participants by Centre and randomised treatment arm [All randomised analysis set, n=xxxx]

			Randomised treatment arm			Total
			C+P	B+P	PA	
Centre	Scotland	Count				
		% within Centre				
	North East	Count				
		% within Centre				
	Yorkshire	Count				
		% within Centre				
	Wales	Count				
		% within Centre				
	London	Count				
		% within Centre				
Total		Count				
		% within Centre				

Table 5: Distribution of participants by site [All randomised analysis set, n=xxxx]

Centre	Site	Number of children randomised
Scotland		
North-East		
Yorkshire		
Wales		
London		

Table 6: Number of participants/site [All randomised analysis set, n=xxxx participants across xx sites]

	Minimum	Lower quartile	Median	Upper quartile	Maximum
Number of participants					

4.2 Dental Practice Characteristics

Practice characteristic information has been collected in order in order that the achieved sample of FiCTION practices can be put into 'context'. The variables collected are: practice size, practice fluoridation status and practice 'index of deprivation'.

Practice characteristics will be presented descriptively, overall and by Centre.

Table 7: Dental practice characteristics, by Centre

This table will be provided by the Clinical Research Fellow.

4.3 Ineligible Participants

Ineligible participants are classed as those randomised participants who are found to subsequently not adhere to the eligibility criteria of the trial (Protocol Section 2). The number of known ineligible participants and reasons for ineligibility will be reported. However, the primary analysis will be by intention to treat, i.e. including all randomised children with at least one CRF in macro [i.e. at least one clinical assessment of the primary outcome], retaining participants in their randomised treatment groups.

Table 8: Criteria for the assessment of eligibility

Criteria	Type	How will eligibility criteria be checked using available data?	Comments
3-7 years of age *at consent*	inclusion	DoB is given in randomisation log. Will use randomisation date to calculate age at randomisation. DoB is given on Adult baseline questionnaire and adult final questionnaire. DOB will be compared across the three sources and a verified DoB will be added to the randomisation log by the database manager.	Where ≥8 years old or < 3 years old at time of randomisation consent date will be checked.
Have at least one primary molar tooth with decay into dentine at consent	inclusion	It will not be possible to verify this criteria based on study data for all participants. Every participant's notes have been monitored at site to check for evidence of decay into dentine in at least one primary molar. If there was no evidence in the notes, the radiograph was checked if available, if no radiograph the ICDAS was checked.	Reasons why not possible to verify using the study data: Radiographs are meant to be taken in line with national guidelines. This means that participants might not necessarily have them taken at baseline as they may not be indicated at baseline. Decay in to dentine = ICDAS codes ending in 3/4/5/6. Primary molars are teeth: 55/54, 65/64, 75/74, 85/84. Baseline ICDAS recording sheets have not been returned for all participants.
Pain or dental sepsis associated with dental caries at consent These children should not have been enrolled, but after	exclusion	If the first study visit is ≤ 7 days from consent and there is evidence of dental pain and/or dental sepsis at the first study visit, the participant is deemed likely to have had dental pain and/or dental	

treatment could have been reassessed for eligibility		sepsis at consent and would therefore have been ineligible.	
Participants with a medical condition requiring special considerations with their dental management, e.g. cardiac defects, blood dyscrasias	exclusion	This information was not documented in the study data – so it will not be possible to verify this criteria.	

Table 9: Summary of ineligible participants by randomised treatment arm, against the criteria given in Table 8 [All randomised analysis set, n=xxxx]

Criteria	**Number (%) of participants who do not meet the criteria**			
	C+P	**B+P**	**PA**	**TOTAL**
3-7 years of age *at consent*				
Pain or dental sepsis associated with dental caries at consent				
TOTAL				

5. WITHDRAWALS/FOLLOW-UP

5.1 Withdrawals

All withdrawals are complete – there is consent to use participants' data up to the point of withdrawal but there is no further follow-up or data collection. Where possible practices ascertained the reason for withdrawal and documented this reason within the Withdrawal CRF.

5.1.1 Reasons for withdrawal

Table 10: Reasons for withdrawal by randomised treatment arm [All randomised analysis set, n=xxxx]

Reason (as stated on withdrawal CRF)	**C&P n=**	**B+P n=**	**PA n=**	**TOTAL n=**
Moving Away (and can't be accommodated in another FiCTION practice)				
Study Fatigue (eg. too many appointments, too much paperwork)				
Dental Reason (eg. traumatic event, GA, co-operation/compliance, unhappy with allocated arm)				
Personal Reason				
Other				
No Reason Given				
Practice has withdrawn				
TOTAL				

5.1.2 Withdrawals: number of study visits

Table 11: Withdrawals: number of study visits, by randomised treatment arm [All randomised analysis set, n=xxxx]

	C+P **n=**	**B+P** **n=**	**PA** **n=**	**TOTAL** **n=**
Number of study visits per withdrawn participant, x (% of withdrawn participants)				
0				
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
≥10				
Number of study visits per withdrawn participant, Min Median (LQ,UQ) Max				

5.1.3 Withdrawals: time in study

A withdrawn participant's time in the study will be calculated as time from randomisation to time of last known study visit (date of last CRF in MACRO). [The withdrawal date on the withdrawal form is not being used to calculate time in study as withdrawal forms were sometimes completed several months after the participant was last seen by the practice and so does not always represent a withdrawn participant's time in the study]

Table 12: Withdrawals: time in study (in months), by randomised treatment arm [All randomised analysis set, n=xxxx]

	C+P n=	B+P n=	PA n=	TOTAL n=
Time in study (months), Min Median (LQ,UQ) Max				

5.2 Follow-up

The study outcome analyses are based on the assumption of (approximately) equal follow-up across randomised treatment groups. Hence it is important to assess this assumption as differential follow-up can bias the analysis of the results.

Attendance at a study visit is evidenced by a CRF in MACRO (Question 1: Date of treatment).

5.2.1 Attendance at final study visit [All randomised analysis set, n=xxxx]

All participants have a final study visit date (FVD) around which a final visit window (FVW) is defined [see 'Final visit process' document for details]. A final visit process is in place to maximise attendance at final study visit. If participants do not attend their final visit in their FVW, practices are provided with 'non-attendance' questionnaires to send out to participants and their parents.

Note: a final study visit can be carried out for a participant who does not attend in their FVW but attends after their FVW and up to their practice's study end date (end of FVW for a practice's last participant). In addition, some final visits may occur close to but just before the scheduled FVW.

Follow-up will be reported by randomised treatment arm as:

- number (%) that attended their final visit in their scheduled final visit window (FVW)

- number (%) that attended a final visit outside of their scheduled FVW, either before or after [but this visit was designated as a final visit]
- number (%) that did not attend a final visit but completed a final visit 'non-attendance' questionnaire
- number (%) who had neither a final visit nor completed a final visit 'non-attendance' questionnaire [this will include the withdrawals].

5.2.2 Time in study [All randomised analysis set, n=xxxx]

A participant's time in the study will be calculated as time from randomisation to time of last known study visit (date of last CRF in MACRO). The following summary statistics will be reported for time in study by randomised treatment arm: min, LQ, MEDIAN, UQ, max.
Time in study=zero if no CRF in MACRO.

5.2.3 Completeness of follow-up [All randomised analysis set, n=xxxx]

The definition of loss to follow-up from the CONSORT website is: "the circumstance that occurs when researchers lose contact with some participants and thus cannot complete planned data collection efforts".

Completeness of follow-up will be calculated, by randomised arm, as: the total observed person-time of follow-up as a percentage of the total potential time of follow-up in the study. If a participant has a final visit in their FVW (or beyond the end of their FVW), their completeness of follow-up will be 100%. For participants whose last study visit was before their allocated FVW their 'potential time' will be defined as the time from randomisation to the start of their allocated FVW. The following summary statistics will be reported for completeness of follow-up by randomised treatment arm: min, LQ, MEDIAN, UQ, max.

The FVW is defined in the document Final Visit Pack Distribution Process V1.4 04.05.2016.pdf.

The references in relation to this section are references 1-4.

5.2.4 Number of study visits [All randomised analysis set, n=xxxx]

A 'study visit' is evidenced by a CRF in MACRO (Question 1: Date of treatment).

The following summary statistics will be reported for number of study visits by randomised treatment arm: min, LQ, MEDIAN, UQ, max.
Number of study visits=zero if no CRF in MACRO.

Table 13: Follow-up summaries, by randomised treatment arm [All randomised analysis set, n=xxxx]

	C+P	B+P	PA	Total
n				
Time in study (months) Min Median (LQ,UQ) Max				
Number of study visits Min Median (LQ,UQ) Max				
Completeness of follow-up Min Median (LQ,UQ) Max	% 	% 	% 	%

5.3 Definition of the Intention to Treat (ITT) analysis set

All randomised children with at least one CRF in macro [i.e. at least one clinical assessment of the primary outcome], retaining participants in their randomised treatment groups. Primary outcome data is from completed CRFs

5.3.1 Follow-up summaries for the ITT analysis set

Table 14: Follow-up summaries, by randomised treatment arm [ITT analysis set, n=xxx]

	C+P	B+P	PA	Total
n				
Time in study (months) Min Median (LQ,UQ) Max				
Number of study visits Min Median (LQ,UQ) Max				
Completeness of follow-up	%	%	%	%

Note: the analyses specified in Section 9 are dependent on approximate balance across the treatment arms in follow-up.

6. ADHERENCE TO PROTOCOL

6.1 Adherence to Clinical Protocol

The three treatment strategies for managing caries in the primary dentition are:

Arm 1: Conventional management of decay, with best practice prevention

Conventional management is commonly known as the 'drill and fill' method. This is the traditional approach to managing caries that has been taught and practiced for many years. It is based on active management of carious lesions by complete removal of carious tissue. For dentinal caries in primary teeth this means teeth are numbed with local anaesthesia (a dental injection), then carious tissue is mechanically removed using rotary instruments (drill) or by

hand excavation (using hand tools) and a restoration (filling) is placed in the tooth to fill the cavity. If the dental pulp is exposed during carious tissue removal or there are symptoms of pulpitis, a pulpotomy may be carried out. Retained roots, and teeth for which the crowns are unrestorable or the pulp chamber is open, are managed by extraction (removal) of the tooth following local anaesthesia.

Best practice prevention is carried out in line with current guidelines and as per Arm 3.

Arm 2: Biological management of decay, with best practice prevention

This approach to managing carious lesions involves sealing caries into the tooth, and separating it from the oral cavity by application of an adhesive filling material over the decay, or by covering with a metal crown. Decay may, on occasion, be partially removed prior to the tooth being sealed. Injections are rarely needed. Retained roots, and teeth for which the crowns are unrestorable, or dental nerves (pulps) exposed, are managed on a tooth by tooth risk analysis basis. Those with active carious lesions (still progressing) or where the clinician decides the tooth is likely to give the patient pain or sepsis before it exfoliates (falls out) are managed by extraction following local anaesthesia.

Best practice prevention is carried out in line with current guidelines and as per Arm 3.

Arm 3: Best practice prevention alone

With good oral hygiene it is possible to slow down the rate of tooth decay. For the best practice prevention alone arm, no drilling, filling or sealing of primary teeth will occur. Dentists and other members of the dental team will base treatment plans for patients on best practice preventive care for teeth and oral health. This will involve four strands (all carried out according to current guidelines):

- Toothbrushing/ self-applied topical fluoride use;
- Dietary investigation, analysis and intervention;
- Fissure sealants for secondary teeth; and,
- Fluoride varnish applied to primary and secondary teeth.

6.1.1 Adherence to randomised treatment arm operative treatment protocol [ITT analysis set, n=xxxx]

Deviations from the randomised treatment arm operative treatment protocol are recorded on the Treatment Deviation Form (TDF). These forms are entered in to MACRO and then verified by the Clinical Research Fellow and classified as a 'major' deviation from the randomised treatment arm operative treatment protocol (i.e. a major cross-arm tooth treatment change), or otherwise. For the purposes of assessing adherence to the operative treatment protocol only 'major' deviations are considered.

Adherence to the operative treatment protocol for each randomised treatment arm cannot be evaluated at a tooth level because TDFs did not collect tooth numbers and as multiple teeth can be treated at a visit a TDF could not be linked to a tooth, or number of teeth. In addition, tooth numbers were not collected for prevention activities. Adherence to the operative treatment protocol is therefore evaluated using child level summaries.

6.1.1.1 Child level summaries by randomised treatment arm *[ITT analysis set, n=xxxx]*:

Table 15: Summary of the number of TDFs per participant classified as involving a 'major' deviation from the randomised treatment arm operative treatment protocol, by arm and overall [ITT analysis set, n=xxxx].

Number of TDFs per participant involving a 'major' deviation from arm	**C+P** **n=**	**B+P** **n=**	**PA** **n=**	**Total** **n=**
0	x(%)			
≥1	x(%)			
Total Min Median (LQ,UQ) Max	x(%)			

Table 16: Summary of the number of study visits per participant involving a 'major' deviation [ITT analysis set, n=xxxx].

Number of visits per participant involving a 'major' deviation from arm	**C+P** **n=**	**B+P** **n=**	**PA** **n=**	**Total** **n=**
Zero visits involved a 'major' deviation	x(%)			
Between 1 and (n-1) visits involved a 'major' deviation	x(%)			
All visits involved a 'major' deviation	x(%)			

6.1.1.2 TDF level summaries by randomised treatment arm [ITT analysis set, *n=xxxx*]:

Table 17: Reasons for 'major' deviation from the randomised treatment arm operative treatment protocol (n=)

Reason for 'major' deviation	**Number**	**%**
Parent Factors		
Child pre-cooperative for LA		
Dentist's clinical judgement		
Child anxiety		
Food packing (PA arm only)		
Child Factors (not anxiety/ coop)		
Other		

Table 18: Direction of 'major' deviations only (n=)

Arm randomised to	Arms treatment deviated to[a]	Number of 'major' deviations by arm (n=)	Randomised arm deviated from – group total (%)
C+P			
C+P			
B+P			
B+P			
PA			
PA			

[a]**Note we will add as many rows as necessary to cover deviations to more than one arm.**

6.1.2 Radiographs [ITT analysis set, n=xxxx]

Participants in the trial should have radiographs taken as an aid to diagnosis and treatment planning when indicated in line with the Faculty of General Dental Practitioners (UK) Guidance.

Whether a radiograph was taken at an appointment is recorded in question 9 of the CRF (question 9a records radiographic findings and question 9b records why radiographs were not taken).

The frequency of radiographs will be tabulated by randomised treatment group.

Reasons why radiographs were not taken, will be tabulated by randomised treatment group.

6.1.3 Tooth treatment received [ITT analysis set, n=xxxx]

The aim of this section is to 'paint a picture' of what it means to be treated in each of the arms (preventive and operative treatments)

Tooth treatment received will be reported by randomised treatment group as:

- median (range) time of first treatment visit from the date of randomisation
- plot of time to first treatment visit

- median (range) number of treatment visits
- a summary of restoration materials used (Q12, CRF)
- a summary of operative treatments (Q12, CRF)
- a summary of prevention experience by pillars of prevention (q10b CRF) [where denominator is 'course of treatment']. Note: fissure sealants are age related so will be summarised separately. It is expected that for every course of treatment a participant would receive fluoride varnish plus at least one of the remaining two pillars: brushing/plaque control advice or diet investigation/advice.

6.2 Definition of the per protocol analysis set

The per protocol analysis set will exclude participants from the ITT analysis set who:

- were deemed likely to have had dental pain and/or dental sepsis at consent, and/or
- were 'non-compliant' with their randomised treatment arm operative treatment protocol (i.e. defined as having a TDF involving a 'major' deviation from the randomised treatment arm operative treatment protocol at every study visit). This approach has been taken due to the expectation that the number of visits per participant will be low and therefore to prevent excluding large amounts of data (e.g. using a criteria of 80% of visits without a 'major' deviation for a participant to be classified as per protocol would mean that a participant with ≤4 visits in total would be excluded if they had one visit with a 'major' treatment deviation). If the average number of visits is higher than expected then the definition of compliance will be revisited.

7. PROGRESS OF PARTICIPANTS THROUGH THE TRIAL

Figure 2: Consort flow chart of the progress of participants through the trial

Flow chart will be inserted here.

8. BASELINE PARTICIPANT CHARACTERISTICS

Demographic and clinical baseline characteristics will be compared across treatment groups descriptively. No significance testing will be carried out due to the randomised nature of the study.

Baseline will be defined for each characteristic.

Descriptive statistics will also be tabulated by Centre. [Randomisation was stratified by site, but it is not feasible to summarise baseline characteristics by site because of the number of sites and the small number of participants within some of the sites].

8.1 Participant characteristics at randomisation

Table 19: Participant characteristics, by randomised treatment arm [ITT analysis set[a], n=xxxx]

Participant characteristic	*n*	**C+P**	*n*	**B+P**	*n*	**PA**	**Total**
Age (years) Mean (sd)							
Gender (%) Female							
Ethnicity (%) White Black Indian, Pakistani or Bangladeshi Chinese Mixed race Other							

[a]A table for the 'All randomised analysis set' will be included in an appendix for comparison

Table 20: Participant characteristics, by Centre [ITT analysis set, n=xxxx]

8.2 Caries experience at first treatment visit (ICDAS)

Table 21: Summary of caries experience in primary dentition at baseline, by randomised treatment arm.

	Primary dentition (maximum: 20 teeth)			
	C+P n=	**B+P n=**	**PA n=**	**Total n=**
Total number of teeth per child Min Median (IQR) Mean (sd) Max				
Number of caries free teeth (ICDAS summary code 00) Min Median (IQR) Mean (sd) Max				
Decayed teeth (dt) Min Median (IQR) Mean (sd) Max **$d_{ICDAS\ 0\text{-}2}$ number of teeth whose highest surface caries severity code is ICDAS 0-2** **$d_{ICDAS\ 3\text{-}4}$ number of teeth whose highest surface caries severity code is ICDAS 3-4**				

$d_{ICDAS\ 5\text{-}6}$ **Number of teeth whose highest surface caries severity code is ICDAS 5-6** **$d_{ICDAS\ 4\text{-}6}$ [equivalent to d_3]** **number of teeth whose highest surface caries severity code is ICDAS 4-6**				
Missing teeth, due to caries (ICDAS summary code 97) Min Median (IQR) Mean (sd) Max				
Filled (but not decayed) teeth (No. of teeth with at least one surface with ICDAS restoration code 3-7 and caries severity code 0-3) Min Median (IQR) Mean (sd) Max				
d_3mft				

Table 22: Summary of caries experience in permanent dentition at baseline, by randomised treatment arm.

	Permanent dentition **First permanent molars: teeth 16/26/36/46**			
	C+P **n=**	**B+P** **n=**	**PA** **n=**	**Total** **n=**
Total number of first permanent molars per child Min Median (IQR) Mean (sd) Max				
Number of caries free teeth (ICDAS summary code 00)				

Min Median (IQR) Mean (sd) Max				
Decayed teeth (Dt) Min Median (IQR) Mean (sd) Max **$D_{ICDAS\ 0\text{-}2}$** **number of teeth whose highest surface caries severity code is ICDAS 0-2** **$D_{ICDAS\ 3\text{-}4}$** **number of teeth whose highest surface caries severity code is ICDAS 3-4** **$D_{ICDAS\ 5\text{-}6}$** **Number of teeth whose highest surface caries severity code is ICDAS 5-6** **$D_{ICDAS\ 4\text{-}6}$ [equivalent to D_3]** **number of teeth whose highest surface caries severity code is ICDAS 4-6**				
Missing teeth, due to caries (ICDAS summary code 97) Min Median (IQR) Mean (sd) Max				
Filled teeth (ICDAS restoration code 3-7 and caries code 0-3) Min Median (IQR) Mean (sd) Max				
Caries experience in first permanent molars				

9. EFFECTIVENESS ANALYSIS

9.1 Primary Outcome

9.1.1 Definition of the co-primary outcomes

The co-primary outcomes are:

- the proportion of children with at least one episode of pain due to caries and/or dental sepsis during the follow up period (incidence), and
- the total number of episodes of pain due to caries and/or dental sepsis for each child during the follow-up period.

9.1.2. Primary outcome measure

The primary outcome measure is a binary indicator of pain due to caries and/or dental sepsis at each treatment visit during the follow-up period (minimum of 23 months to a maximum of 36 months). Treatment visits are scheduled appointments and unscheduled/emergency appointments.

- Pain due to caries is defined on the CRF by a yes to question 7 and yes to question 7a (caries)
- Dental sepsis is defined as confirmed infection on the CRF by yes to question 8

9.1.3 Definition of an episode

Several treatment visits (i.e. a course of treatment) can be associated with the same 'episode' of pain and/or dental sepsis. As such we need a definition of an 'episode' of pain due to caries and/or dental sepsis.

Episodes are defined on a tooth by tooth basis.

Defining an episode of pain and/or dental sepsis using CRF data:

Let Y=pain and/or dental sepsis at a single treatment visit; N otherwise

Let YY= pain and/or dental sepsis at consecutive treatment visits (i.e. on consecutive CRFs)

- Any number of consecutive yeses on same tooth regardless of timeframe = a single episode [e.g. YYYYY over 5 months]
- YY on different teeth (regardless of timeframe) = two separate episodes
- YNY on the same tooth = two separate episodes (regardless of timeframe)

Although episodes are defined on a tooth by tooth basis, within child if there are two teeth with pain due to caries and/or sepsis at the same visit this will be recorded as one episode for that child.

9.2 Primary analysis of the co-primary outcomes

The primary outcome analysis is a comparison of children's experience of pain due to caries and/or dental sepsis, during the follow up period, across the three treatment arms. This will be analysed in two ways, as the proportion of children with at least one episode of pain due to caries and/or dental sepsis during the follow up period (incidence), and also as the total number of episodes of pain due to caries and/or dental sepsis for each child during the follow-up period.

The original power calculation for the study was based on a comparison of proportions and as such is the only powered analysis. However, as the trial progressed it became clear that the number of episodes experienced by a child is a more clinically relevant outcome and statistically a more sensitive measure (compared with dichotomising the number of episodes into zero episodes and at least one episode). It was decided therefore that that the number of episodes should be a co-primary outcome. As it's not possible to retrospectively do a power calculation for a comparison of the mean number of episodes between groups, an exploratory hypothesis test for the unpowered comparison of the mean number of episodes will be reported.

Further, the original study design assumed a fixed follow-up period of 3 years, but an extension to the study recruitment period resulted in maximum potential follow-up ranging from 23 to 36 months. It also became clear over the course of the study that there were participants who were not reaching their potential maximum follow-up, even though they had had the opportunity to do so. To account for this observed variable follow-up (due to lack of opportunity, loss to follow-up or withdrawal), length of follow-up in years will be included as a covariate in all statistical models.

Age of participant in years at randomisation will also be included in all statistical models to account for the opportunity for exposure to refined sugars, a primary aetiological factor for dental decay (and therefore pain due to caries and/or dental sepsis); older children, in general, will have had a longer exposure to this key risk factor.

All continuous covariates will be initially included as linear terms, but assessed against other simple transformations based on an appropriate goodness of fit test.

The following proposed outcome analyses are based on the assumption of (approximate) balance between randomised treatment arms in regards to follow-up time and reasons for loss to follow-up. It also assumes that a reasonable estimate of the underlying rate of pain due to caries and/or dental sepsis can be made for each participant. Sensitivity analyses will be included to assess the robustness of these assumptions.

9.2.1 The primary analysis of the proportion of children with at least one episode of pain due to caries and/or dental sepsis during the follow up period (incidence), [ITT analysis set]

The incidence of pain due to caries and/or dental sepsis during the follow-up period, will be analysed using logistic regression.

The dependent variable is a binary indicator of whether there was a reported incidence of pain due to caries and/or dental sepsis during the follow-up period. Data are from completed CRFs.

Differences between dental practices will be included as a random effect.

Length of follow-up in years will be included as a covariate. Follow-up is defined as time from randomisation to date of last CRF in MACRO.

Age, in years at randomisation, will be included as a continuous covariate.

Randomised treatment arm will be included in the model as a factor with three levels; with the conventional arm the reference group.

97.5% confidence intervals will be generated for the difference between study treatment arms (Prevention versus Conventional and Biological versus Conventional) expressed as odds ratios.

P-values will be reported.

Advantages: analysis is very similar to that specified in the original protocol when we were planning on three year follow-up for all children; the adjustment for randomisation strata is efficient (we lose only one of the residual error degrees of freedom as there is only a single parameter to be estimated).

Disadvantages: requires an assumption that the risk of developing pain and/or dental sepsis is proportional to the length of time that the child is followed up; we only utilise information relating to the first occurrence of pain or dental sepsis.

Model checking and sensitivity analyses

Both model fit summary statistics and graphical examination of model residuals will be used to assess the adequacy of the specified model. Sensitivity analyses will be performed around any possible misspecification identified in the model checking (e.g. influential observations). All participants had the opportunity to have at least 23 months follow-up. The influence of shorter lengths of follow-up on the treatment effect estimates will be assessed re-fitting the model including only participants with at least 23 months follow-up.

9.2.1.1 Descriptive statistics, binary outcome [ITT analysis set]

Table 23: Pain due to caries and/or dental sepsis ever [ITT analysis set]

Outcome	**C+P** **n=**	**B+P** **n=**	**PA** **n=**	**Total** **n=**
Pain due to caries ever (%)				
Yes	x (%)	x (%)	x (%)	x (%)
No	x (%)	x (%)	x (%)	x (%)
Missing	x (%)	x (%)	x (%)	x (%)
Dental sepsis ever (%)				
Yes	x (%)	x (%)	x (%)	x (%)
No	x (%)	x (%)	x (%)	x (%)
Missing	x (%)	x (%)	x (%)	x (%)
Pain due to caries and/or dental sepsis ever (%)				
Yes	x (%)	x (%)	x (%)	x (%)
No	x (%)	x (%)	x (%)	x (%)
Missing (on both)	x (%)	x (%)	x (%)	x (%)

9.2.1.2 Exploratory univariate analyses [ITT analysis set]

The relationship between the incidence of pain due to caries and/or dental sepsis during the follow-up period and the following variables will be explored descriptively and in univariate logistic models:

- Age of participant in years at randomisation, as a continuous covariate.
- Number of decayed teeth at baseline from ICDAS charting [level 5/6 cavitation] – for each participant.
- Participant ethnicity. There are 6 ethnicities listed in the adult baseline questionnaire: ‘white’, ‘black’, ‘Indian, Pakistani or Bangladeshi’, ‘Chinese’, ‘mixed race’, ‘other’.

Ethnicity will be explored as far as possible within the limitations imposed because of the distribution of participants across the categories and incomplete data.

- Fluoride level in drinking water. Dental practice tap water fluoride level (fluoride ppm) will be used as a proxy for a child's fluoridation status, in terms of the tap water supply they receive at home.
- Index of deprivation. Dental practice index of deprivation (using dental practice postcode to determine index of deprivation at super output area level) will be used as a proxy for a child's index of deprivation. The index will be extracted from census data collected during the recruitment phase of the study. Index of deprivation can change significantly both spatially and temporally (dependent on the neighbourhood) and so is expected to be a very approximate measure here.

9.2.1.3 Exploratory multivariable analyses [ITT analysis set]

The variables listed in Section 9.2.1.2 will be included in an exploratory multivariable logistic regression analysis, regardless of their univariate association with the outcome.

9.2.2 The primary analysis of the number of episodes of pain due to caries and/or dental sepsis during the follow up period [ITT analysis set]

The number of episodes of pain due to caries and/or dental sepsis, will be analysed using negative binomial regression.

The dependent variable is the total number of episodes reported by a child. Data are from completed CRFs.

Differences between dental practices will be included as a random effect.

Length of follow-up in years will be included as a covariate. Follow-up is defined as time from randomisation to date of last CRF in MACRO.

Age, in years at randomisation, will be included as a continuous covariate.

Randomised treatment arm will be included in the model as a factor with three levels; with the conventional arm the reference group.

97.5% confidence intervals will be generated for the difference between study treatment arms (Prevention versus Conventional and Biological versus Conventional) expressed as rate ratios.

Exploratory P-values will be reported.

Advantage: it uses all the available data.

Model checking and sensitivity analyses

Both model fit summary statistics and graphical examination of model residuals will be used to assess the adequacy of the specified model. Sensitivity analyses will be performed around any possible misspecification identified in the model checking (e.g. influential observations). In particular, if the negative binomial model does not fit adequately, a zero inflated negative binomial model will be considered.

All participants had the opportunity to have at least 23 months follow-up. The influence of shorter lengths of follow-up on the treatment effect estimates will be assessed re-fitting the model including only participants with at least 23 months follow-up.

9.2.2.1 Descriptive statistics, count data [ITT analysis set]

Table 24: Number of episodes of pain due to caries and/or dental sepsis [ITT analysis set]

Outcome	**C+P** **n=**	**B+P** **n=**	**PA** **n=**	**Total** **n=**
Number of episodes of pain due to caries Min Median (IQR) Mean (sd) Max Dental sepsis Min Median (IQR) Mean (sd) Max Pain due to caries and/or dental sepsis Min Median (IQR) Mean (sd) Max				

Figure 4: Number of episodes of pain and/or dental sepsis by randomised treatment arm [ITT analysis set]

Insert plot here.

9.2.2.2. Exploratory univariate analyses [ITT analysis set]

The relationship between the number of episodes of pain due to caries and/or dental sepsis and the variables specified in 9.2.1.2 will be explored descriptively and in univariate logistic models:

9.2.2.3 Exploratory multivariable analyses [ITT analysis set]

The variables listed in Section 9.2.1.2 will be included in an exploratory multivariable negative binomial regression analysis, regardless of their univariate association with the outcome.

9.3 Secondary analysis of the primary outcome

Time to first episode of pain due to caries and/or dental sepsis has been identified as particularly important in relation to the age of the child; the burden on younger children and their capacity to tolerate the dental treatment.

There will be an analysis of time to first episode (pain due to caries and/or dental sepsis) using a Cox proportional hazards model (or a parametric alternative if the proportional hazards assumption is not satisfied). Randomised treatment arm will be included in the model as a factor with three levels; with the conventional arm the reference group. 97.5% confidence intervals will be generated for the difference between study treatment arms (Prevention versus Conventional and Biological versus Conventional). Results will be given in the form of 97.5% confidence intervals for the hazards ratio.

A frailty model will be considered to account for differences between dental practices.

Model checking and sensitivity analyses

Both model fit summary statistics and graphical examination of model residuals will be used to assess the adequacy of the specified model. Sensitivity analyses will be performed around any possible misspecification identified in the model checking (e.g. influential observations). In particular, if the data suggest that the assumption of proportional odds is not satisfied alternative models will be considered.

9.3.1 Descriptive statistics, time to first episode [ITT analysis set]

Table 25: Time to first episode [ITT analysis set]

Including median follow-up by randomised treatment arm using reverse Kaplan-Meier estimate.

Figure 5: Kaplan-Meier estimates of survivor functions by randomised treatment arm [ITT analysis set]

Insert plot here.

9.4 Additional analyses

9.4.1. Primary outcome analyses: Imputed ITT analysis set

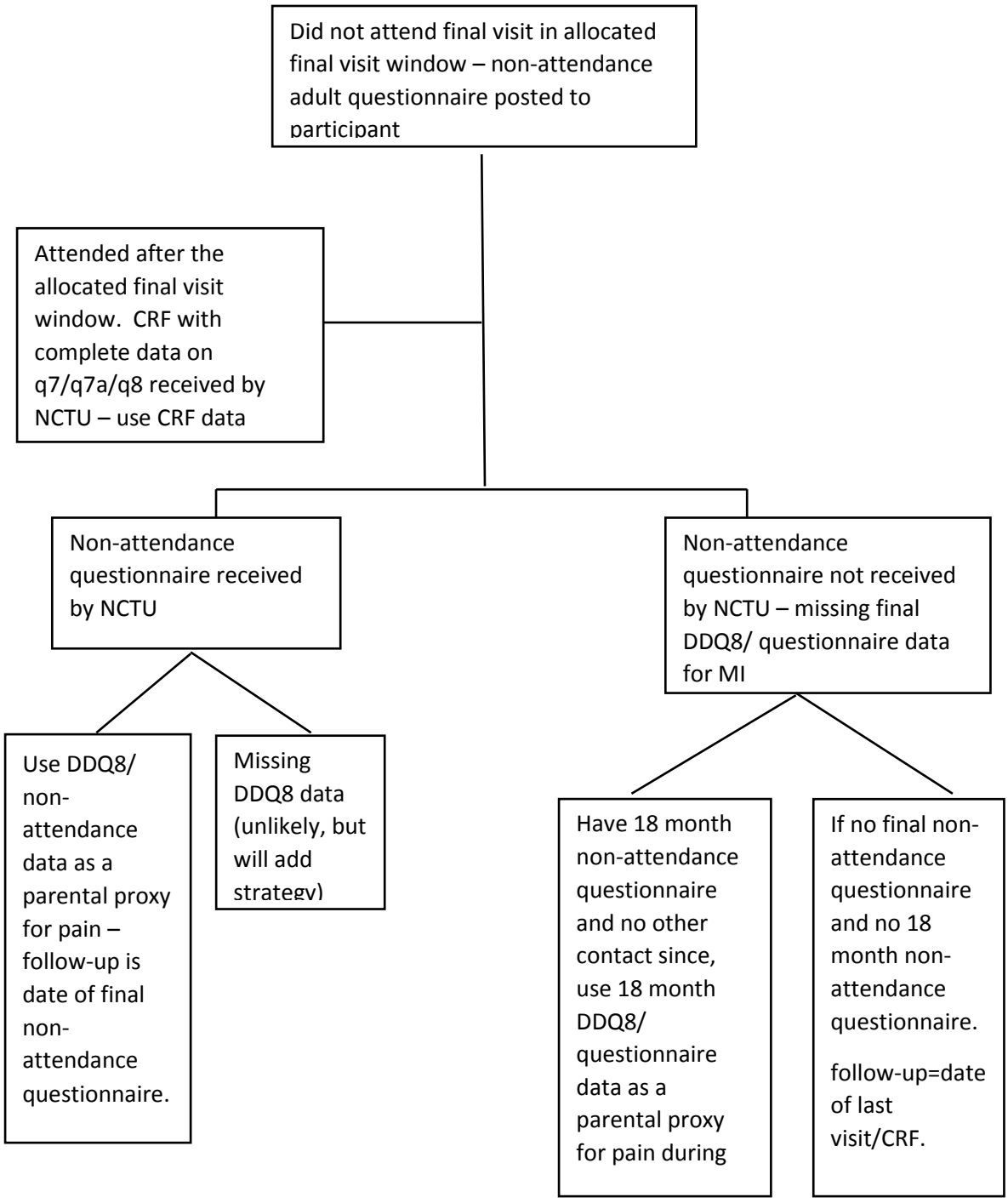
This analysis will only be carried out if ≥ 80% of non-attendance questionnaires are completed and returned.

A key issue to be addressed is how to handle children who do not return for their final follow-up visit in clinic and so have no final visit clinical assessment of pain and/or dental sepsis.

If a participant does not attend their final visit in their FVW the practice will post out 'non-attendance' child and adult questionnaires. The non-attendance adult questionnaire includes items which could be used to impute pain due to caries at the missed final clinic visit. In particular, the non-attendance adult questionnaire includes the 8 item Dental Discomfort Questionnaire (DDQ8) which has been used as a parental proxy for the identification of toothache in children.

An initial ROC analysis to establish (if it exists) a 'threshold' of responses to the DDQ8 which corresponds to "clinical pain" due to caries on the CRF was carried out in August 2015.
These analyses suggested that DDQ8 alone would perhaps not be an adequate proxy for pain due to caries. The conclusion at that time was that multiple imputation should be explored (and incorporated) as an option, as this is now considered a 'standard' approach. A summary of possible approaches for missing clinical assessment of pain at final visit was presented to the FiCTION team at a teleconference in September 2015. The document presented at that meeting is given in Appendix 3.

The following is a proposed strategy for the analysis of *the number of episodes of pain and/or dental sepsis during the follow-up period*, assuming DDQ8 or multiple imputation which includes data from the non-attendance questionnaire can be used as a parental proxy for "clinical pain" due to caries:



9.4.2 Primary outcome analyses: Per protocol analysis set

This won't involve imputed data and will be the same analyses as for the ITT analysis set using the per protocol analysis set.

9.4.3 Primary outcome additional imputed/sensitivity analyses

9.4.3.1 'No' to dental sepsis at question 8 CRF, but dental sepsis "acted upon"

CRF question 21 is about antibiotic prescribing. There are very few reasons to prescribe antibiotics so it is likely to be for dental pain/dental sepsis

Rule: If yes to Q21 (antibiotics) but no to Q8 (dental sepsis) and a DCR has been raised and the data have been verified, then include as a yes to Q8 (dental sepsis)

10. SECONDARY OUTCOMES

10.1 Incidence of caries in primary and permanent teeth

See Appendix 1: Assessing Caries

10.2 Child and parent reported outcomes (quantitative)

See Appendix 2: Child and parent reported outcomes (quantitative).

10.3 Cost effectiveness

The economic analysis is defined in a separate document.

11. SAFETY ANALYSIS

11.1 Descriptive reporting of serious adverse events (SAEs)

Assuming a small number of SAES each will be described separately.

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APPENDIX 1: ASSESSING CARIES

1. ICDAS DATA

We will have two sets of codes: one for primary teeth; one for permanent teeth scored at baseline and final follow-up. Permanent teeth differ systematically from primary teeth in both morphology and enamel thickness; it is expected that the rate of disease development/progression may be slower in permanent teeth. The proposal is to look at primary and permanent teeth separately.

For each child, for each tooth we will have a score for each surface (five surfaces for molars, four surfaces for other teeth) which is a two digit code. The second digit (caries severity code) is given in Table 1.

Table 1: ICDAS caries codes

<table>
<tr><td rowspan="2">ICDAS Code</td><td rowspan="2">Status of surface</td><td colspan="4">Aggregation of codes[a]</td></tr>
<tr><td colspan="2">Ordinal</td><td colspan="2">Binary</td></tr>
<tr><td>0</td><td>Sound</td><td rowspan="3">0</td><td rowspan="3">None/ initial caries</td><td rowspan="3">0</td><td rowspan="3">None/initial caries</td></tr>
<tr><td>1</td><td>First visual change in enamel</td></tr>
<tr><td>2</td><td>Distinct visual change in enamel</td></tr>
<tr><td>3</td><td>Enamel breakdown, no dentine visible</td><td rowspan="2">1</td><td rowspan="2">Moderate</td><td rowspan="4">1</td><td rowspan="4">Worse than “initial” caries</td></tr>
<tr><td>4</td><td>Dentine shadow (not cavitated into dentine)</td></tr>
<tr><td>5</td><td>Distinct cavity with visible dentine</td><td rowspan="2">2</td><td rowspan="2">Extensive</td></tr>
<tr><td>6</td><td>Extensive distinct cavity with visible dentine</td></tr>
<tr><td>7</td><td>Extracted due to caries (ICDAS code 97)</td><td>2[b]</td><td></td><td>1[b]</td><td></td></tr>
<tr><td>8</td><td>Missing for other reason (ICDAS code 98)</td><td>0[b]</td><td></td><td>0[b]</td><td></td></tr>
<tr><td>9</td><td>Unerupted (ICDAS code 99)</td><td>-</td><td></td><td>-</td><td></td></tr>
<tr><td colspan="6">[a] Suggested thresholds for defining simpler but more reliable indices of caries. This takes into account that enamel lesions charted may be inactive/reversible.
[b] Can be used to infer a “whole tooth” score but not to infer a “tooth surface” score</td></tr>
</table>

The first digit relates to the presence or absence of restorative intervention. Altogether there are eighty one possible codes that can be given to each surface. We need to define the status of surfaces and teeth at baseline and follow-up. The algorithm is given in the following table:

Table 2: Assessment of surfaces at baseline ("caries assessment score": CAS)

	Caries Code Digit									
Restoration code digit	**0** Sound	**1** Initial enamel	**2** Distinct enamel	**3** Enamel cavity	**4** Dentine shadow	**5** Distinct cavity	**6** Extensive cavity	**7** Extracted caries	**8** Extracted other	**9** Unerupted
0 = Sound	0	0	0	1	1	2	2	9	9	9
1 = Part sealed	0	0	0	1	1	2	2	9	9	9
2 = Fully sealed	0	0	0	1	1	2	2	9	9	9
3 = Tooth coloured	2	2	2	2	2	2	2	9	9	9
4 = Amalgam	2	2	2	2	2	2	2	9	9	9
5 = Stainless Steel crown	2	2	2	2	2	2	2	9	9	9
6 = Crowns etc	2	2	2	2	2	2	2	9	9	9
7 = Lost/broken	2	2	2	2	2	2	2	9	9	9
8 = Temp filling	2	2	2	2	2	2	2	9	9	9
9 = Missing tooth	9	9	9	9	9	9	9	3	4	5

The assumption that has been made is that the placement of any restoration (restoration codes 3-8) is equivalent to there having been an ICDAS caries severity code 4, 5 or 6. We can't really say whether the caries prior to restoration was actually a 3, 4, 5 or 6 as all may result in a filling being placed (depending on radiographic and/or other diagnostic findings). The numbers in the above table in coloured cells will be referred to as the CAS "caries assessment score" – these are defined in Table 3.

Table 3: Definition of caries assessment scores (CAS)

CAS	comment
0	surface has initial or no caries
1	surface has unrestored dentinal caries without cavitation exposing dentine
2	surface cavitated and exposing dentine or restored
3	extracted due to caries
4	extracted or missing (not due to caries)
5	unerupted
9	invalid combination of codes

We will use the same coding of ICDAS codes at both baseline and follow-up.

Table 4: The terms used to describe dental caries status in the FiCTION trial

Terms used in this study (designation)	ICDAS caries severity codes (second digit of two-digit ICDAS code)	Traditional description	Notes
Sound/caries free	0	Sound/caries free	In our definition of sound we have included sound teeth with fissure sealants
Sound/ Reversible	0, 1, 2	Sound (0) and d/D_1 carious lesions (1, 2)	Fissure sealed teeth are also considered in this grouping of conditions which reflect teeth that are either sound or have carious lesions restricted to non-cavitated enamel. These are often seen as reversible lesions
Cavitated enamel caries	3	d/D_2 carious lesions	Enamel caries with breakdown of the surface
Dentine caries	4, 5, 6	Dentine caries d/D_3	Carious lesions involving dentine, also referred to as obvious dental decay
Cavitated dentine caries	5, 6	Cavitated dentine carious lesions including pulpal decay	These lesions have cavities exposing dentine. ICDAS 6 lesions are also referred to as pulpal decay.

2. SUMMARY OF BASELINE CARIES EXPERIENCE

Table 5: Summary of caries experience in primary dentition at baseline, by randomised treatment arm, ITT analysis set, n=xxxx [with reference to Appendix 1.1 – Calculating caries experience using ICDAS]

	Primary dentition (maximum: 20 teeth)			
	C+P **n=**	**B+P** **n=**	**PA** **n=**	**Total** **n=**
Total number of teeth per child Min Median (IQR) Mean (sd) Max				
Number of caries free teeth (ICDAS summary code 00) Min Median (IQR) Mean (sd) Max				
Decayed teeth (dt) Min Median (IQR) Mean (sd) Max **d** $_{\text{ICDAS 0-2}}$				

number of teeth whose highest surface caries severity code is ICDAS 0-2				
$d_{ICDAS\ 3-4}$ number of teeth whose highest surface caries severity code is ICDAS 3-4 **$d_{ICDAS\ 5-6}$ Number of teeth whose highest surface caries severity code is ICDAS 5-6** **$d_{ICDAS\ 4-6}$ [equivalent to d_3] number of teeth whose highest surface caries severity code is ICDAS 4-6**				
Missing teeth, due to caries (ICDAS summary code 97) Min Median (IQR) Mean (sd) Max				

Filled (but not decayed) teeth (No. of teeth with at least one surface with ICDAS restoration code 3-7 and caries severity code 0-3) Min Median (IQR) Mean (sd) Max				
$d_3$mft				

Table 6: Summary of caries experience in permanent dentition at baseline, by randomised treatment arm, ITT analysis set, n=xxxx [with reference to Appendix 1.1 – Calculating caries experience using ICDAS]

	Permanent dentition **First permanent molars: teeth 16/26/36/46**			
	C+P **n=**	**B+P** **n=**	**PA** **n=**	**Total** **n=**
Total number of first permanent molars per child Min Median (IQR) Mean (sd) Max				
Number of caries free teeth **(ICDAS summary code 00)** Min Median (IQR) Mean (sd) Max				
Decayed teeth (Dt) Min Median (IQR) Mean (sd) Max **D** $_{\text{ICDAS 0-2}}$ **number of teeth whose highest surface caries severity code is ICDAS 0-2**				

	Permanent dentition **First permanent molars: teeth 16/26/36/46**			
	C+P **n=**	**B+P** **n=**	**PA** **n=**	**Total** **n=**
D $_{\text{ICDAS 3-4}}$ **number of teeth whose highest surface caries severity code is ICDAS 3-4** **D** $_{\text{ICDAS 5-6}}$ **Number of teeth whose highest surface caries severity code is ICDAS 5-6** **D** $_{\text{ICDAS 4-6}}$ **[equivalent to** D_3**]** **number of teeth whose highest surface caries severity code is ICDAS 4-6**				
Missing teeth, due to caries (ICDAS summary code 97) Min Median (IQR) Mean (sd) Max				

	Permanent dentition **First permanent molars: teeth 16/26/36/46**			
	C+P **n=**	**B+P** **n=**	**PA** **n=**	**Total** **n=**
Filled teeth **(ICDAS restoration code 3-7 and caries code 0-3)** Min Median (IQR) Mean (sd) Max				
Caries experience in first permanent molars				

3. INCIDENCE OF CARIES

Incidence of caries will be defined in terms of observations made on an ICDAS scored at baseline and an ICDAS scored at the end of follow-up. Scores on individual tooth surfaces are unlikely to be independent. Observations on surfaces of the same tooth are likely to be correlated and observations between adjacent surfaces on different teeth are likely to be correlated. The simplest way of dealing with this lack of independence to develop a single "whole mouth" score for each child.

3.1 Scoring algorithm

Based on the above mapping of ICDAS codes into CAS scores at baseline and follow-up, we will develop an algorithm to define for each child whether there has been disease development/progression (from baseline to end of follow-up).

Possible "whole mouth" scores include

- A binary indicator to show disease development/progression in at least one surface
- The number (or proportion) of teeth on which there has been disease development/progression

- The number (or proportion) of surfaces on which there has been disease development/progression

Primary and permanent teeth will be analysed separately.

3.2 Primary teeth

Inclusion in the analysis set for the evaluation of disease development/progression in primary teeth will be at the whole tooth level; the entire tooth at baseline will need to have been caries free or had only initial caries.

Thus for inclusion in the algorithm every surface of a tooth at baseline will have:

- a CAS of 0 [i.e. a caries code digit of 0, 1 or 2; and a restoration code of 0, 1 or 2. [Note that for primary teeth a CAS score of 9 at baseline will be treated as an invalid code].

The main analysis will be based on disease development/progression in surfaces (of primary teeth). In general terms, we score each surface, which will then be aggregated to a score for each tooth which will then be aggregated to a whole mouth score.

To achieve this we will define a number of (interim) variables that will then be used to define our analyses.

3.2.1 For each **surface** we define (**based on scores at follow-up)**:

- A surface caries development/progression indicator (which will take the value 0 = “no” or 1 = “yes” or 8 “tooth extracted due to caries” or 9 “not valid”)
    - 0 = CAS of 0 (ICDAS codes: 00, 01, 02, 10, 11, 12, 20, 21, 22) or CAS = 4 (ICDAS = 98)
    - 1 = CAS of 1, 2 or 3 (ICDAS code = 97 - tooth extracted due to caries)
    - 9 = CAS of 5 or 9 (OR a CAS at baseline of 1 or 2)

3.2.2 For each **tooth** we define (**based on surface scores)**:

- A tooth caries development/progression indicator (which will take the value 0 = "no" or 1 = "yes" or 9 "not valid")
    - 0 = ALL surfaces have a caries progression indicator of 0
    - 1 = At least one surface has a progression indicator of 1
    - 9 = Any other option
- Binary indicator of tooth presence in mouth at final assessment
    - 0 = no
    - 1 = yes
- Number of tooth surfaces that were caries free at baseline
    - *User defined missing value (e.g. 999)* if baseline ICDAS = 97, 98 (or for primary teeth ICDAS = 99)
    - will be imputed for permanent teeth with baseline ICDAS of 99 (unerupted)
    - or the number of surfaces with baseline ICDAS codes: 00, 01, 02, 10, 11, 12, 20, 21, 22.
- Number of tooth surfaces with caries development/progression
    - Missing (not defined) if ICDAS codes 98, 99 OR CAS = 9
    - The number of surfaces with a "caries development/progression indicator of 1"

3.2.3 For each child we will define

- The total number of primary teeth present at final assessment
    - Sum of the tooth level binary indicator variables
- Number of teeth with caries development/progression
    - Sum of the binary tooth caries development/progression indicator variables
- Child caries indicator
    - Will take the value 1 if any of the tooth caries development/progression indicators take the value "1"
    - Will take the value 0 if all the individual tooth caries indicators take the value "0".

3.2.4 Analysis

We will analyse

- Child caries indicator (has there been caries development/progression in at least one surface)
    - Should be able to use standard methods based on logistic regression to estimate the relative odds of at least one incidence of caries in each arm of the trial.
- A measure related to the ratio of diseased surfaces to caries free surfaces
    - An issue with this variable is that there is no contribution to this score from any teeth that have been extracted (either due to caries or otherwise) and thus the results will require careful interpretation.
    - Ratios can be tricky to analyse – can possibly use the number of diseased surfaces as the numerator in total number of surfaces (= diseased + caries free) as the denominator in a negative binomial regression model

3.2.5 Explanatory variables

- Trial groups as a fixed effect
- Potentially dental practice as a random effect
- Possibly time between first visit and last visit as proxy for time between ICDAS assessments.
- Possibly an exposure variable—dental age (an older child may have less chance of developing caries in a primary tooth before the corresponding permanent tooth erupts than a younger child)

3.3 Permanent teeth

The analysis of the incidence of caries in permanent teeth will focus on the first permanent molars: 16/26/36/46 (as has been reported by others[1,2])

For us to look for disease progression the tooth

- must be either unerupted or have initial or no caries at baseline [CAS code of zero]

Additionally, for the child to be included in the analysis,

- there must be at least one erupted permanent tooth at follow-up.

In principle we can define exactly the same set of variables as we have for primary teeth.

With permanent teeth we will need an additional explanatory variable allow for the amount of time a surface or tooth has been at risk of developing caries. The issue is that an older child will have had their permanent teeth for longer than a younger child (and therefore had more time to develop caries). Rather than simply use age of child we will investigate the use of the information provided in Shour and Massler (1940) to develop an appropriate exposure variable.

Reference: Studies in Tooth Development: the Growth Pattern of Human Teeth. I. Schour, M. Massler. US: Journal American Dental Association. 1940

4. OTHER ANALYSIS

Looking at the magnitude of progression will be part of any additional analyses that are performed.

4.1 The extent of disease progression [magnitude of progression]

4.1.1 For each **surface** we define (**based on scores at follow-up)**:

The magnitude of surface caries progression

- 0 = CAS of 0 or 4 (ICDAS codes: 00, 01, 02, 10, 11, 12, 20, 21, 22, or 98)
- 1 = CAS of 1
- 2 = CAS of 2 or 3 (ICDAS code = 97 - tooth extracted due to caries)
- 9 = CAS of 5 or 9 OR a CAS at baseline of 1 or 2

4.1.2 For each **tooth** we define (**based on surface scores)**:

Tooth caries score (will take the value 0, 1, 2, 8 or 9)

- 0, 1, 2 the maximum “magnitude of caries progression” (as defined above) across the individual surfaces.
- 9 all other options (will be a treated as a user defined missing value: magnitude of caries cannot be assessed)

4.1.3 Analysis

- Number of teeth with caries development/progression (a natural indicator of the magnitude of caries progression)
    - Should be able to use standard methods based on a negative binomial regression to estimate the incidence rate ratio of caries between trial arm

References:

1. Chestnutt I, Chadwick B, Hutchings S, *et al.* Protocol for "Seal or Varnish?" (SoV) trial: a randomised controlled trial to measure the relative cost and effectiveness of pit and fissure sealants and fluoride varnish in preventing dental decay. BMC Oral Health 2012, **12**:51 http://www.biomedcentral.com/1472-6831/12/51
2. Milsom KM, Blinkhorn AS, Walsh T et al. A cluster-randomized controlled trial: fluoride varnish in school children. Journal of Dental Research 2011 90(11):1306-11 http://www.ncbi.nlm.nih.gov/pubmed/21921250

APPENDIX 1.1: Calculating caries experience using ICDAS (full ICDAS codes with severity scores of 1-6)

Author: Professor Gail Douglas, November 2014

When looking at conventional Decayed, Missing or Filled counts of teeth in an individual (DMFT) I apply rules to determine whether a surface is decayed, missing or filled and then consequently a count of DMFT (or DMFS) can be reported for each patient and a group mean reported for the sample. Each tooth or tooth surface is given a two digit code to denote its condition. The first code relates to the presence or absence of restorative intervention and the second relates to the stage or severity of caries lesions if present.

First digit of ICDAS code	***Second digit of ICDAS code***
Restoration Codes	**Caries Severity Codes**
0 = Sound	0 = Sound
1 = Part sealed	1 = Initial enamel
2 = Fully sealed	2 = Distinct enamel
3 = Tooth coloured	3 = Enamel cavity
4 = Amalgam	4 = Dentinal shadow
5 = Stainless Steel crown	5 = Distinct cavity
6 = Crowns etc	6 = Extensive cavity
7 = Lost/broken	
8 = Temp filling	

When there is caries on multiple surfaces of one tooth the worst code on that tooth is used to denote whether overall the tooth falls into the count of Decayed or Filled teeth, the rules to apply here differ slightly according to which diagnostic threshold you are applying. For $DMFT_3$, dentinal caries codes take precedence over (or are worse than) enamel caries or filling codes (with or without enamel caries). For $DMFT_1$ dentinal caries codes take precedence over all other codes and filling codes take precedence over enamel caries codes.

The caries severity code (see above) falls into a number of closely related categories:

- Code 0 = sound
- Code 1 and 2 are both enamel caries codes without any surface breakdown of enamel
- Code 3 is cavitation of the enamel but with no exposed dentine, when dentine is exposed it becomes a code 5
- Codes 4, 5 and 6 are all dentinal caries.

Codes 3 and 4, whilst different on the surface characteristics of the teeth, are often a similar histological depth into the tooth surface. Following WHO and other epidemiological thresholds caries codes 1-3 would be seen as sound at the D3 diagnostic threshold while codes 4-6 would be counted as caries. Note however, that in some countries the dentinal threshold of decay is lower and ICDAS caries severity code 3 is included as dentinal decay.

To avoid confusion when you are reporting caries experience from a survey utilising ICDAS it is important to convey the diagnostic threshold you have elected to use for reporting caries experience.

- $DMFT_{(ICDAS\ 4\text{-}6)}$ would indicate that the caries threshold utilised records teeth with ICDAS caries severity codes of 4, 5 and 6 as decayed (and codes 0, 1, 2 and 3 as sound), in other words reported caries prevalence levels would be limited to those with dentinal caries.
- If you chose to include in the prevalence measure all visual enamel and dentinal caries (ICDAS caries severity codes 1 to 6) you should denote the threshold as $DMFT_{(ICDAS\ 1\text{-}6)}$ which would indicate that any tooth with a caries severity code other than 0 was included as having caries experience.

How each of the two digit ICDAS codes translates into a D or F component is listed below.

Count of decayed teeth (or surfaces)

With regard to the D component (decayed), we first look at the 2nd digit in the coding record (the ICDAS code that indicates the stage or severity of caries if present). The first threshold for decay is called the D_3 threshold and considers that any 2nd digit above 3 denotes decay. The 2nd threshold is called the D_1 threshold and considers that any 2nd digit above 0 denotes decay.

- For the D_3 criteria -- count the surface/tooth as decayed if the 2nd digit is 4,5,6
- For the D_1 criteria -- count the surface/tooth as decayed if the 2nd digit is 1,2,3,4,5 or 6 (i.e anything other than zero)
- For either the D_3 or the D_1 criteria -- count the surface/tooth as decayed if the filling code (1st digit) is 8
- For either the D_3 or the D_1 criteria -- the filling code (1st digit) is irrelevant if the tooth is considered decayed by the above criteria

Count of filled teeth (or surfaces):

- For the D_3 criteria : Count the tooth/surface as filled if the 1st digit code is between 3 and 7 and the second digit is 0,1,2 or 3
- For the D_1 criteria : Count the tooth/surface as filled if the 1st digit code is between 3 and 7 and the second digit is 0
- A surface with a 1st digit value of 1 or 2 is a sealant and is not considered as a filling

Count of missing teeth:

As DMFT is used as a measure of caries experience the only missing tooth code which should contribute to the Missing teeth count are those coded 97 which are missing as a result of extraction due to caries.

APPENDIX 2: CHILD AND PARENT REPORTED OUTCOMES [QUANTITATIVE]

1. THE PARENT PERCEPTION QUESTIONNAIRE (PPQ)

The PPQ is a parental report of perceived child quality of life. It is made up of 16 items in four domains: oral symptoms, functional limitations, emotional wellbeing and social wellbeing. The 16 items in the PPQ used in FiCTION are different to later published versions of the P-CPQ-16 [see Appendix 2.1 for details].

The PPQ is included in the baseline visit, final visit and subsequent/final non-attendance Adult Questionnaires "About your child's teeth".

There are 6 possible responses to each item: Never (scored 0), Once or twice (scored 1), Sometimes (scored 2), Often (scored 3), Every Day or almost every day (scored 4), Don't know (identified in the data set by a 7).

A total score on the PPQ will be calculated, ranging from 0 to 64 (a lower score indicating a better QoL)

Domain scores will also be calculated, ranging from 0 to 16 – as there is no research question about differences between arms within domain, domain scores will be only be reported descriptively.

For the ITT analysis set, the completeness of the PPQ data will be described by randomised treatment arm and overall:

- Number of baseline, final visit, subsequent DNA and final DNA questionnaires
- Number of questionnaires at baseline and 'final' visit (where a final DNA questionnaire completed at the time of the final visit will be counted as a final visit questionnaire, assuming no final visit questionnaire is available)
- Number of children with a questionnaire at both baseline and 'final' visit
- Missing items per questionnaire (e.g. 95% of PPQs were complete, 4% had one missing item, etc…)

- Distribution of item responses (% of respondents) at baseline and final visit [see the tables in: PPQ approaches to imputation 300816.docx]

To assess the internal consistency of the 16 item PPQ scale in this study population, Cronbach's alpha reliability coefficient will be calculated.

1.1 Treatment of missing items and don't know responses in the calculation of a score on the PPQ

A thorough examination of the extent and pattern of missing and don't know (DK) responses, using baseline PPQ data from a snap shot taken for the May 2016 IDMC meeting (n=993), was carried out [see: PPQ approaches to imputation 300816.docx]. This analysis revealed that very few respondents displayed a mixture of missing and DK responses. Rather, it seemed that both types of response may represent a genuine inability on behalf of the parent to provide a valid response. The decision was to treat both missing and DK responses as 'missing data', and the same methods of imputation are applied to both, without distinction or prioritisation.

Ten possible methods of imputation were considered and assessed against the criteria set out by Fayers *et al* (1998)[1]. After discussion amongst the team, and with reference to the literature[2,3,4] the method adopted was the 'subject subscale mean' (the respondent-specific mean across a minimum of 2 valid, 0-4, responses in the item's own PPQ subscale) imputed to missing and DK responses within the subscale (only if 2 or more of the constituent subscale have originally valid (0-4) responses).

There will be no imputation for participants with missing or DK for all 16 items of the PPQ. .

1.2 Summaries of baseline PPQ [ITT analysis set]

Baseline descriptive statistics will be tabulated by randomised treatment arm and overall. No significance testing will be carried out due to the randomised nature of the study.

1.3 Change in QOL (using PPQ) from baseline to final [ITT analysis set]

Change in QOL using the PPQ will be calculated as baseline score minus final score so that a positive change indicates an improvement in QOL. The possible range in the change in global score from baseline to final is -64 to +64. The difference in the change in mean score between treatment groups will be analysed using mixed models with appropriate error structure (treatment, baseline score, age at baseline and length of follow-up will be included as fixed effects). Differences between dental practices will be included as a random effect. This approach is consistent with models specified for the primary outcome.

Issues for consideration:

Pattern of missing adult questionnaires at final visit – related to treatment arm?

Assumption of missing at random?

Strategy for completely missing adult questionnaire for a child at one time-point: either baseline or final? Complete case analysis or use of covariance pattern mixed models which allow appropriate estimation of the mean change (and associated SE) between baseline and final, allowing for missing PPQ at either time point [this is only useful for a 'small' amount of missing[5]].

2. THE MODIFIED CHILD DENTAL ANXIETY SCALE -FACES (MCDASF)

The MCDASf is a child completed visual analogue scale (faces) to measure dental anxiety. It is a 'trait' measure.

It is made up of 6 items.

The MCDASf is included in the Child Questionnaire "Questions about your teeth" and completed at <u>every</u> visit – before treatment (and is included in the DNA questionnaire)

There are 5 possible responses to each item: relaxed/not worried (score=1), to very worried (score=5)

The total score ranges from 6-30 (with lower scores indicating less anxiety)

For the ITT analysis set, the completeness of the MCDASf data will be described by randomised treatment arm and overall:

- Number of child questionnaires at baseline
- Total number of child questionnaires (including DNA questionnaires)
- Number of questionnaires per child (where expectation is that there will be an MCDASf completed at each visit)
- Missing items per questionnaire (e.g. 95% of MCDASf were complete, 4% had one missing item, etc…)
- Distribution of item responses (% of respondents) [see the tables in: PPQ approaches to imputation 300816.docx]

To assess the internal consistency of the 6 item MCDASf in this study population, Cronbach's alpha reliability coefficient will be calculated.

2.1 Treatment of missing items in the calculation of a score on the MCDASf

The same method as used for the PPQ will be used here. Although as there are no subscales this will effectively be 'subject overall mean' imputation, if 3 or more of the 6 items have originally valid (1 to 5) responses.

2.2 Summaries of baseline MCDASf [ITT analysis set]

Baseline descriptive statistics will be tabulated by randomised treatment arm and overall. No significance testing will be carried out due to the randomised nature of the study.

2.3 Change over time, repeated measures [ITT analysis set]

The research question of interest: Is there a difference in the overall mean level of anxiety between treatment groups?

To address this question we can fit a random effects model allowing appropriate estimation of the difference between group means (and associated standard errors) taking into account varying numbers of measurements within patient and varying time between measurements. Models will include treatment, baseline score, age at baseline and length of follow-up as fixed effects and

differences between dental practices as a random effect. This approach is consistent with models specified for the primary outcome.

Issues: missing visit data – i.e. no questionnaire but a CRF, assumptions will always need to be made whatever strategy is employed

Drop out? Pattern of missingness – related to treatment arm? Assumption of missing at random?

The appealing feature of the random effects models is that the parameter estimates are unbiased in the presence of missing data (as long as the missing can be assumed to be missing at random…).

An AUC approach was considered but the literature suggested that the individual raw AUC summary measure approach is useful where there are fixed visit time points and where there is complete data (we have neither). A recent simulation study[6] concluded that "AUC summary measures on individuals should not be used to analyse patient reported outcome data in the presence of missing data". [Professor Graeme MacLennan, Health Services Research Unit, University of Aberdeen, who has expertise in this area was contacted by EMcCall and the conclusion reached was that a modelling approach would be preferable under these circumstances.

Exploratory analyses: stratification by caries experience had been considered for the randomisation. Need to include an exploration of how anxiety[7] is related to the number of teeth with caries at baseline (as measured by scores of 3/4/5/6 on ICDAS).

3. PRE-TREATMENT ANTICIPATORY ANXIETY AND TREATMENT-RELATED ANXIETY

These anxieties are measured by two questions in the child questionnaire at every visit (which are <u>not</u> included in the DNA questionnaire) and by two questions in the adult questionnaire at every visit (<u>not</u> in the DNA questionnaire).

The completeness of the anxiety data will be described:

For the ITT analysis set, the completeness of the anxiety data will be described by randomised treatment arm and overall:

- Total number of child questionnaires (excluding DNA questionnaires)
- Total number of adult questionnaires (excluding DNA questionnaires)
- Number of questionnaires per child and per adult (where expectation is that there will be a questionnaire completed at each visit)
- Missing items per adult and child questionnaires (e.g. 95% of the questionnaires were complete, 4% had one missing item, etc…)
- Non-response per item

3.1 Child reported pre-treatment anticipatory anxiety, repeated measures [ITT analysis set]

Anticipatory anxiety is measured at every visit before treatment, in the form of a visual analogue scale (faces): Before you saw the dentist today, were you? Not at all worried (scored 1), a little worried (scored 2), very worried (scored 3).

This will be analysed as a standalone measure over time in the trial.

Research question: is there a difference in the overall level of child anticipatory anxiety between treatment groups?

Baseline descriptive statistics will be tabulated by randomised treatment arm and overall. No significance testing will be carried out due to the randomised nature of the study.

Multilevel mixed effects ordinal logistic regression will be used to model the relationship between child-reported pre-treatment anticipatory anxiety and treatment arm. This analysis depends on the proportional odds assumption being valid which can be assessed graphically by plotting the predicted logits from individual logistic regressions with a single predictor (e.g treatment group) where the outcome groups are ≥ 2 or ≥ 3. The approximate likelihood ratio test of proportionality of odds or the Brant test of parallel regression assumption will be used to assess this assumption. If this assumption does not hold multilevel mixed effects multinomial logistic regression will be used. A disadvantage to this technique is that there would be two coefficients for each covariate e.g. age. These models are multilevel as random effects will be added to account for the nested structure of children within dental practices. Time will be incorporated as a fixed effect. The relationship with

age will be explored. The justification for this adjustment is that children will become less anxious as they get older and that younger children may be effected by the parent's anxiety[8].

The above analysis strategy depends upon all three levels of the outcome being chosen, if it is the case that one level tends not to be chosen we will consider combining levels (2 & 3) to create a binary outcome (not at all worried, worried) and using multilevel mixed effects logistic regression using random and fixed effects as described above.

3.2 Child reported treatment-related anxiety, repeated measures [ITT analysis set]

Treatment-related anxiety is assessed at every visit by answering the question immediately after treatment, in the form of a visual analogue scale (faces): Thinking about your visit to the dentist today, were you? Not at all worried, a little worried, very worried.

This will be analysed as a standalone measure over time in the trial.

Research question: is there a difference in the overall level of child treatment-related anxiety between treatment groups?

The analysis strategy described in Section 3.1 will be used to explore the relationship between child reported treatment-related anxiety and treatment arm.

3.3 Parent reported child pre-treatment worry, repeated measures [ITT analysis set]

Parent reported pre-treatment worry is measured at every visit before treatment: Before seeing the dentist today, do you think your child was? Not at all worried (scored 1), to very worried (scored 5).

The analysis strategy described in Section 3.1 will be used to explore the relationship between parent reported child pre-treatment worry and treatment arm. Levels of the outcome may be combined if necessary. Models assuming the outcome is numerical (rather than ordinal) may also be fit.

3.4 Parent reported child treatment-related worry, repeated measures [ITT analysis set]

Parent reported treatment-related worry is assessed at every visit by answering the question immediately after treatment: Thinking about being at the dentist today, do you think your child was? Not at all worried (scored 1) to very worried (scored 5).

The analysis strategy described in Section 3.1 will be used to explore the relationship between parent reported child treatment-related worry and treatment arm. Levels of the outcome may be combined if necessary. Models assuming the outcome is numerical (rather than ordinal) may also be fit.

4. PARENTAL REASON FOR NON-ATTENDANCE (DNA QUESTIONNAIRE)

Analyses will be descriptive by randomised treatment arm (and by time-point, 18m and final DNA). Free comments will be listed. Numbers sent out and %returned will be reported.

5. PARENT AND CHILD RELATED TREATMENT DEVIATIONS

Dentist report on treatment deviation, Q4 TDF

Analyses will be descriptive by randomised treatment arm

6. DISCOMFORT DURING TREATMENT

Analyses for the outcomes in this section will be descriptive

6.1 Child reported hurt

Child reported hurt is assessed at every visit by answering the question immediately after treatment, in the form of a visual analogue scale (faces): Thinking about being at the dentist today, did it? Not at all hurt, hurt a little, hurt a lot.

6.2 Parent reported pain

Parent reported child treatment-related pain is assessed at every visit by answering the question immediately after treatment: Thinking about being at the dentist today, how do you think your child found the treatment? Not at all painful (scored 1) to very very (scored 5).

6.3 Dentist reported child discomfort

Dentist reported child discomfort is assessed at every visit by answering question 14 in the CRF: What was your estimation of the discomfort experienced by the child? No apparent discomfort (scored 1) to significant and unacceptable (scored 5).

6.4 Dentist reported child-behaviour and compliance

CRF Q15 – child behaviour

CRF Q16 – difficulties providing treatment

CRF Q17 – use of Inhalation sedation

7 ADDITIONAL ANALYSIS

This section lists analyses that are additional to those described above and ones that won't be included in the final report.

7.1 Michigan Oral-Health-Related Quality of Life Questionnaire (MOHRQOL)

The MOHRQOL is a parental report of perceived child quality of life. It is made up of 11 items. This scale is not validated but has been included to compare with the PPQ and global questionnaires [meeting in Leeds GD and VR May 2015]. The original Filstrup paper (2003)[7] has 10 items which are differently worded to the 11 item version used in FiCTION. The only other reference is a one page document listing the 11 items but with the heading:

Michigan Oral Health Related Quality of Life Scale (MOHRQOL) – Parent Version. Inglehart, MR, Lawrence, L, & Briskie, D. Parents' Assessments of Children's Oral Health-related Quality of Life . Under review. ..[see: \journal articles\MOHRQoL\MOHRQoL-Parent.doc]

The MOHRQOL is completed at baseline and final visit (but is not included in the DNA questionnaire as it is a 'state' measure)

Response are on a 5 point scale where 1 is labelled 'disagree strongly' and 5 is labelled 'agree strongly'

Items i and j need to be reversed so that their rating is in the same direction of the other items in the scale and hence they contribute to an overall score correctly.

The total score ranges from 11-55 (with lower scores indicating a better QoL)

7.2 Change in anxiety within visit from before to after treatment, repeated measures

Two possible approaches for change within visit:

A change score can be calculated as 'before score minus after score' so that a positive change indicates an improvement in anxiety and a negative change indicates a worsening.
Summarise anxiety at each visit from before to after as worsened/stayed the same/improved

Possible analyses under consideration are:
Comparison of number of occasions during follow-up where anxiety worsened – negative binomial adjusted for time in the study (same approach as number of episodes of pain analysis)
Analysis of change score – ranges from -2 to +2 – needs further consideration.

Fitted models will be consistent with models specified for the primary outcome (so for example will include age at baseline).

References:

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4. Marshman Z, Rodd H, Stem M, Mitchell C, Robinson PG. (2007) Evaluation of the Parental Perceptions Questionnaire, a component of the COHQoL, for use in the UK. *Community Dent Health*, 24(4):198-204.

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APPENDIX 2.1: Comparison of FiCTION PPQ (2011) with published P-CPQs (2013/2014)

The FiCTION protocol says the 16 item PPQ came from a personal communication with Murray Thomson in 2011

The following paper was then published in 2013:

Thomson WM, et al Short-form versions of the Parental-Caregivers Perceptions Questionnaire (P-CPQ) and the Family Impact Scale (FIS). *Community Dent Oral Epidemiol* 2013, 41:441–450.
And followed up in 2014:
Thomson et al. Comparison of the ECOHIS and short-form P-CPQ and FIS scales. *Health and Quality of Life Outcomes* 2014, 12:36 http://www.hqlo.com/content/12/1/36

Domain	Item	PPQ FiCTION 2011	P-CPQ 2013	P-CPQ 2014
OS	Had pain in the teeth, lips, jaw or mouth	Y	Y	Y
OS	Had bleeding gums	Y		
OS	Had bad breath	Y	Y	Y
OS	Had food caught between the teeth	Y	Y	Y
FL	Breathed through the mouth	Y		Y
FL	Had trouble sleeping	Y	Y	Y
FL	Had difficulty biting or chewing firm foods	Y	Y	Y
FL	Had difficulty drinking or eating hot or cold foods	Y	Y	
EW	Been irritable or frustrated	Y	Y	Y
EW	Worried that he/she is not as healthy as other people	Y		
EW	Worried that he/she is different from other people	Y		
EW	Acted shy or embarrassed	Y	Y	Y
SW	Not wanted or been unable to spend time with other children	Y		
SW	Not wanted to speak or read out loud in class	Y		
SW	Not wanted to talk to other children	Y	Y	Y

SW	Been asked questions by other children about his/her teeth, lips, mouth or jaws	Y		
OS	Food stuck in the roof of the mouth		Y	Y
FL	Taken longer than others to eat a meal		Y	Y
EW	Been upset		Y	Y
EW	Been anxious or fearful		Y	Y
SW	Had a hard time paying attention in school		Y	Y
SW	Avoided smiling or laughing when around other children		Y	Y
SW	Missed school or pre-school		Y	Y

The number of PPQ (2011) items remaining in each domain of the P-CPQ (was the same for both 2013/2014 versions):

oral symptoms 3/4

functional limitations 3/4

emotional wellbeing 2/4

social wellbeing 1/4

APPENDIX 3: MISSING CLINICAL ASSESSMENT OF PAIN AT FINAL VISIT

This is a report presented at the FiCTION whole team teleconference in September 2015.

QUESTION: DDQ8 as a parental proxy for pain due to caries?

The primary outcome for the FiCTION trial is a binary indicator of pain due to caries and/or sepsis at each treatment visit during the follow up period (minimum of 23 months to a maximum of 36 months). Children are expected to have treatment visits every 3 to 6 months during follow-up.

- Pain is defined as confirmed pain due to caries on the CRF (yes to question 7 and yes to question 7a (caries))
- Sepsis is defined as confirmed infection on the CRF (yes to question 8)

Pain and/or sepsis at first treatment visit

I'm mentioning this here as it may have implications for the analysis strategies suggested.
One of the exclusion criteria is pain or dental sepsis associated with dental caries at consent – so it follows that you would not expect to observe pain due to caries (and/or sepsis) on the first treatment visit CRF.

Data collection (pain related)

A CRF and an adult questionnaire are completed at each treatment visit

Treatment of missing data (primary outcome)

A final visit window will be calculated for all randomised participants who are continuing in the trial (i.e. have not withdrawn or do not belong to a practice which has withdrawn). If a participant does not attend their final visit in their final visit window the practice will post out 'Final non-attendance' child and adult questionnaires (DNA questionnaires).
The final non-attendance adult questionnaire includes the 8 item Dental Discomfort Questionnaire (DDQ8) which has been developed[1,2] for use as a parental proxy for the identification of toothache in very young children.
The final DNA questionnaire also includes Health Economic questions about absence from school because of pain, time off paid work for the parent, pain-killing medicine and ability for child/parent to continue with usual activities [Questions 8 to 20 in the final adult DNA questionnaire].

Table 1: Pain-related questions in the adult questionnaires

	Adult questionnaire			
Question	**Baseline**	**Scheduled/ recall unscheduled / emergency**	**Final**	**DNA**
DDQ8	Q10	Q2	Q8	Q7
Has your child had toothache since the last visit		Q3	Q9	
… was your child absent from school because of the pain arising from tooth decay?		Q4	Q10	Q8
*How long was your child absent from school…		Q5	Q11	Q9
*Did you, or anyone else, need to take time off work…		Q6	Q12	Q10
*How much time was taken off paid work?		Q7	Q13	Q11
…additional paid child-care…		Q8	Q14	Q12
Did your child need any pain-killing medicine (which was not prescribed) because of the pain arising from tooth decay?		Q10	Q16	Q14
*6 further questions relating to cost of pain needing pain-killing meds		Q11-Q16	Q17-Q22	Q15-Q20

*could be used to imply a response if related question about pain is missing

Possible approaches for consideration:

Approach 1: The Receiver Operating Characteristic curve approach using DDQ8 score only (or perhaps using the score from a subset of the DDQ8?)?

Analyses will be carried out to establish (if it exists) a 'threshold' of responses to the DDQ8 which corresponds to "clinical pain" due to caries on the CRF. This threshold (if it exists) will then be used to define pain due to caries using the DDQ8 on the final non-attendance adult questionnaire (and also on the subsequent visit non-attendance questionnaire posted out to participants who have had no contact with their practice for 18 months).

We can identify 3 mutually exclusive groups for pain using Q7 and Q7a on the CRF:

Group 1: pain (due to caries),

Group 2: pain (other cause)

Group 3: no pain.

The DDQ8 is made up of 8 questions with the possible responses: never, sometimes and often which are scored as 0, 1, 2 respectively. The total score on the DDQ8 therefore ranges from 0 to 16.

Statistical issues relating to the ROC analysis:

- Should we omit the cases where there is pain due to an 'other' cause when building a rule?
    - in the n=2817 matched CRF/questionnaires we looked at recently there were 63 cases (2.2%) with pain (other), 205 (7.3%) pain due to caries, and 2549 (90.5%) no pain.
- Currently we have approx. 4000 CRFs and matched adult questionnaires from 1019 children – so non-independent observations (and we still have 2 years further follow-up time) – how to deal with this? How to perform an ROC analysis with dependent observations?
- Finally there is the issue of accounting for the uncertainty associated with using the parental proxy in place of the clinical assessment. For example, if we have say 10% missing at the final visit and we 'impute' their pain (using a cut-off on the DDQ8 score), then when we do the comparison between treatment arms we will be treating the data as if it were based on impeccable records where everyone complied and no one had any missing data? This introduces a problem, namely, that the analysis will be over-precise, because imputed missing data have imprecision that the observed data do not have.

Approach 2: Discriminant analysis/Logistic regression approach using DDQ8 score (or using just a sub-set of the 8 items – the ones which are individually more discriminatory) and possibly pain-related HE questions? And possibly previous pain?

Approach 3: Multiple imputation – need to explore this option further. MI respects the uncertainty in the imputation.

References:

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