APPENDIX M

Protocol Changes

Changes to the protocol were made with the consultation of and agreement from the advisory panel. The changes to the original protocol were mainly to clarify or simplify the intent of the inclusion criteria. The range of analyses undertaken was broader than had been described in the protocol. Due to extremely limited evidence, the inclusion criteria for Objective 3 were expanded to include studies of level C evidence, and limited to studies from the UK.

1. The objectives of the review were re-phrased into questions
Objective 1:
Original: 1. Assessment of the effects of fluoridation of public water supplies in preventing caries (is a causal relationship likely?).
New: What are the effects of fluoridation of drinking water supplies on the incidence of caries?

Objective 2:
Original: If fluoridation is shown to have beneficial effects, what is the effect over and above that offered by the use of alternative interventions and strategies (i.e. fluoridated toothpaste, educational programmes, and increased self awareness of health issues?).
New: If water fluoridation is shown to have beneficial effects, what is the effect over and above that offered by the use of alternative interventions and strategies?

Objective 3:
Original: Determination of whether fluoridation results in a reduction of caries across social groups and between geographical locations.
New: Does water fluoridation result in a reduction of caries across social groups and between geographical locations, bringing equity?

Objective 4:
Original: Assessment of the negative health effects of fluoridation.
New: Does water fluoridation have negative effects?

Objective 5:
Original: Comparison of the effects of natural and artificial fluoridation to investigate any possible differences
New: Are there differences in the effects of natural and artificial water fluoridation?

Searching:
The protocol describes searching of electronic databases. In addition, other forms of searching were conducted, including searching the World Wide Web, hand searching, and a request for submissions on a web site dedicated to the review. Update searching was undertaken, which was also not described in the protocol.

Inclusion criteria (all changes are marked in Italics)
Changes to the quality inclusion criteria are shown below.

Level A (Highest quality of evidence, minimal risk of bias)
Original:
1. Prospective (planned) studies that started at either initiation or discontinuation of water fluoridation and have a follow up of at least two years for positive effects and at least 5 years for negative effects
2. Studies address at least three possible confounding factors and make corrections in the analysis where appropriate
3. Studies with the lowest bias where primary outcomes were blinded to examiners for fluoridation status of participants.

New:

- Prospective studies that started *within one year* of either initiation or discontinuation of water fluoridation and have a follow up of at least two years for positive effects and at least 5 years for negative effects.
- Studies *either randomised or* address at least three possible confounding factors and adjust for these in the analysis where appropriate.
- Studies where fluoridation status of participants was unknown to those assessing outcomes.

The major change in the definition of Level A evidence was to allow the start of the study up to a year before or after the change in fluoridation status of the study area. This was allowed because it was thought that no significant change would have occurred in one year, and to allow sufficient time for study procedures to be implemented.

Level B (Evidence of moderate quality, moderate risk of bias)
Original:

1. Studies that started less than one year after fluoridation was initiated or discontinued and had a prospective follow up of outcomes
2. Studies that measured and made corrections for less than three but at least one confounding factor
3. Studies that failed where primary outcomes were not blinded to examiners for fluoridation status, but made other provisions to prevent measurement bias

New:

- Studies that *started within 3 years of the* initiation or discontinuation of water fluoridation, with a prospective follow up for outcomes.
- Studies that measured and adjusted for less than three but at least one confounding factor.
- *Studies in which fluoridation status of participants was known to those assessing primary outcomes, but other provisions were made to prevent measurement bias.*

The main change to the definition of Level B evidence was to increase the allowed time period between change of fluoridation status of the study area and start of the study. It was felt that the original criteria of one year was too strict, in light of the change made to the definition of Level A evidence. The change in wording of the third point under Level B was to improve clarity, but not meaning.

Level C (Lowest quality of evidence, high risk of bias)
Original:

1. Studies of other designs (prospective or retrospective, concurrent or historical control) that meet other inclusion criteria
2. Studies that failed to account for confounding factors
3. Studies that did not prevent measurement bias

New:

- *Studies of other designs (e.g. cross-sectional), prospective or retrospective, using concurrent or historical controls, that meet other inclusion criteria.*
- Studies that failed to adjust for confounding factors.
- Studies that did not prevent measurement bias.

The major changes in the definition of Level C evidence were to improve clarity, but not meaning.

Objective Specific Criteria: (all changes are marked in Italics)
Objective 1
Original: Assessment of the effects of fluoridation of public water supplies in preventing caries
Participants:

1. Populations receiving fluoridated water (either naturally or artificially)
2. Populations receiving non fluoridated water

Intervention:
A defined fluoride -concentration present in drinking water, either controlled or naturally occurring
Outcomes:
Number of decayed, missing or filled teeth (DMFT, dmft, deft) and/or number of decayed, missing or filled surfaces (DMFS, dmfs) or percentage of caries free teeth or caries free subjects in those receiving fluoridated compared to non-fluoridated water
Study designs:
Prospective studies comparing two populations, one receiving fluoridated the other non-fluoridated water

New: Does fluoridation of drinking water supplies prevent caries?
Participants:
- Populations receiving fluoridated water (naturally or artificially)
- Populations receiving non-fluoridated water

Intervention:
- *A change in the level of fluoride in the water supply of at least one of the study areas, within three years of the baseline survey.*

Outcomes:
- *Any measure of dental decay*

Study designs:
Prospective studies comparing at least two populations, one receiving fluoridated the other non-fluoridated water, *with at least two points in time evaluated.*

The changes in the inclusion criteria for Objective 1 were changed as follows. Under intervention, the words were changed to indicate that there had to be a before and after fluoridation period studied. This is more specific than the original wording, and clarified the intent. The outcomes were changed to include any measure of dental decay that was presented by a study to allow for other measures. The study design wording was also changed to clarify that two points in time had to be studied.

Objective 2:
Original: If fluoridation is shown to have beneficial effects, what is the effect over and above that offered by the use of alternative interventions and strategies
Participants:
1. Populations receiving fluoridated water (either naturally or artificially) who receive fluoride from other artificially supplemented sources (e.g. food, toothpaste, fluoride tablets, bottled drinks)
2. Populations receiving non fluoridated water who receive fluoride from other artificially supplemented sources

Intervention:
Fluoride at any concentration present in drinking water
Outcomes:
Number of decayed, missing or filled teeth (DMFT, dmft, deft) and/or number of decayed, missing or filled surfaces (DMFS, dmfs) or percentage of caries free teeth or caries free subjects in the four different participant groups
Study designs:
Prospective studies comparing the four populations outlined above, to investigate the differences in levels of tooth decay between the populations

New: If fluoridation is shown to have beneficial effects, what is the effect over and above that offered by the use of alternative interventions and strategies?
Participants:
- Populations receiving fluoridated water (naturally or artificially) *in addition to* other interventions.
- Populations receiving non-fluoridated water in *addition to other interventions*.

Intervention:
- *A change in the level of fluoride in the water supply of at least one of the study areas, within three years of the baseline survey.*

Outcomes:

- *Any measure of dental decay.*

Study designs:

- Prospective studies comparing at least two populations, to investigate the differences in levels of tooth decay between the populations *in the presence of other sources of fluoride, e.g. fluoridated toothpaste. Where specific information on the use of other sources of fluoride is not supplied, populations in studies conducted after 1975 in industrialised countries were assumed to have been exposed to fluoridated toothpaste.*

The population criteria were changed only to make it more clear that the effects of having fluoridated or non-fluoridated water in addition to other interventions were being studied. Intervention and Outcomes wording were changed as in objective 1, for clarification that two points in time, before and after fluoridation/discontinuation of fluoridation had to be studied. The study design criteria was altered to allow for the possibility that person-level use of fluoride was not adequately measured.

Objective 3
Original: Determination of whether fluoridation results in a reduction of caries across social groups and between geographical locations bringing equity
Participants:

1. Populations receiving fluoridated water (either naturally or artificially), from different social groups and geographic locations
2. Populations receiving non fluoridated water, from different social groups and geographic locations

Intervention:
Fluoride at any concentration present in drinking water, either controlled or naturally occurring
Outcomes:
Number of decayed, missing or filled teeth (DMFT, dmft, deft) and/or number of decayed, missing or filled surfaces (DMFS, dmfs), or percentage of caries free teeth or caries free subjects in those receiving fluoridated compared to non-fluoridated water compared between different social groups and geographic locations within the two participant groups
Study designs:
Prospective studies comparing two populations, one receiving fluoridated the other non-fluoridated water, across different social groups and geographic locations

New: Does fluoridation result in a reduction of caries across social groups and between geographical locations?
Participants:

- Populations from different social groups and geographic locations receiving fluoridated water (naturally or artificially).
- Populations from different social groups and geographic locations receiving non-fluoridated water.

Intervention:

- Fluoride at any concentration present in drinking water, either controlled or naturally occurring

Outcomes:

- *Any measure of dental decay.*

Study designs:

- *Any study design comparing two populations, one receiving fluoridated the other non-fluoridated water, across different social groups and geographic locations.*

The outcome measure criteria was altered as in other objectives. The study design was altered to allow for the lack of sufficient before-after study designs.

Objective 4:
Original: Assessment of the negative health effects of fluoridation
Participants:

1. Groups receiving fluoridated water (either naturally or artificially)
2. Groups receiving non fluoridated water

Intervention:
A defined fluoride -concentration present in drinking water, either controlled or naturally occurring
Outcomes:
Dental fluorosis, skeletal fluorosis, hip fractures, cancer, congenital malformations, mortality and any other adverse effects reported in the literature compared between those receiving fluoridated compared to non-fluoridated water
Study designs:

1. Prospective study design which follows up 2 or more exposure groups with different levels of exposure to fluoride and continues for several years to allow comparison of possible adverse effects in the different groups
2. Retrospective study design comparing risks of adverse effects in two or more exposure groups
3. Retrospective design comparing odds of exposure to differing levels of fluoride in groups of people experiencing adverse effects which may be linked to water fluoridation compared to those without the condition under study
4. Geographical study comparing average exposure of the population to fluoride with the rate of the adverse effect for several populations to look for a relationship between the two

New: Does fluoridation have negative effects?
Participants:

- *Populations* receiving fluoridated water (either naturally or artificially).
- *Populations* receiving non-fluoridated water.

Intervention:

- *Fluoride at any concentration present in the water supply, either naturally occurring or artificially added.*

Outcomes:

- Dental fluorosis, skeletal fluorosis, hip fractures, cancer, congenital malformations, mortality and any other *possible negative effects reported in the literature.*

Study designs:

- *Any study design comparing the incidence of any possible adverse effect between two populations, one with fluoridated water and the other with non-fluoridated water.*

Under participants, the word groups were changed to populations for clarity. The wording of the criteria for intervention and outcomes were changed for clarity. The wording of the study design criteria was simplified to allow any study design.

Objective 5:
Original: Comparison of the effects of natural and artificial fluoridation to investigate any possible differences
Participants:

1. Populations receiving artificially fluoridated water
2. Populations receiving naturally fluoridated water
3. Populations receiving non-fluoridated water

Intervention:
Fluoride at any concentration from a naturally and an artificially fluoridated water source
Outcomes:
Positive effects: Number of decayed, missing or filled teeth (DMFT, dmft, deft) and/or number of decayed, missing or filled surfaces (DMFS, dmfs), or percentage of caries free teeth or caries free subjects in those receiving artificially fluoridated compared to naturally fluoridated and non-fluoridated water
Negative effects: Dental fluorosis, skeletal fluorosis, hip fractures, cancer, congenital malformations, mortality and any other adverse effects reported in the literature compared between those receiving artificially fluoridated compared to naturally fluoridated and non-fluoridated water
Study designs:

1. Prospective study design which follows up 2 or more exposure groups, at least one of which receives artificially fluoridated and another receives naturally fluoridated water,

with different levels of exposure to fluoride and continues for several years to allow comparison of possible adverse effects in the different groups

2. Retrospective study design comparing risks of adverse effects in two or more exposure groups, at least one of which receives artificially fluoridated and another receives naturally fluoridated water.
3. Retrospective design comparing odds of exposure to differing levels of fluoride, at least one of which receives artificially fluoridated and another receives naturally fluoridated water, in groups of people experiencing adverse effects which may be linked to water fluoridation compared to those without the condition under study
4. Geographical study comparing average exposure of the population to fluoride with the rate of the adverse effect for several populations to look for a relationship between the two

New: Are there differential effects of natural and artificial fluoridation?
Participants:

- Populations receiving artificially fluoridated water.
- Populations receiving naturally fluoridated water.
- Populations receiving non-fluoridated water.

Intervention:

- Fluoride at any concentration from a naturally or an artificially fluoridated water source.

Outcomes:

- Possible positive effects: *Any measure of dental decay.*
- Possible negative effects: Dental fluorosis, skeletal fluorosis, hip fractures, cancer, congenital malformations, mortality and *any other possible negative effects reported in the literature.*

Study designs:

- *Any study design comparing populations exposed to different water fluoride concentrations, results obtained from areas using artificially and naturally fluoridated water supplies were compared to investigate any differences in effect.*

The outcomes for dental decay were changed as in the other criteria, the wording for outcomes of possible negative effects and study design were changed for clarity and simplicity, as in criteria for other objectives

Other changes to the protocol include:
The Review Manager software package was not used; other packages including StatsDirect, Stata and Microsoft Access were used instead. The protocol states that reasons for heterogeneity will be investigated and explanations provided. This was done using meta-regression as an exploratory analysis of heterogeneity, but had not been specified in the protocol. Cost- effectiveness is briefly mentioned in the protocol, as a part of a comparative analysis of positive and negative effects. Evaluating cost-effectiveness was not one of the identified objectives, and under advice from the advisory panel was not pursued. Publication bias was to have been evaluated using funnel plots and an assessment of studies appearing only as abstracts. However, the data were not suitable for producing funnel plots (e.g. too few studies of a given age group/outcome combination). The number of studies presented as abstracts but not as papers was negligible, and therefore not useful in estimating publication bias.