CALM

The CALM trial: the clinical and cost-effectiveness of a guided self-help cognitive behavioural therapy intervention to reduce dental anxiety in children.

STATISTICAL ANALYSIS PLAN

V1.1

York Trials Unit
Department of Health Sciences
York, YO10 5DD

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Authors: Fraser Wiggins, Caroline Fairhurst, University of York, Prof Catherine Hewitt

Chief Investigator: Prof Zoe Marshman

Trial Manager/Coordinators: Natasha Mitchell, Victoria Exley, Liz Cross

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1 Document scope and relevant SOPs and guidance documents

This statistical analysis plan (SAP) deals only with the statistical analysis of effectiveness; the cost-effectiveness analysis will be detailed in a separate plan prepared by the Health Economist(s). This current version of the analysis plan was written prior to the completion of recruitment, following York Trials Unit (YTU), University of York, SOPs, templates and guidance documents.

There are no current plans to embed any SWATs (study within a trial) within CALM; however, should any be introduced, a SAP for the SWAT will be added as an appendix to this document.

This SAP was prepared according to YTU SOPs and guidance documents.

2 Definition of terms/acronyms

CBT	*Cognitive behavioural therapy*
CACE	*Complier average causal effect*
CI	*Confidence interval*
CONSORT	*Consolidated standards of reporting trials*
DA	*Dental Anxiety*
DMFT	*Decayed missing and filled permanent teeth*
GA	*General anaesthesia*
HRQoL	*Health related quality of life*

MCDAS	*Modified child dental anxiety scale*
MDAS	*Modified dental anxiety scale*
OHRQoL	*Oral health related quality of life*
PPI	*Patient and public involvement*
RCT	*Randomised controlled trial*
SAP	*Statistical analysis plan*
SWAT	*Study within a trial*
TSC	*Trial steering committee*
YTU	*York Trials Unit*

3 Design

This 4-year study is a multi-centre, two-arm randomised controlled trial (RCT) involving 600 children in need of treatment who have dental anxiety (DA). These children will be attending one of 30 sites to receive dental treatment. Sites will be based in 5 regions in England and Wales: South Yorkshire, West Yorkshire, North East, East Midlands and Wales, each with a clinical lead. Within each site, two or more dentists will take part in the trial, half will be trained in the intervention, and the others will not be. Eligible and consenting participants will be randomised into one of two treatment arms: to be treated by a dentist who has had the CBT (cognitive behavioural therapy) training and will deliver the guided self-help CBT intervention; or to be treated by a dentist who has not had CBT training and who will not deliver the guided self-help CBT intervention.

This trial will also include some of the parents and carers of the children randomised into the study. These parents and carers will answer a questionnaires which measure their DA before and after the treatment is delivered to the child. This will be done to investigate the impact of the intervention on the DA of the parent. Parent/carers will be asked if they want to consent to provide information; we hope to achieve a participation rate for patent/carers of 80%.

This study will include an internal pilot trial and embedded health economic and process evaluations. Full details of the background and design of the trial are given in the published trial protocol [1].

4 Trial Objectives

The aim of this study is to evaluate the clinical and cost effectiveness of a CBT intervention to reduce DA in children attending primary dental care sites relative to usual dental care.

4.1 Primary objective

The primary objective is to investigate how effective the self-guided CBT intervention is in reducing DA in children at 12 months post-randomisation, compared to usual care, as measured by the modified child dental anxiety scale (MCDAS).

4.2 Secondary objectives

The secondary objectives of this study are to:

- Investigate how effective the self-guided CBT intervention is in reducing DA in children immediately after treatment, compared to usual care, as measured by the MCDAS.
- Determine the effectiveness of the self-guided CBT intervention on health-related and oral health-related quality of life (HRQoL and OHRQoL) of children who suffer from dental anxiety.
- Investigate the need for secondary care and general anaesthesia (GA) in both treatment groups.
- Investigate the effects of the self-guided CBT intervention on attendance and missed appointments.

- Investigate the impact of the self-guided CBT intervention on the DA of the parents/carers of the children who received it.
- Establish the cost effectiveness of the self-guided CBT intervention (health economic evaluation – not detailed in this SAP).

5 Follow-up

Participants randomised into the study will be followed-up at baseline (pre-randomisation, before treatment), at the end of the course of treatment (follow up 1, FU1) and 12-months post-randomisation (follow up 2, FU2). Patient and parent/carer data will be collected using paper questionnaires at the dental appointment or following the appointment (via post or telephone).

The information collected in this study is listed below:

- Necessary personal information about the participant to check that they meet the eligibility (inclusion and exclusion) criteria of the study.
- Participant assent and parent/carer consent.
- Baseline data: socio-demographic data, clinical data and whether or not the dental professional treating the participant has previously seen the participant.
- The dental anxiety of the child will be recorded at each time point by measuring their MCDAS score.
- The HRQoL of each child will be assessed at each time point using the Child Health Utility 9D (CHU9D) questionnaire.
- The OHRQoL of each child will be assessed at each time point using the CARIES-QC scale.
- The DA of the parent/carer will be assessed by the modified dental anxiety scale (MDAS) score at each time point.
- Details of attended, missed and cancelled appointments across 12-month follow-up will be collected at FU1 and FU2, including details of the delivery of the treatment and intervention administered and need for sedation and local anaesthetic.
- Details regarding the need for a referral to secondary care, sedation and GA will be collected at FU2 for 12-month follow-up.
- Data on how the child feels their dental anxiety has changed compared to baseline, assessed by the single-item Global Rating of Change (GRC) outcome measure, will be collected at FU1 and FU2.
- Data on how the dental professional perceives the dental anxiety of the child to have changed from baseline to after treatment, as measured by Clinical Global Impressions: Improvement (CGI-I) item, will be recorded on the case report form by the dental professional at FU1.

Table 1 below shows the data collected at each follow up.

Table 1. Schedule of assessments

Assessment	**Follow up time point**		
	Baseline	After treatment (FU1)	12 months post-randomisation (FU2)
Eligibility and consent			
Eligibility	X		
Consent	X		
Background & Follow-up questionnaires			
Baseline data	X		

Dental Anxiety of child - Modified child dental anxiety scale (MCDAS)	X	X	X
Health related quality of life - Child Health Utility Questionnaire (CHU9D)	X	X	X
Oral health related quality of life – CARIES-QC	X	X	X
Dental anxiety of parent/carer - Modified dental anxiety scale (MDAS)	X	X	X
Change in dental anxiety (child's perspective) - Global rating of change (GRC)		X	X
Change in dental anxiety (dental professional's perspective) - Clinical Global Impressions: Improvement (CGI-I)		X	
Details of delivery of treatment administered		X	X
Details of attendance patterns for child's dental appointments		X	X
Need for secondary care and/or pharmacological interventions		X	X
Change of Circumstance	Ongoing collection		

6 Outcomes

6.1 Primary outcome

The primary outcome is the dental anxiety of the child as measured by the modified child dental anxiety scale (MCDAS). The MCDAS score is calculated by giving the children an 8-item questionnaire where the participants rate their anxiety in various scenarios on a scale of 1-5 with 1 corresponding to the lowest level of anxiety and 5 corresponding to the highest level of anxiety [2]. The scores from each question are summed to give a total score out of 40. For the purposes of the trial, the following data decisions were made: if two consecutive responses are ticked by the participant, then the 'worse case' option (e.g. higher score, indicating more worried) is used; if more than two options, or two non-consecutive options, are ticked, the item is treated as missing. If one item is missing from the score, then it can be substituted with the average score of the non-missing items. Questionnaires with two or more missing values are not scored. DA for children is measured at three points during the study, but the primary outcome is at 12 months post-randomisation.

6.2 Secondary outcomes

6.2.1 Health related quality of life (HRQoL)

Child HRQoL will be assessed using the Child Health Utility 9D (CHU9D) [3] at baseline, end of the course of treatment (FU1) and 12 months post-randomisation (FU2). This outcome is used in the cost effectiveness evaluation and so its scoring and analysis will be detailed in the health economics analysis plan.

6.2.2 Oral health related quality of life (OHRQoL)

Child Oral HRQoL will be assessed using the CARIES-QC [4], a measure of the impact of caries, which is validated in children aged 5-16 years, at baseline, end of the course of treatment (FU1) and 12 months post-randomisation (FU2). CARIES-QC contains 12 items and one global question. The items are scored on a 3-point Likert scale of 0 = "Not at all", 1= "A bit" and 2 = "A lot", with a higher score indicating increased impact. For the purposes of the trial, the following data decisions were made: if two consecutive responses are ticked by the participant, then the 'worse case' option (e.g. higher

score) is used; if more than two options, or two non-consecutive options, are ticked, the item is treated as missing. Up to two missing items can be replaced with the mean of the completed items, otherwise if there are more than two missing items the scale is considered missing. A total score is then calculated by summing the 12 items scores (excluding the global score) which takes values in the range 0-24.

As CARIES-QC focuses on aspects of oral health that are not directly measurable, such as pain and emotional impacts, the raw score is only indicative of a rank along the scale. Therefore, when comparing data longitudinally, this raw score is converted to an interval scale to allow accurate comparison between time points. This can be achieved by transforming the ordinal score to a logit score [12]. The conversion table below, produced following Rasch analysis [13], is used to convert the ordinal raw score to an interval scale score (Table 2). Both raw and interval scores will be summarised at each time point to allow comparison with other studies; however, only raw scores will be used in the hypothesis testing to compare the intervention and control groups at the different time points.

Table 2. Conversion table for raw and interval scores for CARIES-QC

Raw score	Interval score	Raw score	Interval score
0	0	**13**	13.03
1	2.63	**14**	13.62
2	4.50	**15**	14.22
3	5.84	**16**	14.84
4	6.90	**17**	15.48
5	7.80	**18**	16.17
6	8.60	**19**	16.92
7	9.32	**20**	17.76
8	10.00	**21**	18.75
9	10.64	**22**	19.96
10	11.26	**23**	21.65
11	11.86	**24**	24.00
12	12.45		

The global item is summarised separately.

6.2.3 Parent/carer dental anxiety

The dental anxiety of the parent/carer will be measured on the modified dental anxiety scale (MDAS) [5] at baseline, after the child's treatment and 12 months post-randomisation. The MDAS score of the parent/carer is obtained by giving them a 5-item questionnaire where participants can respond with a number from 1 to 5 where 1 corresponds to "not anxious" and 5 corresponds to "extremely anxious". The MDAS score is calculated as the sum of the responses to give a total score out of 25. Higher scores correspond to greater levels of dental anxiety, with a score of 19 or greater indicating a highly dentally anxious participant. If a response for one of the five items is missing, then the missing item may be imputed using the mean of the four non-missing responses. If responses are missing for more than one item in the questionnaire then the MDAS score is to be treated as missing. For the purposes of the trial, the following data decisions were made: if two consecutive responses are ticked by the participant, then the 'worse case' option is used; if more than two options, or two non-consecutive options, are ticked, the item is treated as missing.

6.2.4 Referral and use of pharmacological approaches

The need for referral to secondary care and use of sedation or GA will be recorded for children in both groups, along with treatment provided (e.g. prevention, restoration, extraction, local anaesthesia), throughout the 12-month follow up period.

6.2.5 Attendance patterns

Details on the appointments attended, cancelled and missed will be recorded throughout the 12-month follow up period. The duration of attended appointments and the type of dental professional seen will also be recorded. The dentist will be asked to record the following for the child at each visit: Considering your clinical experience with children, how dentally anxious was the patient at this visit? This is measured on a 7-point Likert scale from "Not at all dentally anxious" to "Among the most extremely dentally anxious patients".

6.3 Other collected variables

6.3.1 Anchor ratings

As part of the CALM trial, an anchor-based approach will be used to determine the change in MCDAS that represents a minimal clinically important difference (MCID) [8]. The anchors will include the single-item Global Rating of Change (GRC) outcome measure used to gain the participant's perspective on how meaningful the change to their anxiety has been. The GRC item asks participants to rate their condition (DA) following the intervention 'Compared to when you started the project, please say whether you feel any different about going to the dentist and what happens there'. Responses are on a 5-point Likert scale ("I feel much worse", "I feel a little worse", "Nothing has changed", "I feel a little better", or "I feel much better") [9]. Participants can then be further categorised based on whether they report that their DA has improved/not changed/deteriorated using this anchor. For the purposes of the trial, the following data decisions were made: if two consecutive responses are ticked by the participant, then the 'worse case' option is used; if more than two options, or two non-consecutive options, are ticked, the item is treated as missing. This will be recorded at both FU1 and FU2.

The Clinical Global Impressions - Improvement (CGI-I) item will also be used as an anchor to capture 'meaningful' change in children's dental anxiety levels from the perspective of the dental professionals [10]. The dental professional will be asked to rate the participant's DA after the intervention compared to baseline using a 7-point response scale (1=very much improved since the initiation of intervention; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse since the initiation of the intervention). Participants can then be further categorised based on whether the dental professional reports that their DA has improved/not changed/deteriorated using this anchor. This data will be recorded on a case report form by the dental professional at the end of the course of treatment.

6.3.2 Baseline data

Following recruitment but before randomisation, dental professionals will provide baseline data on the participant's 1) socio-demographic characteristics including age, sex, ethnicity, first language (if not English), postcode, medical history and additional learning/behavioural needs, 2) their clinical status including: caries experience (dmft/DMFT), date of previous dental attendance (prior to this one), and previous experience of local anaesthetic, sedation or GA, and 3) information on past history of whether dental professionals involved in the trial from that site have previously seen the participant.

6.3.3 Details of treatment administered

Details on how the treatment was delivered, including protocol deviations will be collected throughout the 12-month follow period from case report forms filled in by the dental professional.

6.3.4 Resource use and cost data

Costs and resource use related to dental anxiety for inclusion in the economic evaluation will be collected from parent/carers via questionnaires at baseline, FU1 and FU2 and from dental sites (for the base case analysis; NHS perspective) throughout the 12-month follow up period. Further costs (e.g. travel time/costs for attending appointments, time missed from school, time off work for parent/carers, out of pocket expenditure on medications) will also be collected via parent/carer questionnaires (for the secondary analysis; societal perspective). These data will be used in the cost-effectiveness analysis, which will be detailed in a separate Health Economics Analysis Plan.

7 Data

7.1 Case Report Forms

All CRFs are paper-based and have been designed using the Teleform software. Copies of these are available to the trial statisticians at Y:\Project -- CALM - Statistics\1 Statistics\Documentation\Trial Documentation\CALM CRFs. Validation plans are saved here: Y:\Project – CALM – Statistics\1 Statistics\Documentation\Trial Documentation\CALM Validation Plans. All data will be identified by participant trial ID number only.

7.1.1 Participant CRFs

'Young Person First Questionnaire' – completed by the young person at baseline.
'Young Person Questionnaire – after treatment' completed by the young person at FU1.
'Young Person Questionnaire – one year after treatment' completed by the young person at FU2.

7.1.2 Parent/carer CRFs

'Parent/carer questionnaire' – completed by the parent/carer at baseline.
'Parent/carer questionnaire after treatment' completed by the parent/carer at FU1.
'Parent/carer questionnaire one year after treatment' completed by the parent/carer at FU2.

7.1.3 Dental CRFs

'About the Patient' – completed at baseline.
'Course of treatment form' and 'Supplementary booklets' – completed during the course of treatment and returned once the course of treatment has been completed (FU1); supplementary booklet(s) to be used if more than four visits are required during the course of treatment.
'Longer term follow-up' and 'Supplementary booklets' – completed to record details of any visits the patient attends between FU1 and 12 months from their initial assessment; supplementary booklet(s) to be used if more than two additional visits are required.

7.1.4 Return of data

The baseline CRFs - child, parent (if applicable) and dental - should all be completed at the assessment appointment, prior to randomisation.

The FU1 CRFs are completed at the end of the course of treatment. For the most part this will be at the final appointment and returned by the dental practice in a pre-paid envelope but there is the option (if patient requests or no time etc) for child/parent to take these away with them and complete them at home and return in a pre-paid envelope. If the participant doesn't attend the follow up appointment the dental practice can trigger the CRF(s) to be sent postally to the patient from the YTU.

The FU2 forms are due to be completed 1 year after randomisation. The dental practice will book an appointment to complete the CRFs. If the appointment cannot be arranged, or the participants does

not attend their scheduled appointment, then participants and their parents/carers will be posted their questionnaires.

7.1.5 Participant Withdrawal Form

This CRF is completed by the dental professionals at site to record participant changes of status (i.e. parent/carer no longer willing to complete parent/carer questionnaires and/or child no longer willing to complete participant questionnaires and/or no longer willing for dental practice to complete dental forms relating to participant. The date, type and reason for withdrawal are recorded. These CRFs are returned to YTU via email or post.

7.2 External datasets

7.2.1 Eligibility logs

Paper eligibility logs, with preprinted participant trial id numbers on them, are completed at site to record date of eligibility assessment, patient initials and age, eligible (Y/N) and reason if ineligible, main language spoken if not English, consented (Y/N), date of consent and reason if declined. Images of these screening logs are emailed to YTU monthly, and the data are transferred to an Excel spreadsheet, saved for the statisticians here: Y:\Project -- CALM - Shared\Screening logs\Eligibility log spreadsheets.

7.3 Management database

Extra data held in the trial management database are:

- Participant ID
- Randomisation date
- Allocation
- Site details: Site ID, Site name, name of dentists involved and their unique id number and allocation (to intervention or control)
- Parent/Carer consent date for child
- Parent/Carer consent for their own participation
- CRF due, sent, completed and returned dates, including reminders
- Treatment completion date
- Postcodes
- Participant status in study (e.g. full participation, full withdrawal, etc)

8 Sample Size

There is little information on the minimal clinically important difference (MCID) for MCDAS score to be confident in stating what a reliable estimate of this is. However, using an anchor-based method the feasibility study found that the MCID for MCDAS score was 5 and the standard deviation was 6.5. However, since the sample size of the feasibility of the study was low the trial will be powered to detect a smaller MCID of 2.5. The sample size calculation assumes that there will be a degree of clustering of participants at each of the 30 dental sites, with an average cluster size of 20 participants and an intra-cluster correlation coefficient (ICC) of 0.03. In order to detect a MCID of 2.5 under the assumptions of 90% power, a significance level of 5% and a 20% attrition rate we would need to recruit 600 participants, 30 dental sites and 60 dental professionals.

In addition, based on literature [6,7], it is anticipated that 80% of the parent/carers of the children randomised into the study will also consent to taking part in the study and having their dental anxiety measured, giving 480 parents/carers that are randomised into the study. As a result, the total sample size for this study will be 1080.

9 Randomisation

Participants (children) will be randomised 1:1 to intervention or control. Block randomisation will be used, stratified by site, using varying block sizes. The randomisation sequence will be generated by an independent statistician at YTU, and implemented using a central, web-based randomisation at YTU.

In this trial it will not be possible to blind either the participants or the dentist to the allocated treatment. In addition, members of the research team, the trial statistician and the trial health economist will also be unblinded.

10 Analysis of internal pilot trial/phase

A 12-month internal pilot trial (from start of recruitment) is proposed to assess trial feasibility, recruitment rates (of dental practices and participants), and engagement with the intervention (where possible). To recruit 600 participants over 24 months requires an average monthly recruitment rate of 25 participants, though it is anticipated that the recruitment rate will start modestly and increase as more dental practices open to recruitment.

The pilot study outcomes of number of sites open to recruitment, number of participants recruited, average recruitment rate per site per month and percentage of participants in the intervention group who complete the 'message to the dentist' component of the CBT intervention will be reported and assessed using a traffic light system. The grading criteria of these outcomes is given in

Table 3.

Relevant data from the internal pilot trial will be summarised descriptively prior to progression to the main trial to help determine whether progression is warranted. Recruitment rate per dental site per month will be calculated as the total number of participants recruited across all sites since the first site opened divided by the sum of the number of months each site has been open for. Participants in the intervention group engaging with the intervention is measured as a proportion and is calculated as the number of participants who completed the 'message to the dentist' component of the CBT during at least half of their dental visits, divided by the total number of participants in the intervention group.

If all four of the progression criteria are graded green in the traffic light system then the main trial will commence with minimal changes from the pilot trial (barring unanticipated factors).

If all progression criteria are amber or red, then we will discuss, with the independent Trial Steering Committee (TSC) and the funder, the viability of completing the trial with and without major modifications and/or strategies to improve recruitment and intervention engagement or address other unforeseen barriers. The trial may be deemed not to be feasible and the TSC may recommend to the funder that the trial is stopped.

If there is a mix of red, amber and green (at least one green), then the trial may be considered viable to continue but with some modifications to improve recruitment and intervention engagement or to address other unforeseen barriers. This would be subject to discussion with the independent TSC and funder.

Table 3. Progression criteria following internal pilot

	Red	Amber	Green
Recruitment rate per dental site per month	<0.5	0.5-1.09	1.1+
Number of dental sites opened	<25	25-29	30
Total number of participants recruited	<80	80-199	200
Participants in the intervention group engaging with the intervention based on completion of the 'message to dentist' component of the self-help CBT resources	<70%	70-99.9%	100%

NOTE: the pilot trial progression criteria were assessed at the end of May 2023. Originally planned to be formally assessed in March 2023, 12 months after planned start of recruitment in March 2022. However, recruitment commenced two months late, in May 2022.

The funders asked for a short review of progress against the progression criteria by the end of May, based on 12 months recruitment. We fed back that our TSC and DMEC members had given their support to continue with the trial when they met in March 2023. The TSC Chair, Professor Iain Pretty provided a letter of support to the NIHR, which will was considered by the NIHR with the feasibility report.

Progress against the progression criteria:

- 28 sites are open to recruitment = AMBER
- 200 (child) participants have been recruited = GREEN
- The average number of participants recruited per site per month is 0.92 = AMBER
- 81.6% of intervention participants who completed or talked through the 'message to dentist' component of the CBT intervention during at least half of their dental visits to date = AMBER

Trial continued with no major changes.

11 Final analysis

11.1 Analysis software

All analyses will be conducted in STATA v18 (StataCorp, 4905 Lakeway Drive, College Station, Texas 77845 USA), or later (to be confirmed in final report).

11.2 Analysis principles and populations

Analyses will follow the principles of intention-to-treat with participant's outcomes analysed according to their original, randomised group, where data are available, irrespective of deviations based on non-compliance. Statistical tests will be two-sided at the 5% significance level and 95% confidence intervals (CIs) shall be used.

11.3 Screening, eligibility, recruitment and follow-up data

The number of sites recruited will be reported, with the number of dental professionals who took part in each site. We shall report on training of intervention dental professionals and any instances where

we become aware of a 'control' dentist accessing the CBT resources. The postcode of participating sites will be used to obtain their Index of Multiple Deprivation (IMD) decile, via https://imd-by-postcode.opendatacommunities.org/imd/2019 for sites in England, and https://apps.dataunitwales.gov.uk/welshindexofmultipledeprivation/ for Wales. These will be summarised separately for sites in England and Wales as these indices are calculated differently for the devolved nations and are not directly comparable. These data will be compared with the eligibility criteria, stated in the trial protocol, that 80% of participating sites be in the lowest three quintiles (equivalent to the lowest six deciles) for deprivation.

The number of participants screened, eligible, consenting and randomised will be reported. Reasons for non-participation (ineligible or non-consenting) will be provided where available. The flow of participants through the trial will be depicted in a CONSORT diagram (see Appendix). Recruitment graphs presenting the overall recruitment by month, and the actual vs target recruitment will be produced. We shall also present recruitment by site. Participant and parent/carer recruitment will be described separately.

Type and timing of withdrawals will be presented overall and by randomised group, with reasons where available. Follow-up rates will be presented overall and by group for each time point and CRF. The average time (from randomisation) of each follow-up will also be summarised by group.

11.4 Baseline data

All participant baseline data will be summarised descriptively by trial arm both as randomised and as analysed in the primary analysis. No formal statistical comparisons will be undertaken. Continuous measures will be reported as means and standard deviations and categorical data will be reported as counts and percentages.

This will include:

From the 'About the Patient' CRF:

- Age
- Sex
- Ethnic group
- First language spoken, if not English
- Planned treatment details
- Past medical and dental history
- Whether the patient has seen the dentist they were randomised to before for treatment at the practice

Participant postcode will be used to calculate IMD, which will be summarised separately for participants recruited from sites in England and Wales.

From the young person baseline questionnaire:

- MCDAS total score
- CARIES-QC total score (raw and interval)

From the parent/carer baseline questionnaire:

- MDAS total score

11.5 Outcome data

Follow-up data will be summarised by group and time point. This will include:

From the young person FU1 and FU2 questionnaires:

- MCDAS total score
- CARIES-QC total score (raw and interval)
- GRC item

From the parent/carer FU1 and FU2 questionnaires:

- MDAS total score

11.6 Treatment details

The following will be summarised by trial arm for the course of treatment (up to and including FU1):

- Time between randomisation and end of course of treatment
- Number of visits required to complete course of treatment and number of missed visits
- The role of the dental professional seeing the patient at the visit and whether the patient ever saw a dental profession who did not align with their allocated treatment (e.g. a control participant saw an intervention or non-trial dentist, or vice versa).
- Treatment undertaken
- Planned and actual length of visits
- DA of the child at each visit based on the opinion of the dental professional ('Considering your clinical experience with children, how dentally anxious was the patient at this visit?' – 7-point scale from 'Not at all dentally anxious' to 'Among the most extremely dentally anxious patients')
- Delivery of CBT (whether patient completed or talked through 'message to dentist' component (visit 1 only), whether any ideas were discussed with the patient regarding different 'tools' the patient could use, whether the patient appeared to accept the CBT resources, and how many minutes were spent introducing the CBT approach).
- Whether any control participant or their parent/carer reported using any CBT-type dental resources that they had obtained themselves.
- Whether treatment was completed as originally prescribed (fully, partially, or no)
- Whether a referral was made and if so, where to and what treatment was requested.
- Whether treatment under GA or sedation was requested or required
- CGI-I

11.6.1 Longer-term follow-up

The following will be summarised by trial arm for the period between the end of the course of treatment and the final visit the patient attends until they reach one year from randomisation:

- Number of visits attended, if any, and number of missed visits
- The role of the dental professional seeing the patient at the visit and whether the patient ever saw a dental profession who did not align with their allocated treatment (e.g. a control participant saw an intervention or non-trial dentist, or vice versa).
- Treatment undertaken
- Planned and actual length of visits
- DA of the child at each visit based on the opinion of the dental professional ('Considering your clinical experience with children, how dentally anxious was the patient at this visit?' – 7-point scale from 'Not at all dentally anxious' to 'Among the most extremely dentally anxious patients')
- Delivery of CBT (whether any ideas were discussed with the patient regarding different 'tools' the patient could use, whether the patient appeared to accept the CBT resources, and how many minutes were spent introducing the CBT approach).

- Whether any control participant or their parent/carer reported using any CBT-type dental resources that they had obtained themselves.
- Whether a referral was made and if so, where to and what treatment was requested.
- Whether treatment under GA or sedation was requested or required

11.7 Primary analysis

The MCDAS score will be modelled using a linear mixed effects regression model incorporating the outcome at all post-randomisation time points. The model will adjust for baseline MCDAS score, time point, trial arm, and trial arm by time interaction as fixed effects. Participant and site will be included as random effects, to account for the repeated measures of scores by participants over time, and the clustering of participants within sites. The different covariance structures for repeated measurements that are available as part of the analysis software will be applied to the model. The most appropriate pattern will be used for the final model based on diagnostics including Akaike's information criterion (smaller values are preferred). The treatment effect in the form of the adjusted mean difference in MCDAS score will be extracted with its 95% CI and p-value for each time point and overall. The difference between the two groups at 12 months from randomisation will be the primary endpoint, but differences at FU1 and over the 12 months will be extracted for secondary investigations aimed at determining the potential pattern of change. Model coefficients for the covariates with 95% CIs will additionally be presented to aid understanding of the fitted model. Participants will only be included in the model if they have a valid baseline MCDAS score and outcome data (valid MCDAS score) for at least one post-randomisation time point; the model assumes any missing data are missing at random. Model assumptions will be checked as follows: the normality of the standardised residuals will be checked using a qq plot, and homoscedasticity will be assessed by means of a scatter plot of the standardised residuals against fitted values. If the model assumptions are in doubt, transformations of the outcome data will be considered in sensitivity analyses. A log transformation will be tried in the first instance, and then others as suggested by the Stata ladder command as appropriate.

The correlation between baseline and outcome (MCDAS score at both FU1 and FU2) will be reported with a 95% CI. The ICC associated with site will be estimated, with a 95% CI.

The correlation between baseline and both FU1 and FU2 MCDAS scores will also be reported with a 95% CI.

11.8 Sensitivity analyses

The primary analysis will be repeated adjusting, additionally, for other baseline factors: age, sex, intended treatment, and whether the patient has seen the dentist they were randomised to before for treatment at the practice.

Through the trial, it has become apparent that a small number of baseline child questionnaires are either missing or have been completed after randomisation. Therefore, a sensitivity analysis will be conducted which does not adjust for baseline MCDAS score.

The protocol states that the primary model will include participants, primary treating dentist and region as random effects; however, since site was a stratification factor we feel that adjustment for site should be included in the primary analysis. In addition, such a number of random effects may cause issues with convergence of the model. Therefore, this analysis will be presented as a sensitivity analysis.

Since the timing of FU2 has been quite variable, we will conduct a sensitivity analyses which only includes children whose FU2 child questionnaires are completed within a defined window around 12 months from randomisation. This window will be defined as 10-14 months.

We will present a Complier Average Causal Effect sensitivity analysis for the primary outcome (MCDAS at 12 months) to account for non-compliance with the intervention, with engagement determined by participant self-report and dentist's assessment including evidence of completion of the 'message to dentist' component of the intervention. Two-stage least squares instrumental variable (IV) regression will be used, with randomised group as the IV. Compliance will be defined at the patient-level as participants completing their course of treatment, the 'message to the dentist' component of the CBT being delivered during at least half of their dental visits, and the treating dentist having undertaken the intervention training.

11.9 Missing data

The model used for the primary analysis assumes that missing data are missing at random (MAR) conditional on the fixed effects and non-missing outcomes included in the model. However, if outcome data for both repeated measures are missing, i.e. the participant did not return both FU1 and FU2 questionnaires, they will not be included in the primary model. We will conduct a sensitivity analysis, that will include the baseline MCDAS as a repeated measure in the model, which will allow us to include all randomised children, with missing MCDAS at both FU1 and FU2 timepoints imputed under the MAR assumption. The model will adjust for time point, trial arm, and trial arm by time interaction as fixed effects with participant and site included as random effects. The most appropriate covariance pattern will be selected as stated for the primary model.

It is possible that participants who failed to attend their follow-up appointments (or did not return a FU2 questionnaire) differed from those who did return their questionnaire (e.g. a participant had worse dental anxiety, and therefore would have score higher on the MCDAS if they had attended the follow-up appointment). Hence, we will also conduct an analysis to investigate departures from the MAR assumption. The sensitivity of the primary analysis results to departures from the MAR assumption will be explored using a pattern-mixture model, implemented using the *rctmiss* command [14, 15]. Currently this command does not support mixed-effects models, therefore a linear regression model comparing the primary outcome at 12-months post-randomisation will be used, adjusting for baseline MCDAS score, time point, trial arm, and trial arm by time interaction.

The pattern mixture model works by including a sensitivity parameter quantifying the departure from the MAR assumption. For example, if we expected that those who failed to complete the follow-up at 12-months post randomisation on average would have scored two points lower on the MCDAS than those who did attend the follow-up, the sensitivity parameter would be equal to 2. Imputation will be performed allowing the sensitivity parameter of the pattern mixture model to vary from 0 (mean score among those with missing outcome data is the same as the mean score among those with non-missing outcome data, conditional on the covariates) to +/-10 (mean score among those with missing outcome data is +/-10 points larger/smaller than among those with non-missing outcome data, conditional on the covariates) in each group separately and across both groups.

Another source of missingness of the primary outcome could be attributed to the validity of the scoring, where scoring is not possible due to two or more items missing on the MCDAS. If the amount of missing data due to this is deemed significantly large, the MAR assumption will be evaluated using similar methods described above. If the amount of missing data is negligible, no further missing data analyses will be conducted.

The results of these sensitivity analyses will be summarised in tabular and graphical format. While the results of this sensitivity analysis will not be directly comparable to the primary analysis model, it will be able to give an indication of how sensitive the estimate of the treatment effect is to departures from the MAR assumption in the primary outcome data.

11.10 Subgroup analyses

A subgroup analysis will consider whether children with lower or higher baseline DA benefit more from the intervention, by including an interaction between continuous baseline MCDAS score and treatment group in the analysis model.

A range of other exploratory moderator analyses will be investigated and reported in the process evaluation:

- sex of the patient (dichotomous, M/F)
- age of the patient (continuous)
- deprivation level of patient, based on IMD (dichotomised as above/below median calculated separately for participants in England and Wales, analysed in one model)
- if the participant has a parent/carer with self-reported DA at baseline (dichotomised as MDAS score <19/≥19 – this analysis will can only include participants whose parents/carers consented to take part)
- In relation to the whether the planned treatment (as recorded in About Patient baseline CRF) involves local anaesthetic injection(s) or not, which the literature suggests is the among the most feared dental procedures.

11.11 Analysis of secondary outcomes

11.11.1 HRQoL, OHRQoL and parent/carer DA

CHU9D utility scores will be calculated and summarised descriptively by trial arm and timepoint as part of the economic evaluation. Further details of scoring and analysis are provided in the health economics analysis plan.

CARIES-QC raw score and parent/carer MDAS score will be analysed as described for the primary outcome, adjusting for baseline value of the outcome.

11.11.2 Referral and use of pharmacological approaches

The need for referral to secondary care and use of sedation or GA will be analysed by mixed effect logistic regression, adjusting for baseline MCDAS value and intended treatment as fixed effects, and dental site as a random effect. The published protocol states that, for these models, both dental team member and site will be included as random effects but this won't be possible as dental professional is not always nested within site. We have at least one instance in the trial where a dental profession involved in the study works across two participating sites. In these cases, the dental professional was allocated to the same condition (intervention or control) in both sites to avoid contamination.

11.12 Adverse events

Based on findings from the literature on guided self-help CBT, the feasibility study and discussions with the sponsor and PPI representatives it has been agreed that any adverse events from the study intervention and procedures are extremely unlikely so it can be justified not to include adverse event reporting. However, should any events be reported to us via the sites or from the process evaluation, these will be considered.

11.13 Planned formal interim analyses

There are no planned interim analyses of the primary or secondary outcomes, but we will conduct a descriptive analysis of feasibility outcomes following the pilot phase (see section 10).

11.14 Estimating the MCID for MCDAS

As part of the CALM trial, both distribution and anchor-based methods will be used to estimate the MCID for the MCDAS. We shall used data from both trial arms combined for these analyses.
Using the distribution method, we shall calculate varying estimates of the MCID based on an effect size of 0.2, 0.3, 0.4 and 0.5 by multiplying these figures by the baseline standard deviation of the MCDAS (all participants). The use of multiple, independent anchors is recommended to produce a range of MCID scores for a given patient outcome. The anchors in this study are the GRC item (5 levels), the CGI-I item and the clinical outcomes of referral to specialist services and the use of sedation or general anaesthesia.

Baseline participant data and the mean MCDAS score will be reported for participants stratified by each level of the anchor, for each anchor and timepoint (Table 4). For the binary anchors of whether or not the participant was referred to specialist services, and whether or not they required the use of sedation or GA, we will calculate an estimate of the MCID as the difference in mean score between participants who were 'yes' and those who were 'no'. For the GRC and GCI-I anchors, we will calculate the estimates of the MCID in two ways: 1) as the mean of i) the difference in mean MCDAS score between participants rated at least a little better/at least minimal improvement and participants rated as no change, and ii) the difference in mean MCDAS score between participants rated as no change and those rated at least a little worse/at least minimally worse; and 2) difference in mean MCDAS score between participants rated at least a little better/at least minimal improvement and those rated at least a little worse/at least minimally worse.

Table 4. Calculation of MCID estimates for different anchors by follow-up timepoint

Anchor	Response levels	Summary statistics	MCID estimate
Condensed GRC at FU1	1="I feel worse" (combining "I feel much worse" and "I feel a little worse")	Mean (SD) MCDAS score at FU1	Mean of difference between levels 1 and 2 and levels 2 and 3 AND Difference in mean of levels 1 and 3.
	2="Nothing has changed"	Mean (SD) MCDAS score at FU1	
	3="I feel better" (combining "I feel much better" and "I feel a little better")	Mean (SD) MCDAS score at FU1	
Condensed CGI-I at FU1	1=at least minimal improvement	Mean (SD) MCDAS score at FU1	Mean of difference between levels 1 and 2 and levels 2 and 3 AND Difference in mean of levels 1 and 3
	2=no change	Mean (SD) MCDAS score at FU1	
	3=at least minimally worse	Mean (SD) MCDAS score at FU1	
Condensed GRC at FU2	1="I feel worse" (combining "I feel	Mean (SD) MCDAS score at FU2	Mean of difference

	much worse" and "I feel a little worse")		between levels 1 and 2 and levels 2 and 3 AND Difference in mean of levels 1 and 3
	2="Nothing has changed"	Mean (SD) MCDAS score at FU2	
	3="I feel better" (combining "I feel much better" and "I feel a little better")	Mean (SD) MCDAS score at FU2	
Referral to specialist services up to FU1	1=Yes	Mean (SD) MCDAS score at FU1	Difference in mean of levels 1 and 2
	2=No	Mean (SD) MCDAS score at FU1	
Need for sedation or GA up to FU1	1=Yes	Mean (SD) MCDAS score at FU1	Difference in mean of levels 1 and 2
	2=No	Mean (SD) MCDAS score at FU1	
Referral to specialist services up to FU2 (including FU1)	1=Yes	Mean (SD) MCDAS score at FU2	Difference in mean of levels 1 and 2
	2=No	Mean (SD) MCDAS score at FU2	
Need for sedation or GA up to FU2 (including FU1)	1=Yes	Mean (SD) MCDAS score at FU2	Difference in mean of levels 1 and 2
	2=No	Mean (SD) MCDAS score at FU2	

12 SAP amendment log

All changes that are made to the Statistical Analysis Plan following initial sign-off will be detailed in the box below.

Amendment/addition to SAP and reason for change	New version number, name and date
SAP completed and signed-off	*V1.0, C Fairhurst, 08/04/2024*
Missing data section added within Final analysis: *The follow-up rate at the 12-month time point is much lower than what has been accounted for within the sample size calculation. Therefore, analyses have been included to impute the missing data and test underlying assumptions.* *This includes a sensitivity analysis, that takes advantage of linear mixed models to impute missing repeated outcome measures – here the baseline measurement has been included as a repeated measure to maximise the number of participants included in the model. Departures from the MAR assumption will be tested using a pattern mixture model.*	*V1.1 F Wiggins, 24/06/2024*

13 Signatures of approval

Sign-off of the final approved version of the Statistical Analysis Plan by the principal investigator and trial statistician(s) (can also include Trial Manager/Co-ordinator)

Name	**Trial Role**	**Signature**	**Date**
Zoe Marshman	Principal Investigator	Z Marshman	21/5/24
Caroline Fairhurst	Senior Statistician	C.M.Fairhurst	08/04/2024
Fraser Wiggins	Statistician	FWiggins	08/04/2024

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15 Appendices – template CONSORT diagram

