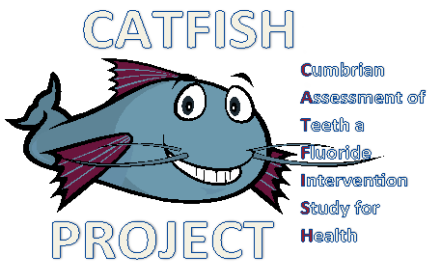

PROTOCOL

CATFISH PROJECT - TOPICAL & SYSTEMIC FLUORIDE EXPOSURE

(Protocol on the 'Topical only effect - available separately)

PROTOCOL COVER SHEET

STUDY TITLE:	An evaluation of a water fluoridation scheme in Cumbria: Population based comparative cohort studies of topical and systemic fluoride exposure.
INVESTIGATOR:	Professor Iain A Pretty Professor of Dental Health C/O Rachel Georgiou Associate Director of Research and Development 3rd Floor Mayo Building Salford Royal NHS Foundation Trust Stott Lane Salford M6 8HD
STUDY PHASE:	Intervention - effectiveness and impact
OBJECTIVES:	To assess the effects and overall cost impact of the re-introduction of a Water Fluoridation scheme on a contemporary population of an evaluation described by both the York Centre for Reviews and Dissemination and Medical Research Council reviews.
PARTICIPANTS:	Birth Cohort from exposed population (West Cumbria) and a non-exposed population (North/ East Cumbria)
STRUCTURE:	Prospective, comparative, population based Birth Cohort study
NUMBER OF CENTRES:	NA - Cumbria
PRIMARY OUTCOME:	Proportion of caries free individuals in each study group
SAMPLE:	A population based approach will be taken: All children born within the fluoridated and non-fluoridated areas will be informed of the study over a period of 1 year for the birth cohort. All schools over the two areas will be approached to determine if they wish to take part in the study - all children from these schools will have a letter sent home to parents inviting them to take part
ESTIMATED TOTAL SAMPLE SIZE:	Census circa 3200 across population (1600 in each area). However The minimum sample size required is 1044
ADVERSE REACTIONS:	N/A none anticipated within the duration of the study - fluorosis only an issue in birth cohort and then only later than we are evaluating them.
STUDY ORIGINATORS:	Professor Iain A Pretty

CONTENTS

I. INTRODUCTION

BACKGROUND

The two most important reviews of water fluoridation (WF) in the United Kingdom have been the York Review (McDonagh, Whiting, & Bradley, 2000) and the Medical Research Council (MRC) Report on water fluoridation and health (MRC, 2002a). The main conclusions of these reviews was that whilst there was evidence to suggest water fluoridation provided a benefit in caries reduction, there was a need to improve the evidence base in several areas:

- *A recommendation that fluoride exposure in children should be explored against a background of exposure to other sources of fluoride, particularly toothpaste*
- *Researchers needed to address issues surrounding bias in caries examinations, with consideration given to blinding of assessments and a more objective approach to assessments.*

A more recent review (Rugg-Gunn & Do, 2012) focused on studies undertaken between 1990 and 2010. The review revealed a marked decrease in the number of studies performed compared to prior to 1990 and concluded that the more recent studies are predominantly cross-sectional in nature (a design criticized in the York Review) but with improved analytical techniques to control for confounding factors. A number of studies explored the effect of fluoridated toothpaste use in conjunction with water fluoridation (Whelton et al., 2004, 2006). The studies included in the review revealed caries reductions as a result of water fluoridation were less than previously reported, although they were still substantial. It is also suggested the inclusion of other variables such as economic considerations and reduction in hospital episodes for general anaesthetic extractions would be important to consider.

Risks and benefits This study is concerned with a public health intervention – optimally 1PPM fluoridated water. The only risk recognised in the literature of this intervention is enamel fluorosis. The population under study has been previously exposed to water fluoridation that has been reintroduced as of September 2013. The main risks to the participants in this study are those generally found in epidemiological research; namely protection of personal data, and non-negligent or negligent acts occurring during examinations. The research team has substantial experience in managing subject identifiable data within a research context and believe that their processes and checks afford a substantial protection against risks of loss of data integrity. The occurrence of accidental or non-accidental events during examination phases is managed through not only appropriate study sponsorship and insurance, but by the utilisation of well-trained and experienced examiners throughout the clinical examinations. As a public health intervention the main benefits apply to the whole population receiving the intervention rather than just those participating in the study. There is an overwhelming need for a strong contemporary evidence base for water fluoridation. The changing context of reducing dental disease burden, the consumption of tap water, the diet and cooking habits as well as access to evidence based prevention in dental practice have all been recognised by leading bodies (York Centre For Reviews and Dissemination, Medical Research Council) as requiring a robust evaluation of a new water fluoridation scheme. There is a risk that, without such evidence, new water fluoridation schemes may not be introduced – and hence whole populations will be disadvantaged as they will not receive a highly effective public health measure. Conversely should the intervention prove marginally effective in the current context then there may be a rationale for withdrawal of such interventions elsewhere in England and Wales as populations may be exposed to the risk of fluorosis without any benefit. Society as a whole needs to be informed about decisions regarding the introduction or withdrawal of water fluoridation schemes.

Rationale for current study: Dental caries remains a significant public health problem. It is certainly the most prevalent disease affecting children; the last national survey (*National*

Children's Dental Health Survey 2003, n.d.) reported that 43% of 5-year-olds had tooth decay. Prevalence varied; 41% in England, 52% in Wales and 61% in Northern Ireland (data for Scotland was not reported). The survey showed little change since the 1993 national survey (O'Brien, 1994) reported a prevalence of 45%. More recent data from NHS surveys showed little sign of improvement (Pitts, Boyles, Nugent, Thomas, & Pine, 2007). Due to changes in how parental consent is obtained, data from the latest NHS surveys are not comparable and difficult to interpret (Davies et al., 2011). Tooth decay is strongly associated with poverty. Young children from poor families carry a disproportionate amount of the population disease burden (Harris, Nicoll, Adair, & Pine, 2004; Lader et al., 2004). A UK prospective cohort study of 3-6-year-olds (Milsom, Blinkhorn, & Tickle, 2008) showed that once a child develops the disease it progresses rapidly. It also has a significant impact; children with caries have a 25% risk of experiencing pain and an 11% risk of having an extraction each year (Tickle, Blinkhorn, & Milsom, 2008). If the disease is unchecked multiple extractions under general anaesthetic (GA) are the norm. Dental extractions are the commonest reason why young children have a GA. Exact figures are difficult to quantify (Robertson, Ní Chaollaí, & Dyer, 2012) but recent national guidance (*Association of Paediatric Anaesthetists of Great Britain and Ireland Guidelines For The Management Of Children Referred For Dental Extractions Under General Anaesthesia*, 2011) estimated between 60,000 and 100,000 cases are carried out each year. We know General Anaesthetic extractions have a significant negative impact on young children and their families (Bridgman, Ashby, & Holloway, 1999) and that there is a strong association between dental extractions and dental anxiety, which can continue to affect individuals in later life (Martin Tickle et al., 2009). The disease in the permanent teeth has fallen rapidly over the last 30 years; the prevalence of obvious decay experience in 12 years olds in England was 81% in 1983, 52% in 1993 and 34% in 2003 (*National Children's Dental Health Survey 2003*, n.d.). More recent data from the NHS dental surveys reported a prevalence of 33.4% in 2008/9 (NWPHO, 2009). The 2009 Adult Dental Health Survey (The NHS Information Centre for health and social care, 2009) reported that the prevalence of coronal caries fell from 46% to 28% between 1998 and 2009 in England. There were reductions across all age groups, but the largest reduction (21 percentage points) was seen in those aged 25 to 34. This picture of overall improvement in population prevalence masks significant inequalities in tooth decay experience within society. In addition national surveys do not report disease statistics among vulnerable groups. The costs to the NHS of treating tooth decay are very significant. In England alone the NHS dental allocation in 2011-12 was £2.3 billion, this is net of patient charges, which roughly makes up a quarter of the total budget, and does not include the budgets for community and hospital services or the costs of care provided by the private sector. The majority of this funding is to pay for the detection and treatment of dental caries. There are significant inequalities in access and utilisation of dental services, those with greatest need are least likely to access dental services (Milsom et al., 2006). This situation gives cause for concern, even more so, when the main disease that the service in concerned with is totally preventable. Dental caries should be totally preventable by limiting sugar intake and adopting a rigorous self-care regime, which includes optimal use of topical fluorides. However, stringent homecare has not been adopted by significant numbers of the population, reflected in the high prevalence rates of dental caries. Water fluoridation is widely advocated as the most cost effective public health measure in battling this disease. The headline findings of the York systematic review of water fluoridation that the size of the benefit would be an approximate 15% increase in the proportion of children with no experience of tooth decay, and a reduction in the mean number of teeth affected by decay of approximately 2.2 teeth. The review also concluded that the benefits of water fluoridation are in addition to the benefits derived from the use of fluoride toothpaste, a conclusion reiterated by a Cochrane systematic review of the effectiveness of fluoride toothpaste (Marinho, Higgins, Logan, & Sheiham, 2003). However, the York review also concluded that the evidence base for water fluoridation is limited; most of the studies were conducted at a time before widespread use of fluoride toothpaste and the significant fall we have seen in dental caries prevalence in the UK. The Medical Research Council working group report recommended that *'Studies are needed to provide an estimate of the effects of water fluoridation on children aged 3-15 years against a background of widespread use of fluoride toothpaste, and to extend knowledge about the effect of water fluoridation by social class (or other relevant measures of socioeconomic status), taking into*

account potentially important effect modifiers such as sugar consumption and toothpaste usage.' Water fluoridation is believed to have a systemic effect; constant exposure means that fluoride is incorporated into the mineral structure of the teeth as they develop in utero and in the first 5 years of life; and a topical effect once a tooth has erupted by creating an environment at the tooth surface which favours remineralisation. The report also recommended that economic and quality of life outcomes need to be assessed in future studies. The case for fluoridation becomes more difficult to make as dental disease levels in older children and adults continue to fall. A well-conducted study is required to assess the impact on health and assess the value for money of a water fluoridation scheme in the current context. However to satisfy the inclusion criteria for a high quality study set out in the York Review a new scheme needs to be implemented and appraised. A unique set of circumstances in Cumbria provides an opportunity to conduct a high quality evaluation of a reintroduced water fluoridation scheme, which satisfies the inclusion criteria stipulated by the York systematic review (McDonagh et al., 2000) and can address the design issues identified in the Medical Research Council report (MRC, 2002b).). As the fluoride dosing works at Cornhow had been out of operation since April 2006 and from 2011 in Ennerdale and reintroduced to both in 2013. There are two geographically contiguous water fluoridation schemes in West Cumbria; Cornhow and Ennerdale – described in the remainder of the protocol as **West Cumbria**.

It is attractive to undertake a study in Cumbria as there are no impediments to implementing this reintroduced scheme, there is low population mobility and there is a neighbouring relatively homogeneous non-exposed (not receiving fluoridated water, referred to as **North Cumbria** in the remainder of the protocol - although the majority of the population live in North Cumbria it will be made up of those living in the North, South and East of Cumbria) population, and there is a large, salaried dental service experienced in undertaking large dental epidemiological surveys in school and nursery settings. There is also strong support from the public health community in Cumbria and the North of England to undertake an evaluation and a good relationship with the water provider.

Research objectives.

To assess the effectiveness and overall cost impact of the introduction of a Water Fluoridation scheme on a contemporary population of children (with falling disease levels) using a research design that meets the requirements of a new scheme evaluation described by both the York Centre For Reviews And Dissemination and Medical Research Council reviews.

Objectives

- To assess the effects and costs of both systemic and topical exposure (exposure from in utero) to water fluoridation following the introduction of a new Water Fluoridation scheme on a birth cohort of contemporary children (falling disease levels), as compared to a birth cohort of children not exposed to water fluoridation.
- To measure the impact of water fluoridation on social class inequalities in child dental health
- Using a research design that meets the requirements of a new scheme evaluation described by both the York CRD and MRC reviews.

Primary Prevention: The objective of water fluoridation is to decrease caries risk. The primary objective is to measure this risk reduction by the assessment of **prevented cases** – i.e. the proportion of caries-free children at each time point (measured at the caries in dentine level) in both the non-exposed and intervention groups. For this systemic group this will be for all deciduous teeth. This is a simple and elegant outcome that measures a meaningful difference for both individuals and populations. This measurement will be balanced against the effect modifiers of toothpaste use any other reported sources of fluoride, diet, and weaning practices.

III. INVESTIGATORS

The Principal Investigator for this study will be:

Iain A Pretty
Professor of Public Health Dentistry
3rd Floor Mayo Building
Salford Royal NHS Foundation Trust
Stott Lane
Salford M6 8HD

Other individuals involved in this study include:

a. Tanya Walsh (University of Manchester; Statistician)
b. Michaela Goodwin (University of Manchester; Research Assistant)
c. Martin Tickle (University of Manchester; Dental Public Health)
d. Eric Rooney (Consultant in Dental Public Health)
e. Matt Sutton (University of Manchester; Health Economics)
f. Mike Kelly (NICE)
g. Richard Emsley (University of Manchester; Statistician)
h. Rebecca Wagstaff (DPH)
i. William Whittaker (University of Manchester; Health Economics)
j. Julie Fletcher (Barnardo's, Children's Services Manager)
k. Peter Sheran (NICE)

IV. APPROVAL OF THE PROTOCOL

The protocol will be reviewed and approved in writing by NHS ethics through IRAS, Salford Royal Foundation Trust and The University of Manchester as sponsor.

The Principal Investigator will ensure all relevant staff participating in the study has appropriate up to date enhanced checks carried out by the Disclosure and Barring Service (DBS) prior to study commencement.

V. DURATION OF STUDY

7 Years (see timeline).

VI. PARTICIPANTS

Systemic and Topical effect (S&T): This birth cohort will be recruited from two sites – the exposed population (West Cumbria) and a non-exposed population (North Cumbria).

Minimum Sample Size
1044 children is the minimum sample size required for analysis. However as this is a population-based approach there are approximately 3200 eligible for recruitment into the birth cohort.
This is based on an earlier study where the proportion of children who develop caries when 'non-exposed' to fluoride is 0.47; the proportion when 'exposed' is 0.37 (Numbers from an RCT of toothpaste use carried out in the North West of England). To detect a risk difference of 0.1 (Risk Ratio 0.8) at 0.05 level with 90% power a total sample size of 1044 children would be required.

Using the proposed recruitment strategy, we will have more than 90% power to detect a risk difference of 0.1 (0.47 versus 0.37, risk ratio 0.8) at the $p<0.05$ significance level, allowing for refusal rate for a dental exam of 7.5% and loss to follow up 12.5% at each time point.

Assume consent rate of 84% (as per NHS Dental Survey) 2688 available at clinical exam 1
Assuming refusal dental exam of 7.5% and loss to follow up 12.5% is 2150
available at clinical exam 2 and assuming refusal dental exam of 7.5% and loss to follow up 12.5% is 1720 at the final exam.

Inclusion / exclusion characteristics
Due to the population based nature of the intervention the research team expect the recruitment to have broad inclusion criteria with only those with significant health issues being excluded from invitation to participation. This study will recruit both parent and child into the study (one cannot happen without the other as parents must complete questionnaires and children will have a dental exam at 3 and 5 if they agree)

Inclusion Criteria will include:
All women in the population who are expected to give birth between 1st September 2014 and 31st August 2015

Exclusion criteria
Those individuals who are planning to move from the area within the duration of the study
Those who are unable or unwilling to provide consent.
Life threatening conditions (maternal or foetal) identified at the time of recruitment

VII. STUDY DESIGN Prospective, comparative, population based study

Planned interventions:

The exposure is continuous dosing of the water supply with 1mg/litre fluoride in the form of hexafluorosilicic acid. The exposed population will be defined primarily by the geographical coverage of the Cornhow & Ennerdale plants. The exposed population resides within the boundaries of West Cumbria and will be identified by the residential postcodes and addresses in the compliance zones covered by the two plants, which will be provided by the water undertaker. The control population will be the non-exposed population living within North/ East Cumbria. There will be no problems with compliance with the intervention because of the intervention is universally provided and will take place irrespective of whether or not informed consent to participate in the study is given. Water fluoridation will be delivered to these geographical areas, but levels of exposure will differ according to each individual's consumption. The main problems we are likely to encounter are failure to provide consent, refusal of consented children to have a dental examination or be examined and loss to follow up of participants at successive data points. Although West Cumbria is a population with low mobility we have based our estimated consent rates and loss to follow up on recent actual data from NHS dental epidemiological surveys of 3-year-old children undertaken in 2011 and 5-year-old children undertaken in 2008/9 in Cumbria' plus data from the East Lancashire Fluoride Varnish Trial. Parents provided informed consent for their children to participate in these NHS surveys and the requests we will be making to examine children are very similar to those used for the NHS surveys, so we expect similar rates of consent, refusal of consented children to be examined and children to be unavailable for examination when the examination teams turn up at a nursery or school. This latter issue is more likely to cause loss to follow up than active withdrawal from the study.

Time scale (see appendix for more detailed time line)
Year 1 - *recruiting to be performed by trained staff under the supervision of Cumbria R&D managers and research midwives*
S&T:
Months April - May 2014 - Wait period until May 2014
Month June 2013 - February 2014 - PPI around protocol and study development
Month February 2014 - Ethics and protocol complete
Month February 2014 - Staff positions advertised for BC recruiters

Month April 2014 - BC advertising in appropriate settings and staff training
Month May 2014 - BC recruitment begins at appropriate opportunities throughout pregnancy by BC recruiters
Month September 2014 - BC recruitment at birth and questionnaire distributed to those born by BC recruiters

Year 2+
S&T Cohort:
March 2014 2nd round of questionnaires to Birth Cohort September 2015 - 3rd round of questionnaires to Birth Cohort distributed by PM
March 2016 4th round of questionnaires to Birth Cohort
September 2016 – Birthday card (break for questionnaires)
June 2017 - Training and calibration of dental examiners
March 2017 - 5th round of questionnaires to Birth Cohort
All questionnaire will be posted or made available online by the Project Manager UOM)
September 2017 - 3-year-old caries exam begins (carried out by members of the CDS)
January 2019 – CATFISH tooth selfies begins (carried out by the research team at UoM)
September 2019 - 5-year-old caries exam begins (carried out by members of the CDS) 6th round of questionnaires to Birth Cohort

Outcomes

1. **Proposed outcome measures**

Primary: Presence of absence of caries in each child, in each study group (primary dentition).

Secondary: Count of carious teeth per child in whole mouth according to BASCD scoring (incidence) in the those children who develop caries i.e. number of cavities over the follow up period, traditional caries increment, costs and impacts. Additional factors linked to dental problems such as dental pain, Dental General Anesthetic for tooth extraction, trouble sleeping, time off from school due to dental problems, problems talking, eating or being upset due to a dental problem will be looked at between the two groups as well as for those with and without caries. Additional analysis around diet and behavior such as weaning practices, tooth brushing will also be analyzed between the groups and to assess the impact on carious teeth in the fluoridated and non fluoridated area

Assessment of harms:
Water fluoridation has a 70-year history as a safe intervention. However it is important that we undertake some assessment of risk of harm to identify any patterns in serious adverse events in the exposed and not-exposed populations. This will be monitored at regular intervals by an independent Data Monitoring Committee and a separate Oversight Committee from the birth cohort questionnaire, which records hospital admissions. In the event that a pattern of results is found in the questionnaire data which would lead the team to suspect an association between fluoride exposure and a systemic disease or condition we will apply for further funding and ethical permission to ask parents of children in the study to provide consent to access their primary care records to enable further more thorough investigation of any suspected association. A Senior Academic will lead the Oversight Committee and a further senior academic (both who do not have any connection with the Salford Royal Foundation Trust or the University of Manchester) will lead the Data Monitoring Committee. The Oversight Committee will monitor adherence to the protocol and raise awareness to relevant groups of people if any issues are raised. The data monitoring committee will monitor data collection and output and will have the power to stop the project if serious issues or concerns are raised after examining the data. We cannot examine fluorosis at this stage due to the age of the children and length of exposure, however the Research Team will be applying for further funding to continue the study to look at fluorosis at an appropriate time.

Cost effectiveness

The capital expenditure and on-going maintenance costs associated with the re-introduction of the scheme will be quantified. The use of a single water supplier (United Utilities Water PLC) simplifies these cost assessments. In order to assess potential cost savings as a result of the intervention we will measure the following:

- Dental service utilisation by UDA (Unit of Dental Activity or equivalent in the new contract) using NHS Business Services Authority (BSA) data for children in each study arm (prescribing practice). This activity data will be triangulated with clinical findings when the children are examined
- The number of general anesthetic exactions carried out in hospital, undertaken in each group according to HES data (application to CAG to access this data and NHS data is being sought given the changes in consent and meeting the common law duty of confidentiality since the study began in 2013)
-
- Fully anonymised NHS BSA (dental treatment) and HES (dental extractions carried out in hospital) data will also be sought for all children who could have taken part in the CATFISH study. This will be made through an application to CAG, NHS BSA and NHS digital. This data will provide further information on cost effectiveness and can be triangulated with data collected as part of the study to examine potential consent/response bias.

The costs to the family unit for each of the above

Cost-effectiveness will be assessed in accordance with NICE guidelines for technology appraisal (NICE, 2013). The evaluation will assess costs to the NHS and personal and social services.

The clinical outcome will be the number of caries. For the cost-effectiveness analysis outcomes will be collected on child health-related quality of life (HRQOL) that can be transformed into utility scores in accordance with the NICE Reference Case. The recommended instrument is the EQ-5D, however, the EQ-5D measure is not validated for children. We will therefore collect HRQOL via the Child Health Utility 9D (CHU9D) instrument. The CHU9D is a pediatric health related quality of life measure and has been validated for use in children aged 7-11 (Stevens, 2011) and preference weights exist that have been derived from the UK population (Stevens, 2012).

HRQOL to be completed by;

Birth Cohort (0 to 5 years old) will complete one questionnaire
Aged 5 - By parents during first year of school by postal / online questionnaire.

Matching of the birth cohort to the older birth cohort at age 5 will enable the extrapolation of cost and utility for the birth cohort to age 11.

NICE guidance specifies that the time horizon needs to be long enough to capture all-important differences in costs and outcomes. The main analysis will consider the cost-effectiveness of water fluoridation within the trial period. This is a conservative assumption, as we expect benefits and cost savings in the short-term to continue into the long-term. In sensitivity analysis, we will model the future impact of the changes in the primary outcome on future costs and benefits using estimates from the literature and analysis of cohort studies.

The costs and outcomes will then be translated into incremental cost-effectiveness ratios. Uncertainty in the model will be accounted for via cost-effectiveness acceptability curves, probabilistic sensitivity analysis on parameter precision and alternate scenario modeling for extrapolation.

Screening and Selection of Subjects

Parent and Child (Parents will complete questionnaires and child will have a clinical exam)
Child participants in the study must be expected to be born between 1st September 2014 to 31st August 2015 to be within the same school year starting 2019. Parent participants will be the parents of those children born in this time.

All eligible women will be provided with the study information leaflet prior to 20 weeks gestation (by or at the 20 week scan) (Appendix 13)

Eligible women will be identified by an appropriately trained member of the study team who will provide them with the study information pack (Appendix 14) This will occur either in the clinical or community setting between 20 weeks gestation and 12 weeks postpartum.

Sufficient time will be given for the woman to read the study information and have the opportunity to ask questions

When consent is obtained a parent will be nominated as the main contact point for the study (NP) this parent will be the consented parent to complete questionnaires, they will also consent their child to take part (one cannot happen without the other)

If consent is not obtained at this time permission will be sought to contact the respondent by telephone, text or email to discuss the study further

Additional advertising will be placed in appropriate areas around the hospitals and antenatal classes in Cumbria with links to website and contact information

Parents and children born within the time stated will be recruited from west of Cumbria (exposed) and all other areas of Cumbria (not exposed).

The delivery book will be checked each day by the appointed research practitioners and will be recorded in Redcap against those already consented (therefore no one will be approached to fill in a questionnaire until we have confirmation of a successful birth). This information from the delivery book will also be used to approach people we may have missed at birth or at the 20 week scan to be able to contact them in community. Their name address and NHS number will be recorded and the appropriate health visitor will be contacted to take a prepared CATFISH pack out on their home visit. At this point parents will be asked if a CATFISH member can contact them by the health visitor or if they simply want to read through the pack themselves.

C. Monitoring of the study

A steering group, will monitor this study at periodic intervals. This group will include the Principal Investigator, University of Manchester staff, lay member of the community (Public and Patient Involvement (PPI) and Consultants involved to ensure that the study is being conducted according to Good Clinical Practice Guidelines. An Oversight Committee (chaired by Ivor Chesnutt) and Data Monitoring Committee (chaired by Gail Douglas) will monitor and feedback to both the research group and relevant organisation. The groups will work closely with organisation such as Public Health England. Further PPI - patient and public involvement - will be sought for various aspects of the study including visits to hospitals for recruitment opportunities and sure start centres to gain relevant opinions on the study, for example both the questionnaire and leaflet will be given to new parents through sure start centres to fill in to test before the study begins.

D. Data handling
The data controller will be the University of Manchester. Data will be entered directly into a secured electronic data capture system (REDCap). Only the Chief Investigator and Project Manager will have access to the key information which will link subjects to clinical data and questionnaires. Recruiters will have access to data during consent and if they are present during the baseline questionnaire. However as they will only be involved during recruitment

they will not need access to data linking individuals to clinical data after recruitment has been finalized. No other member of the research team will be able to link the patient identifiable information once entered into the electronic system. Research midwives connected with the study will check patients who have agreed to be contacted or have consented against the birth register in order to ensure no one is contacted who did not actually give birth.

D. Randomization

Not applicable. Prospective, comparative, population based study.

IX. DATA ANALYSES

All analysis will be carried out by a blinded statistician and the CI and PI will not access the data for analysis. The primary objective is to determine whether there is a difference in the proportion of children in the fluoridated and non-fluoridated cohorts that develop caries over the period of observation (case is 1 or more carious lesions into dentine). This will be evaluated using the Incidence Rate Ratio / Risk Ratio. The 'natural experiment' in water fluoridation exposure implies an absence of confounders in this study (water fluoridation dosing in the exposed population is independent of social class, other fluoride sources etc.) and so this simplifies the analysis and interpretation considerably. Using data collected through a questionnaire (collected every 6 months until the child is 1.5 years old and subsequently collected annually), we will consider the mediating role of a change in behavioural factors, such as fluoride use and change in diet, in explaining the relationship between WF and outcome. We will also examine potential effect modification of these measures at baseline, and of socio-economic status. These will specifically include; toothpaste use, type and fluoride level, frequency of brushing and age started, fluoride supplements used, dental attendance, diet, specifically what is eaten or drank in the hour before bed, chronic conditions, feeding and weaning behaviour including bottle or sippy cup use. Further information will be collected on demographics, socio demographics impact of any dental problem such as pain, sleep disturbances, visits to hospital for dental extraction. In addition the longitudinal nature of the study will provide a rich dataset on behaviours with which we can identify changes in oral health care and dietary habits in this cohort, and model through multivariable regression the impact this may have, either positively or negatively, on the outcome. For instance parents may place less importance on tooth brushing with fluoride toothpaste when they are receiving fluoridated water. Conversely, parents of children in the non-fluoridated cohort may engage more in caries preventive behaviour. The cost analysis will consider the (discounted) capital expenditure and running and maintenance costs of the fluoridation plant, the Unit of Dental Activity of visits to General Dental Practitioners (costed at standard fees levels), the proportion of General Anaesthetic's required (costed using the national tariff), and the costs of activities to maintain dental health reported by NHS Business Services Authority for each cohort. The analysis will be undertaken at child level with the plant costs apportioned to individual children on a per-child basis.

Cost-effectiveness will be assessed from a NHS personal and social services (NICE compliance) perspective on the primary outcome by estimating incremental cost-effectiveness ratios and cost-effectiveness acceptability curves. Secondary analysis will involve estimation of the long-term utility gains associated with the changes in the primary outcome using the cohort data and published utility estimates. Additionally each child (or parent of child depending on age) will be asked to complete a Child Health Utility 9D instrument to record child health related quality of life (Stevens, 2011). As a General Anaesthetic is a potentially dangerous consequence of treatment of caries in young children, we will also include the health benefits of any General Anaesthetic avoidance in the secondary analysis.

We will record the number of non-responders at each time-point along with their social class and/or IMD (Index of Multiple Deprivation) status. This information will be used to compare the responders and non-responders, with adjustments performed using inverse probability weighting if subsequently required. We will also monitor recruitment rates (3 monthly basis) in

line with projected targets. This information will be passed to the DMC (Data Monitoring Committee) for consideration. We will examine whether the effects differ between social classes by stratifying the analysis of the exposed and non-exposed cohorts. If significant differences in the effects of fluoridation are found between social classes we will quantify the contribution of fluoridation to the extent of inequalities in child dental health using the concentration index. The results of the study will be reported in accordance with the STROBE guidelines for the reporting of observational studies (Von Elm et al., 2007).

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