BRIGHT HEALTH ECONOIMCS ANALYSIS PLAN (HEAP)

HEAP version 1.0.

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Introduction

The purpose of this plan is to provide a clear justification for approach undertaken for the cost-effectiveness analysis relating to the BRIGHT trial. The approach is based on the study protocol but with much more detail relating to the operationalisation of the protocol. The plan should be read in conjunction with the study protocol, and as such, general information relation to the study will not be replicated here.

The development of the HEAP started in April 2022 and was finalised in August 2022, before the final analysis of the clinical data was completed and before the analysis of the economic data had started. A draft HEAP was discussed with the health economist on the Trial Steering Group in June 2022, however, the content of the final HEAP is the sole responsibility of the HEAP authors.

The main issues that this document addresses are those related to low response rates and the role of the decision analytic modelling. Other aspects of the analysis will also be described, for context.

Protocol

The protocol (Marshman, et al., 2019) states that:

"A cost-utility analysis will be conducted. This will estimate the mean differences in costs and quality adjusted life years (QALYs) and report the incremental cost-effectiveness ratio (ICER) for each pathway. The cost-utility analysis will be conducted in line with current recommendations from NICE. In particular, a NHS and Personal Social Services perspective will be taken for costs, and health benefits will be quantified using QALYs. The longer term cost-effectiveness will be modelled to estimate the longer term resource use and HRQoL implications of the intervention.

QALYs will be estimated using the CHU9D [37] reported at baseline and annually thereafter. The CHU9D will be valued using published population tariff values [37, 43], allowing QALYs to be estimated for each arm using the trapezium rule to calculate the area under the curve. NHS resource use will be measured for each participant at baseline and annually up to 36 months. This will include all medication costs (e.g. antibiotics) and visits to dental practices for treatment and health services (e.g. referral to specialists in paediatric dentistry, dental admission for a general anaesthetic) using the parent resource use questionnaire."

[37] Stevens K. Valuation of the Child Health Utility 9D Index. PharmacoEconomics. 2012;30(8):729–47.

[43] Ratcliffe J, Flynn T, Terlich F, Stevens K, Brazier J, Sawyer M. Developing adolescent-specific health state values for economic evaluation: an application of profile case best-worst scaling to the Child Health Utility 9D. PharmacoEconomics. 2012;30(8):713–27.

Analysis plan

Given the short description of the economic analysis above, further information is provided on those issues highlighted in the protocol below. We then proceed to examine in further detail, the analytical issues relating to the modelling and missing data in subsequent sections.

<u>NICE methods</u>

The catch-all, yet vague, phrase "The cost-utility analysis will be conducted in line with current recommendations from NICE" is used in the protocol. We are interpreting this as the following:

- Cost-utility analysis using an appropriate generic preference-based measure of health. As the EQ-5D is not appropriate for the study population, and a tariff is not available for the EQ-5D-Y, the CHU-9D and its associated UK tariff was considered to be the most appropriate measure.
- NHS and Personal Social Services (PSS) perspective will be taken for costs, although PSS costs are not considered relevant for this study question and so are assumed to be zero. Health benefits will be quantified using [the child's] QALYs. NICE methods also allow for the incorporation of health effects on informal carers (e.g. parents); these are assumed to be zero.
- The time horizon of the analysis will be chosen to capture all the health and cost impacts of the intervention.
- Costs and health benefits will be discounted at 3.5% per annum.
- Sensitivity analysis, including a probabilistic sensitivity analysis will be undertaken.
- Cost-effectiveness will be assessed against a threshold of £20,000 per QALY gained in the primary analysis and £30,000 in a secondary analysis. The latter is deemed relevant if it is thought that the primary analysis does not capture all the important benefits of the intervention (and which will be assessed qualitatively).

It should be noted that NICE's recommended methods were updated in January 2022, and as such, the study was originally designed to the previous methods guide. We will continue to follow the previous guidelines; it is not anticipated that the difference in recommended methods is materially different in the context of this study.

<u>Resource use</u>

The items of resource associated with the intervention, together with their source(s) are shown in Table 1. As can be seen, the principal source of resource use is the parent/carer questionnaire.

Table 1: Resource use data collection

Item	Source	Notes
Classroom-based, face-to-face lesson	Protocol.	The lesson, as set out in the study protocol, will be described as part of the clinical analysis.
SMS messages	Study records.	Numbers of messages sent have been recorded.
Messaging infrastructure	Study records and study staff interviews	Staff time required to deal with the messages was estimated for the study proposal. Additional resources will also be required for any roll-out, in order to deal with service-related issues, e.g., safeguarding.
Medication	Parent/carer questionnaire	Available at 12, 24 and 30 months. Questions relate to “the 12 months”. (prescribed and over the counter)
Dental visits and treatments	Parent/carer questionnaire (all countries), administrative data (Scotland only)	This includes the types of treatments (check-up, filling, extraction, other), Available at 12, 24 and 30 months. Questions relate to “the last 12 months”. The questionnaire also asks about use of a general anaesthesia, which implies hospital treatment has been undertaken. However, the specific procedure is not recorded.
Type of dental visit	Administrative data (Scotland only)	For England, treatments can be derived from the study clinical examination (e.g. fillings and extractions), but not which were undertaken in which visits.
Dental treatments	Clinical examination	Extractions and repairs can be deduced from changes observed in the clinical examinations carried out as part of the trial. This alone, does not provide precise information about timing and number of treatments.
Costs to parents/carers	Parent/carer questionnaire	Time taken off to attend appointments, time off as a result of child’s dental problems Available at 12, 24 and 30 months. Questions relate to “the last 12 months”.

As there are multiple sources for community dental treatments/visits, it is important that we pre-specify which should be used for the primary analysis, and the role that the other sources may play. The points to note are:

- Scottish administrative data are likely to be the best, being both complete and accurate; but it is a very limited and non-random sample.
- Parent questionnaire data are likely to be of poor quality, and very incomplete (with trial data monitoring suggesting >70% missing), but it may provide some detail of numbers and types of visits that the clinical examination data cannot.
- The clinical examination data will be reasonably complete and very accurate in relation to which treatments have been undertaken in total, but it will lack the detail of the numbers of treatments undertaken to reach that total and the exact timepoint at which the treatments were carried out.

It was decided that the clinical examination data should be used to estimate resource use in the primary analysis. Sensitivity analyses will be undertaken using the questionnaire data if imputation is deemed appropriate. A sub-group analysis will be undertaken for Scotland using the administrative data from Public Health Scotland.

In order to generate costs from the clinical examination data, for the primary analysis, two steps are required. First, the translation of clinical findings to associated procedures (e.g. a missing tooth implies an extraction has taken place); this process is reasonably uncontentious. Second, the translation of procedures into numbers of visits. This second step generates a lot more uncertainty, and is described below.

There are two extreme assumptions that could be adopted:

- All extractions are undertaken at a single visit and all repairs are undertaken at a single visit.
- All extractions and repairs are undertaken at separate visits.

Both of these are considered highly unlikely when children have high numbers of extractions or repairs over the course of the trial (e.g, six or more). However, they will be reasonably accurate for the majority of participants, who are expected to have low numbers of extractions or repairs over the course of the trial.

A more realistic approach, based on discussions with paediatric dentists who have worked in general practice, is to assume that in the presence of multiple extractions and/or repairs, it is likely that several were undertaken at the same visit. It is considered reasonable that children do not normally have more than 2 extractions or 4 fillings at any visit. Based on this we can calculate the number of visits as such:

- In the case of a child having had n extractions, the number of visits for treatment is $n/2$, rounded up to the next whole number.
- In the case of child having had m repairs, the number of visits for treatment is $m/4$, rounded up to the next whole number.

This approach forms the basis of our primary analysis. An alternative approach, that uses parental questionnaire data will be used in a sensitivity analysis.

<u>Costs</u>

Each item of resource use is associated with a unit cost that reflects the perspective of the analysis (and as such, does not include patient charges which are outside the NHS and PSS perspective). However, with dentistry, the unit costs that are attributed to dental treatments differ across countries due to the different dentist reimbursement structures in place; Scottish unit costs for treatments are more precisely defined, compared to England where broad bands of treatments are defined. Note that even if the value of the resources used in Scotland and England were identical, the unit costs available for the two countries are likely to produce different cost estimates. As such, different unit costs are likely to be a combination of different resource values ('real') and different accounting methods ('artefacts').

The Welsh system is more closely aligned to that of England, but is currently changing and in effect, two different systems are currently in place. Consequently, English costs are considered to be appropriate for Welsh patients.

The proposed approach is to use country-specific unit costs for dental treatments when analysing the full sample as these to offer the opportunity to measure real differences that are thought to exist. However, sub-group analyses will be undertaken for Scotland and England/Wales as these will be based on a consistent set of unit costs for dental treatment, and as such, will be more relevant to decision makers.

The unit costs to be used are shown in Table 2, below, and are at 2020/21 price levels, which represents the most recent year for which earlier costs can be adjusted to using the NHS Cost Inflation Index (NHSCII). Costs derived from previous years are inflated to this level using the NHS Cost Inflation Index taken from *Unit Costs and Health and Social Care*. In the study report, the individual unit costs for different items of treatment in Scotland will be presented from the Statement of Dental Remuneration No. 148 (November 2020), which is the most recent version within the financial year 2020/21. The full list of treatments can only be determined upon examination of the study data and so is currently unknown; consequently, Scottish unit costs are not presented here.

The derivation of English UDA costs is explained in a footnote to Table 2, but of note here is that 2018/19 costs were used as these are unaffected by the impact of Covid on activity (and hence, treatment prices). However, the most recent costs (2020/21) will be used in a sensitivity analysis.

Treatments within the hospital setting are possible, but these are expected to be very rare. Whether a child has received a general anaesthetic (and as such has been treated within the hospital setting) is collected in the parent/carer questionnaire, but further details are not available. Consequently, these data will be used within the sensitivity analysis that uses the parental questionnaire data. The available National Reference Costs for day case procedures relating to children that require general anaesthetic are given in the Box 1 (below). The unit cost used in the sensitivity analysis that incorporates hospital activity is the activity weighted average cost across these procedures, which is £2,029.

Box 1: HRG and National Reference Costs for day case dental activity (2020/21)

		FCEs	Unit cost
CD01B	Major Dental Procedures, 18 years and under	290	£2,723.84
CD02B	Intermediate Dental Procedures, 18 years and under	197	£2,364.76
CD03B	Minor Dental Procedures, 18 years and under	622	£1,548.31
CD04B	Major Surgical Removal of Tooth, 18 years and under	2020	£2,875.32
CD05B	Surgical Removal of Tooth, 18 years and under	2924	£2,327.22
CD06B	Extraction of Multiple Teeth, 18 years and under	15129	£2,027.51
CD07B	Minor Extraction of Tooth, 18 years and under	2268	£1,434.33
CD08Z	Minor Dental Biopsy	782	£666.77
CD09B	Minor Dental Restoration Procedures, 18 years and under	1001	£1,927.54
		25233	£2,029.48

Table 2: Unit costs for primary analysis

Item	Value	Source/notes
Classroom-based, face-to-face lesson	TBD	This is outside the scope of the analysis; however, a cost will be estimated for information.
SMS messages	TBD	Price available to the study.
Messaging infrastructure	Various	Staff salaries, plus on costs and overheads, from *Unit Costs of Health and Social Care*.
Band 1 – check up and simple treatment e.g. examination, x-rays and prevention advice	£24.90	Relevant only to England/Wales and based on 1 Unit of Dental Activity[1].
Band 2 – mid range treatments e.g. fillings, extractions, and root canal work	£74.70	Relevant only to England/Wales and based on 3 Unit of Dental Activity
Band 3 – includes complex treatments e.g. crowns, dentures, and bridges	£298.80	Relevant only to England/Wales and based on 12 Unit of Dental Activity
Scottish dental costs	Various	Relevant only to Scotland and based on Statement of Dental Remuneration (No. 155, Feb 2022, https://www.scottishdental.org/professionals/statement-of-dental-remuneration/)
Medications (for NHS and private expenditure)	Various	Prescription costs analysis (2020/21, https://www.nhsbsa.nhs.uk/statistical-collections/prescription-cost-analysis-england/prescription-cost-analysis-england-202021). • Antibiotics based on activity weighted average for 31 amoxyxillin preparations, calcualted as 5 pence per tablet/dose. Assumed to be taken tds= 15 pence per day. • Painkillers based on activity weighted average for 99 paracetamol preparations, calcualted as 3 pence per tablet/dose. Assumed to be taken as two tables/doses, qds= 24 pence per day.

TBD – to be determined

[1] NHS data relating to payments to dental practices in England 2018-19 was analysed to calculate a cost per UDA. While more recent data were available, the impact of the covid-19 pandemic was such that dental activity for 2019-20 and 2020-21 are not thought to be appropriate. Data on 8581 practices were available, for which UDAs and Net Payment to Dental Contract were available (https://www.nhsbsa.nhs.uk/dental-data/nhs-payments-dentists). Practices that also had non-zero units of orthodontic activity were excluded, to produce 6899 practices. The Net Payment includes several adjustments relating to performance and other activities, and so we have excluded these. Cost per UDA, net of patient charges are calculated for the NHS perspective, and a cost including patient charges for the societal perspective. This produces costs of £23.63 per UDA and £44.65 per UDA, respectively. These are then uplifted 5.36% to 2020/21 price levels (using the NHSCII for pay and prices).

Table 3: Unit costs for sensitivity analysis

Item	Value	Source/notes
Cost per UDA for societal perspective (2018/19)	£47.04	See note to Table 2.
Cost per UDA for NHS perspective (2020/21)	£25.57	Method as per Table 2, but using 2020/21 data.
Inpatient episode	£3,487	Activity weighted average of elective inpatient episodes for dental HRGs relation to patients aged under 18 years. Calculated using National References Costs (2020/21).
Travel costs and production losses associated with dental treatments	To be calculated from trial data	Calculated as the mean of costs derived from all dental visits captured on the patient questionnaires: • Parental and carer time will be valued using national gross mean hourly salary (£19.40, Office for National Statistics (EAR01 and HOUR01 series). • Travel costs relating to car travel to be determined from the Royal Automobile Club (https://media.rac.co.uk/blog_posts/typical-vehicle-running-costs-for-petrol-engine-cars-42585). Inflated to 2020/21 using GDP deflators). • Travel costs relating to taxi, bus and train are yet to be determined.

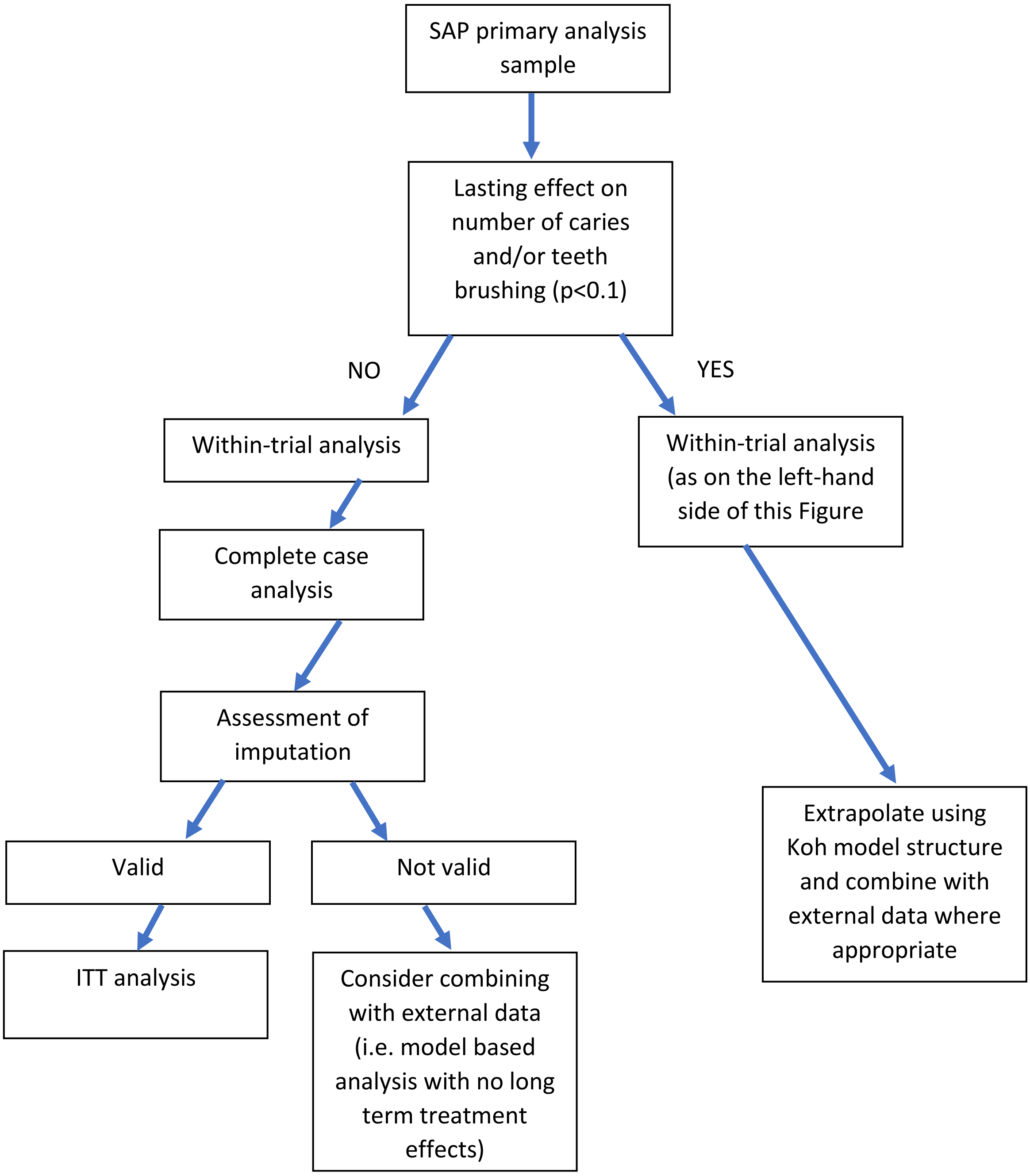
Analysis: Overall approach

The primary analysis will be undertaken in order to capture the costs and health impacts associated with the intervention using the intention to treat principle. *A priori*, we do not know whether there will be any cost or health impacts associated with the intervention. Consequently, the precise nature of the evaluation can only be assessed when the results of the primary analysis are known; if there are no lasting clinical effects, the trial data will be sufficient to assess the cost and health impacts, whilst if there are lasting clinical effects, modelling will be required to estimate the longer-term impact of those effects. This is explained in detail in Analysis: Model-based analysis.

Likewise, the amount and nature of missing data (e.g. unreturned questionnaires or unanswered questions) is not known in advance, but once assessed, it will directly influence the way in which the analysis is undertaken. Two decisions are required in this regard; whether the imputation of missing data imputation is desirable and whether imputation is valid. If imputation is desirable and valid, then it will take place (see Analysis: Within-trial analysis). If imputation is desirable but not valid, other data sources will be examined for use within a model-based analysis (see Analysis: Model-based analysis). Regardless of the validity of any imputation, a complete case analysis will be undertaken for transparency purposes.

This overall approach is summarised in Figure 1, and described in further detail in the following sub-sections.

Figure 1: Schematic of key analysis plan decisions



Analysis: Within-trial analysis

A within-trial analysis that describes the costs and effects up to the end of participant follow-up will be undertaken regardless of the aforementioned assessment of effect. This to allow the impact of any modelling to be clearly seen (as represented by the difference between the within-trial and modelled cost-effectiveness analysis).

The within-trial analysis will follow published recommendations (Ramsey et al., 2015). Analysis will be undertaken within STATA, with incremental costs and QALYs being estimated via regression models with child's baseline age, gender and number of $D_{ICDAS\ 4\text{-}6}MFT$ as covariates, a dummy variable describing the trial arm and a random effect associated with the child's school. Any covariates identified as being associated with missing primary outcome data for the clinical primary analysis (as described in the SAP) will also be included.

The primary analysis will assess the nature of the missing data (Faria et al, 2014) in relation to dental treatments and the CHU-9D, and if appropriate, the missing data will be imputed. First we will check whether missingness is completely at random (MCAR), covariate-dependent CD- MCAR (e.g. whether missingness is a function of socio-economic characteristics), missing at random (MAR) or not at random (MNAR). The method to handle missing data chosen will depend on the type of missingness, the charateristics of the data (non-normal distributions, correlations etc). If imputation is not considered appropriate, then literature searches will be undertaken to identify alternative, more valid, estimates. Imputation will not be considered if the proportion of missing data is greater than 40% for important variables unless data is found to be completely missing at random (Jakobsen et al. 2017). If available, these alternative estimates will be combined with any valid trial data, within a model-based analysis.

<u>Analysis: Model-based analysis</u>

There are two schools of thought relating to this assessment of the need for longer-term modelling:

- The first is to model only those effects that are considered to be robust (or statistically significant). This reflects the view that for any effect that is not statistically significant, there is a realistic chance that it could be the result of random variation. Consequently, projecting that potential random variation forward, and labelling it a 'long-term effect', would be misleading.
- The second is to model regardless of the statistical significance of the effects. This reflects the view that any measurement of effect generated, no matter how uncertain, should be projected forward. Only then is the decision maker provided with all the relevant information. Excluding some effects due to their associated uncertainty prejudges the decision that would be made with full information.

As suggested in <u>Analysis: Overall approach</u>, our analysis will be aligned to the first approach. However, so that we are not too strict on the assessment of an observed effect being due to random variation, we will use a p-value of 0.1 for our assessment, rather than 0.05. In addition, the assessment will be made in relation to the primary outcome measure and the key secondary outcome of frequency of self-reported teeth brushing[2]. A p-value of less than 0.1 at 30 months for either of these will lead to the modelling of the lifetime costs and health effects in relation to the 'statistically significant' outcome measure(s).

For the parameterisation of the model, trial data that allow valid imputation will be used when possible. If trial data are not available for any parameters, targeted literature searches will be undertaken to identify alternative parameters. For each parameter, the alternative sources will be assessed for validity and relevance, and the most appropriate chosen for the primary analysis (Kaltenthaler et al, 2013). Other plausible parameters will be used in sensitivity analyses.

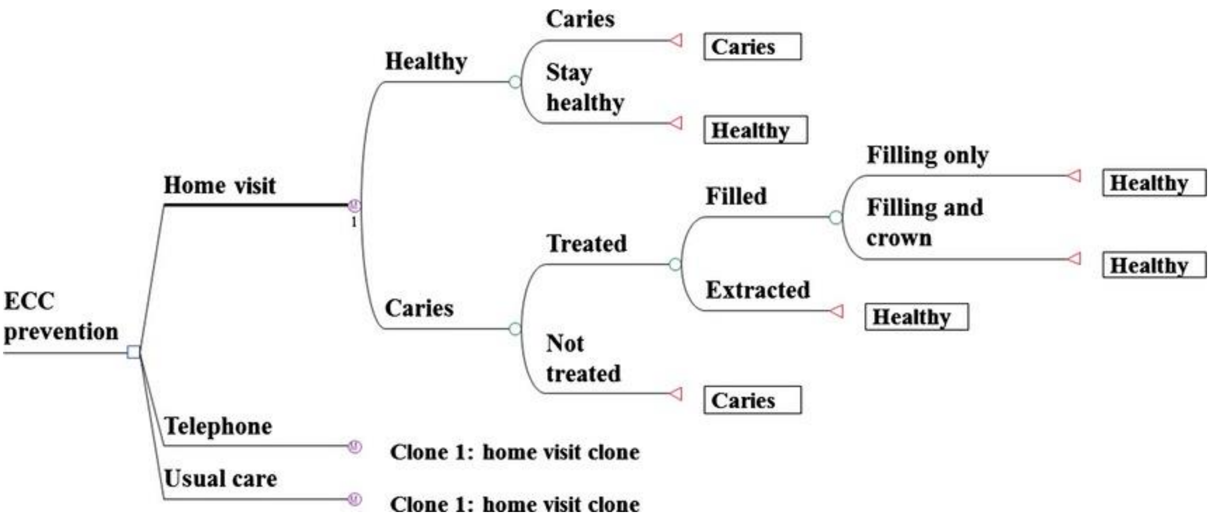
<u>Analysis: Model structure (for the model-based analysis)</u>

[2] These two outcome measures have been chosen as there is robust evidence that shows a link between these and future outcomes. The evidence linking short-term effects and long-term outcomes for the other outcome measures, e.g. plaque, is much less certain.

Two systematic reviews (Qu 2019, Anopa 2020) were identified and the papers within those assessed for relevance. 22 models were identified and assessed in terms of their ability to be populated by BRIGHT, the practicalities of undertaking the analysis within the study resources, their clinical plausibility and the detail of their reporting. So, for example, some models were considered too complex to be used in tandem with BRIGHT, whilst others were not deemed clinically relevant (e.g. predominance of adult restorations) and some were not described in sufficient detail.

The preferred model was that used by Koh and colleagues (2015), which is based on the model of Quinonez (2006) and has been replicated in one other study (Pukallus et al, 2013). This model is appealing for our proposed use as it is relatively simple, is linked to a prevention trial and also includes CHU-9D utilities, and as such, also offers an alternative source of parameters (see Figure 2).

Figure 2: Model structure used in the Koh study



Source: Koh et al (2015)

Its principal weakness is that it may be too simple, and as such, several potential amendments to it were discussed with clinicians, with the main ones being:

- Splitting the caries health state into multiple health states representing different numbers of caries
- Splitting the caries health state(s) into different depths of caries
- Use of arm-specific treatments (as opposed to the assumption, used by Koh, of treatment mixes being the same across arms)

Discussions highlighted the benefits of keeping the model simple (and so the first two amendments were rejected), but that differences in treatments even in the event of similar caries rates was plausible and important to capture (and so the final amendment was agreed).

The final aspect of the model that needs consideration is the time horizon, i.e. over what period should the costs and benefits be projected. Koh and colleagues only looked at costs and effects out to 5.5 years as that was consistent with the time when the permanent teeth started to erupt in their population. In the BRIGHT study, however, participants will already have an established permanent dentition and so differences could be present for a lifetime. However, extrapolating trial effects with this model over children's lifetime is not considered plausible for two reasons. First, the effects seen in the trial are not expected to persist for 70 years or so because there are many other influences on oral health behaviours and dental care choices, during the life course. Second, as more children develop multiple carious lesions, the adequacy of the model to accurately capture the observed effects diminishes as prior treatment will influence the incidence of caries (e.g. most obviously, removed teeth can not decay). Consequently, a 10-year time horizon was considered to be a reasonable time frame that would capture potential longer-term effects, but with scenarios explored in the sensitivity analysis in which the time horizon is changed to 5 and 20 years.

Analysis: Sensitivity analysis

Deterministic sensitivity analyses will be undertaken to test the impact of data, assumptions and analysis methods on results. The following deterministic sensitivity analyses will be undertaken:

- A societal perspective will be taken with respect to costs that will include private expenditure and production losses related to dental treatment/problems. Time taken away from school has also been measured but will not be valued.
- Utilities generated by the CARIES-QC-U, which is a condition specific utility measure generated from the CARIES-QC (Rodgers et al, 2022)
- Inclusion of hospital treatments.
- Alternative time horizons of 5 and 20 years (for model-based analyses that include a long-term effect).
- 2020/21 cost per UDA without patient charges.
- Use of parental questionnaire responses for a CCA.
- Use of parent questionnaire responses for an ITT analysis (if imputation is considered valid).

Probabilistic sensitivity analysis will be undertaken for both the within-trial analysis and the model-based analysis.

Analysis: Sub-group analysis

Two sets of subgroup analyses will be undertaken. The first set provides consistency with the SAP; subgroup analyses will be undertaken in relation to baseline DMFT and pilot vs main trial schools. The second, provides information based on consistent costs of dental treatment, by splitting the full sample into Scotland and 'Other'.

Analysis: Incremental analysis

Incremental analysis will be undertaken using the results of the within-trial regression analyses and/or the model-based probabilistic sensitivity analysis. Results will be plotted on the cost-effectiveness planes with associated cost-effectiveness acceptability curves.

References

Anopa Y, Macpherson L, McIntosh E. Systematic Review of Economic Evaluations of Primary Caries Prevention in 2- to 5-Year-Old Preschool Children. Value in Health 2020; 23(8): 1109-1118.

Faria R, Gomes M, Epstein D, White IR. A guide to handling missing data in cost-effectiveness analysis conducted within randomised controlled trials. Pharmacoeconomics. 2014 Dec;32(12):1157-70.

Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials–a practical guide with flowcharts. BMC medical research methodology. 2017 Dec;17(1):1-0.

Kaltenthaler E, Tappenden P, Paisley S. Reviewing the evidence to inform the population of cost-effectiveness models within health technology assessments. Value Health. 2013 Jul-Aug;16(5):830-6.

Koh R, Pukallus M, Kularatna S, Gordon LG, Barnett AG, Walsh LJ, et al. Relative cost-effectiveness of home visits and telephone contacts in preventing early childhood caries. Community Dent Oral Epidemiol. 2015; 43: 560–568.

Pukallus M, Plonka K, Kularatna S, Gordon L, Barnett AG, Walsh L, et al. Cost-effectiveness of a telephone-delivered education programme to prevent early childhood caries in a disadvantaged area: a cohort study. BMJ Open. 2013; 3.

Rogers HJ, Sagabiel J, Marshman Z, Rodd HD, Rowen D. Adolescent valuation of CARIES-QC-U: a child-centred preference-based measure of dental caries. *Health Qual Life Outcomes*. 2022;20(1):18.

Taylor, G.D., Carr, K., Rogers, H.J. *et al.* A systematic review of the quality and scope of decision modelling studies in child oral health research. *BMC Oral Health* **21,** 318 (2021).

Qu Z, Zhang S, Krauth C, Liu X (2019) A systematic review of decision analytic modelling techniques for the economic evaluation of dental caries interventions. PLoS ONE 14(5): e0216921.

Quinonez RB, Stearns SC, Talekar BS, Rozier RG, Downs SM. Simulating cost-effectiveness of fluoride varnish during well-child visits for Medicaid-enrolled children. Arch Pediatr Adolesc Med. 2006; 160: 164–170.

Ramsey SD, Willke RJ, Glick H, Reed SD, Augustovski F, Jonsson B, Briggs A, Sullivan SD. Cost-effectiveness analysis alongside clinical trials II-An ISPOR Good Research Practices Task Force report. Value Health. 2015 Mar;18(2):161-72.