A critical appraisal of, and commentary on, "50 Reasons to oppose fluoridation"

Introductory Remarks

The document '50 Reasons to oppose fluoridation' (hereafter referred to as the '50 Reasons' document) is not a comprehensive assessment of the benefits and risks of public water fluoridation based on the best available and most reliable evidence. The document has numerous limitations and inadequacies that will be briefly identified in this introduction.

- 1) The '50 Reasons' document consists of a series of statements or assertions about fluorides in general and water fluoridation specifically, with references supplied to literature that ostensibly support the assertions made. There is no indication of the databases searched or the criteria used by the author to identify and select studies for inclusion in this document. The absence of a documented search strategy and explicit inclusion and exclusion criteria introduces the potential for a biased and selective citation of the available literature to support the author's views.
- 2) This document does not address any clearly defined, well-formulated questions nor are there any stated objectives. This results in an unstructured and haphazard review of multiple sources of evidence and the inclusion of studies of highly questionable relevance to an evaluation of the benefits and risks of public water fluoridation for human populations.
- 3) There are a number of instances in this document where either single observational epidemiological studies or only a few such studies are cited to support a particular assertion and no reference is made to other studies in the international literature addressing a similar research question. The scope for chance effects, confounding and bias is such that generally little weight can be given to a single study (particularly observational epidemiological studies) or a small number of such studies in isolation. Such studies must be interpreted in the context of all other studies addressing similar research questions to allow valid

- inferences to be drawn based on the totality of the available evidence in a particular area and not a biased subset of that evidence.
- 4) A critical appraisal of study quality is essential when interpreting the results of epidemiological studies. Judgments about the quality of evidence require assessments of the validity of the results of individual studies and explicit criteria should be used in making these judgments. However, in the '50 Reasons' document there is no assessment of study quality the author a) does not discuss the merits and demerits of different study designs, b) does not discuss the appropriateness of study design or methodology for addressing specific research questions, c) does not generally discuss the methodological strengths and weaknesses of the studies cited. The absence of this information renders it impossible to determine the internal validity of the studies referred to in this document *i.e.* the extent to which systematic error has been minimised or avoided in studies and hence the extent to which one can be confident that the results of these studies are accurate.
- 5) There is no discussion of the external validity of the studies cited in this document. External validity (also referred to as generalisability or applicability) is the extent to which the results of a study provide a correct basis for generalisation to other circumstances *i.e.* the extent to which the results of the studies cited in the '50 Reasons' document can be extrapolated and applied to different populations (other than those included in the cited studies) and different settings.
 - It should also be appreciated that internal validity is a prerequisite for external validity the results of a flawed study are invalid and the question of its external validity becomes redundant. As the author of this document does not refer to the internal validity of the studies he cites, it follows that no assessment can be made of their external validity.
- 6) The author cites a number of animal and laboratory studies but fails to discuss the relevance of these studies to an assessment of the effects of water fluoridation in human populations. Due to inter-species differences or failure to replicate appropriately human pathology or exposure conditions, the results of these studies may be inapplicable to human populations.

In summary, the author of the '50 Reasons' document has not used a search strategy or explicit inclusion or exclusion criteria to identify and select appropriate studies to address well-focussed questions regarding the benefits and risks of public water fluoridation. The author has not considered study quality and has not differentiated between methodologically sound and unsound studies. There is insufficient information provided to assess and discuss the internal and external validity of the studies cited. In addition, there is no acknowledgment or discussion of the relevance and reliability of estimates of effect in animal or laboratory studies for human populations. As a result of these fundamental flaws, no valid inferences or conclusions can or should be drawn from the limited information contained in the '50 Reasons' document.

The Forum on Fluoridation

The '50 Reasons' document was first presented to the Forum on Fluoridation on 13th October 2000. Internet-based versions of this document have since been subject to perpetual revision and modification by its author. As a prelude to responding to this document some comments on the *modus operandi* of the Forum on Fluoridation are warranted.

The Forum on Fluoridation was a panel of some 18 persons with a very wide range of appropriate knowledge, experience and responsibilities. The overall composition of the Forum comprised representatives of the relevant Government Departments (in particular the Department of Health and Children which has the primary responsibility in this field), regional health authorities, university faculties engaged in relevant research areas, consumer bodies, environmental interests, and professional dental and medical bodies. In addition, its members included specialists engaged in the measurement and reporting of fluoride levels in drinking water, authorities on ethical, legal and sociological matters.

The Chairman of the Forum was Professor Pat Fottrell, former President of the National University of Ireland, Galway, who has extensive relevant knowledge and experience but who was/is not engaged in any way with the practice of fluoridation.

The terms of reference of the Forum were:

- to review the fluoridation of public piped water supplies and the programme of research being undertaken on behalf of health boards in the area
- to report to the Minister.

With these terms of reference kept to the fore, the members of the Forum were requested to address three specific questions:

- 1) Has water fluoridation improved the oral health of the Irish population?
- 2) Is there scientific evidence that water fluoridation at a level of 1ppm endangers human health?
- 3) What recommendations would you make?

The Final report was prepared after fourteen plenary meetings and several meetings of subgroups of the Forum. A number of individual members of the Forum made oral presentation to these meetings in their particular area of expertise. In addition, a number of speakers were invited to present to the Forum. These included: Professor Paul Connett, Professor of Chemistry, St Lawrence University, New York; Professor Hardy Limeback, Associate Professor, Faculty of Dentistry, University of Toronto; Dr Doreen Wilson, Chief Dental Officer for Northern Ireland; Dr Patrick O'Sullivan, the Irish Doctors' Environmental Association; Dr Jacinta McLoughlin, Dublin Dental School and Hospital, Trinity College, Dublin; Dr Andrew Rynne, General Medical Practitioner and columnist with the Irish Medical News; Mr Tom Reeves, National Fluoridation Engineer, Division of Oral Health Program, Centre for Disease Control and Prevention, United States; Dr Caswell Evans, executive editor and project director of the Surgeon General's Report on Oral Health (Dr Evans is based at the National Institute of Dental and Craniofacial Research, National Institutes of Health, Department of Health and Human Services, United States of America); Professor Hanau Hausen, Professor of Community Dentistry, University of Oulu, Finland; Professor Elizabeth Treasure, Professor of Dental Public Health, University of Cardiff, and co-author of the "Systematic review of public water fluoridation" (McDonagh et al., 2000). In addition, expert advice was sought and received from Dr Gary Whitford, Regents Professor of oral biology and maxillofacial pathology.

In keeping with the ethos of a Forum as much time as possible was allowed for discussions between presenters and Forum members. As emphasised by the Chairman in

his introduction to the Final Report of the Forum, all presenters were informed that one of the main objectives of the Forum was to examine scientific evidence for and against water fluoridation. Therefore, any claims about the benefits or dangers of water fluoridation had to be substantiated by recognised scientific studies and not by anecdotal evidence or individual experiences. In this regard presenters were requested to provide references in internationally recognised scientific journals to substantiate their claims. By establishing this procedure at the outset, the Forum accepted a fundamental scientific tenet that any single piece of scientific evidence by itself remains hypothetical unless it can be repeated or confirmed by other scientists. Therefore any such evidence must be submitted to examination by other scientists, usually by publication in recognised scientific journals after the submission has been approved by independent referees.

In particular, the Forum considered that the 'Systematic review of public water fluoridation' by McDonagh et al., (2000) represented the best available and most reliable evidence on the benefits and risks of water fluoridation for human populations. For this reason, one of the co-authors of this review (Professor Elizabeth Treasure) was asked to give a presentation to the Forum. The contents of this presentation can be viewed on the website of the Forum on Fluoridation (www.fluoridationforum.ie). Professor Treasure was questioned by the members of the Forum regarding the review methodology, results and conclusions. The review and its implications were considered in detail by the members of the Forum before making its policy and research recommendations. The Forum concurred with the decision of the authors of this review not to consider animal and laboratory studies, on the grounds that "when human data are available, animal or laboratory data provide far less reliable estimates of effect and, as such, do not bear significant weight on decisions about interventions" (McDonagh et al., 2000).

Responding to the '50 Reasons' document

The following explanatory notes outline the approach taken in critiquing the various statements/assertions made in the '50 Reasons' document and identifies specific inclusion/exclusion criteria:

a) The limitations and inadequacies outlined in this introduction are reiterated in relation to particular statements/assertions.

- b) Statements/assertions pertaining to a common/related 'theme' or research question have been grouped together *e.g.* statements concerning the effectiveness of public water fluoridation are grouped together. These statements are responded to collectively rather than individually.
- c) The reader is directed, where appropriate, towards evidence-based sources of information to redress the imbalance introduced by the selective citation of the biomedical literature in the '50 Reasons' document.
- d) Matters of opinion or conjectural statements made by the author are not addressed *i.e.* no response is given to statements that are unsupported by any direct reference to peer-reviewed biomedical literature.
- e) Similarly, the opinions of other individuals or groups cited by the author that are unsupported by any direct reference to the peer reviewed biomedical literature are not addressed.
- f) Issues that are not directly relevant to an assessment of the benefits and risks of water fluoridation based on the best available and most reliable evidence from human epidemiological studies are not addressed, including issues relating to the history and/or the sociology of the fluoridation debate and/or the administration and organisation of regulatory agencies or competent authorities in the United States.
- g) As the fluoridation of public water supplies in Ireland is of particular interest, references are provided, where appropriate, to literature relevant to the Irish context.
- h) Issues already addressed in the report of the Forum on Fluoridation in Ireland (2002) (www.fluoridationforum.ie) and in the systematic review of public water fluoridation (McDonagh *et al.*, 2000) are not revisited.
- No response is given to statements/assertions not directly relevant to the terms of reference of the Forum or the three specific questions addressed by the Forum (see above).

Laboratory and animal studies

Statements 12, 13, 14, 15, 17, 18, 20, 21, 27 have been grouped together because they cite laboratory (test tube) and/or animal studies.

In presenting the results of animal and laboratory studies in the '50 Reasons' document the author does not identify the databases searched or the criteria used to identify and select the studies cited. The absence of explicit inclusion and exclusion criteria allows the author to selectively cite studies that may not be representative of the totality of the relevant evidence in these areas. In addition, the author does not discuss various methodological aspects of animal experiments that are critical in order to allow for a balanced and unbiased interpretation of their results. Specifically, the following points are not discussed or even acknowledged by the author:

- a) The disparate animal species and strains used in the studies, with varying metabolic pathways and drug metabolites, leading to variations in efficacy and toxicity.
- b) The different models used in the studies to induce illness or injury and their relevance to human conditions.
- c) The variations in drug dosing schedules and regimens used in the studies and their relevance to human conditions and exposures.
- d) The relevance of outcome measures used in the studies to human clinical conditions.
- e) The length of follow-up before determination of disease outcome in the studies and whether this corresponds with disease latency in humans.
- f) The different sample sizes used in the studies and the statistical power to detect differences between comparison groups.
- g) The methods used in the studies to control for selection bias, performance bias, detection bias and attrition bias, including:
 - a. Variations in the manner in which animals are selected for study, methods of randomisation and choice of comparison therapy.
 - b. The control of potential confounding factors in the studies.
 - c. Reporting of loss to follow-up and the use of intention-to-treat analyses.

d. Blinding of outcome assessors (see Pound *et al.*, 2004 for a full discussion of these points).

Finally, the author of the '50 Reasons' document does not allude to the concept of a hierarchy of evidence – a schema for grading evidence based on the fact that different grades of evidence vary in their ability to reliably predict clinical outcomes arising from specific interventions. Animal studies and *in vitro* ('test tube') research are consigned to the bottom of the evidence hierarchy because they provide the least clinically relevant evidence. Studies on humans offer more reliable estimates of any potential benefits and harms associated with exposure to public water fluoridation – a point that is not addressed or even acknowledged by the author.

As the '50 Reasons' document does not contain a discussion of any of the issues mentioned above, no inferences can be drawn from the very limited information contained therein.

Unsupported statements/assertions

Statements 1, 11, 16, 33, 34, 36, 37, 40, 41, 42, 43, 46, 47, 48, 49, 50 have been grouped together because they contain no supporting references to peer reviewed biomedical literature and/or represent opinions expressed by the author or the opinions of others with no references to the peer reviewed biomedical literature and/or contain references to the administration or organization of regulatory agencies in United States and/or refer to the history or sociology of the debate over water fluoridation in the United States. As noted in the introduction, no response is provided in this document to any statement that is not directly related to an assessment of the benefits and risks of public water fluoridation based on the best available and most reliable evidence from human epidemiological studies.

The following points should be noted in relation to the above statements in the '50 Reasons' document:

a) The Institute for Medicine at the National Academy of Sciences has published Dietary Reference Intakes for calcium, phosphorus, magnesium, vitamin D and fluoride, to which the reader is referred (Institute of Medicine 1997). These Dietary Reference Intakes (DRIs) are reference values that can be used

- for planning and assessing diets for healthy populations. DRIs include Recommended Dietary Allowances and Adequate Intakes, which are nutrient levels that should decrease the risk of developing a condition related to a nutrient and associated with a negative functional outcome.
- b) Dental caries is a multifactorial disease and results from a combination of four principal factors: host and teeth factors, microorganisms in dental plaque (principally Streptococcus mutans), substrate (principally sucrose) and finally, time. Each factor is *necessary*, but is not *sufficient* for dental caries to occur. In the presence of these risk factors for dental caries, various forms of fluoride can be used to confer a protective effect against this chronic disease. The effectiveness of different fluoride modalities in preventing dental caries has been examined in a number of recent systematic reviews, to which the reader is referred (Marinho *et al.*, 2004 a-f, McDonagh *et al.*, 2000). Given the evidence supporting the role of fluoride in caries prevention, it can be regarded as a beneficial mineral element for humans.
- c) A description of the risk factors for dental caries is presented in Chapter Three of the Final Report of the Forum on Fluoridation (Department of Health and Children 2002, www.fluoridationforum.ie), with particular reference to these factors as they pertain to the Irish population. The reader is directed towards a number of studies reporting on the risk factors for dental caries in the Irish population (Friel *et al.*, 1999, O' Mullane *et al.*, 1986; Whelton *et al.*, 2004).
- d) Fluoride levels in public water supplies in Ireland are closely monitored through daily, monthly and quarterly examinations. The biomarker of fluoride intake of choice to date has been the prevalence of enamel fluorosis in the population. Dental fluorosis has been monitored regularly in Ireland in periodic dental surveys, most recently in the National Survey of Children's Oral Health (Whelton *et al.*, 2004).
- e) The reader is referred to the report of the Forum on Fluoridation (Department of Health and Children 2002, www.fluoridationforum.ie) for a discussion of the fluoridation additive used in Ireland and relevant quality control issues.

f) In an attempt to clarify the meaning and applicability of the precautionary principle, the European Commission (Commission of the European Communities 2000) issued a guidance document in February 2000. This communication was intended to foster a general understanding of the principle both within the Community and internationally. The Commission had identified that '...the precautionary principle was evolving in different policy areas in such a manner that the principle itself was becoming misunderstood, leading to potential, intentional or unintentional abuse' (Byrne 2000). The guidelines of the Commission were an attempt to regulate the principle by introducing certain criteria. The Commission noted that the precautionary principle should be considered within a structured approach to the analysis of risk that incorporates the disciplines of risk assessment, risk management and risk communication. The Commission argued that measures based on the precautionary principle should comply with the basic principles for all other legislation and should incorporate the basic principles of risk management. In particular, it was emphasised that measures based on the precautionary principle must not be disproportionate to the desired level of protection and must not aim at zero risk.

The effectiveness of water fluoridation

Statements 2, 3, 4, 5, 6, 35, 38, 39 have been grouped together as they relate, directly or indirectly, to the effectiveness of water fluoridation. The following points should be noted in relation to these statements:

- a) The author of the '50 Reasons' document makes a series of assertions about the effectiveness of public water fluoridation but does not address any clearly defined questions or state any objectives.
- b) There is no indication of the databases searched or the criteria used by the author to identify and select the studies cited in support of each statement presented above. The absence of explicit inclusion and exclusion criteria allows the author to selectively cite studies that are not representative of the totality of evidence on the effectiveness of public water fluoridation.

- **c**) There is no critical appraisal of the studies cited and hence no judgments can be made regarding the internal validity of these studies.
- **d**) There is no reference to, or discussion of, the external validity of studies cited.
- e) The reader is advised to consider the evidence on the effectiveness of public water fluoridation presented in a systematic review by McDonagh *et al.*, (2000). The authors of this review a) addressed clearly formulated and focussed research questions b) conducted a comprehensive search of 25 electronic databases (with no language restrictions) and the world-wide-web c) used explicit and objective quality inclusion criteria based on a pre-defined hierarchy of evidence d) critically appraised all studies meeting the pre-defined inclusion criteria e) extracted relevant data from included studies and, where appropriate, quantitatively synthesised results and f) prepared a structured report of the findings.
- f) This review (Mc Donagh *et al.*, 2000) was critical of the lack of appropriate analysis and the failure to control for potential confounding factors in many effectiveness studies. The best available and most reliable evidence suggested that water fluoridation reduced caries prevalence, both as measured by the proportion of caries free children and by the mean changes in dmft/DMFT score. The range of mean difference in the proportion of children without caries was 5% to 64%, the median was 14.6% (interquartile range 5.05 22.1%). The range of mean change in decayed, missing and filled primary/permanent teeth was 0.5 4.4 and the median was 2.25 teeth (interquartile range 1.28 3.63 teeth).
- g) The effectiveness of water fluoridation in Ireland has been regularly monitored and the results are summarised in the following publications to which the reader is referred (O' Mullane *et al.*, 1986; O'Mullane and Whelton 1992; Whelton *et al.*, 2004).

Water fluoridation and ethical issues

Reasons 29 and 30 have been grouped together because they deal with the ethics of water fluoridation. The reader is referred to Chapter 13 of the final report of the Forum on Fluoridation in Ireland, where the ethical and legal dimensions of water fluoridation are discussed.

Fluorosis and other potential negative effects of water fluoridation

Reasons 7, 8, 9, 10, 19, 22, 23, 24, 25, 26, 28, 29, 30, 31, 32, 44, 45 have been grouped together because they deal with the risks of water fluoridation. The following points should be noted in relation to these statements:

- a) In assessing the risks of water fluoridation the author of the '50 Reasons' document does not address any clearly defined questions or state any objectives.
- **b)** There is no indication of the databases searched or the criteria used to identify and select the studies cited in support of each statement presented above. The absence of explicit inclusion and exclusion criteria allows the author to selectively cite studies that are not representative of the totality of evidence on potential negative effects of public water fluoridation.
- c) There is no critical appraisal of the studies cited and hence no judgments can be made regarding the internal validity of these studies.
- d) There is no reference to, or discussion of, the external validity of studies cited.
- e) The best available and the most reliable evidence on the benefits and risks of public water fluoridation were addressed in a systematic review by McDonagh *et al.*, (2000). Since the publication of this review there has been no other systematic and rigorous review that would alter the findings of this report.
- f) Dental fluorosis was the most widely studied of the negative effects assessed in this review. Eighty-eight studies were included but were rated as being of low quality. As many of the included studies used different indices to assess fluorosis, the percentage prevalence of fluorosis was selected as the outcome of interest. Using this measure all children with some degree of fluorosis were classified as 'fluorosed' as opposed to normal. Although the term 'fluorosis' was used throughout the report, McDonagh *et al.*, (2000) noted that some of the indices used to measure fluorosis also measured enamel opacities not caused by fluoride. Hence, the levels of fluorosis described were possibly an overestimation of the true prevalence of fluorosis. A secondary analysis by the reviewers assessed the prevalence of what was termed 'fluorosis of aesthetic concern.' With both methods of identifying the prevalence of fluorosis, a significant dose-response relationship was identified through a regression analysis. The results suggested a

- strong association between water fluoride concentration and the proportion of the population with dental fluorosis. The prevalence of fluorosis at a water fluoride level of 1.0 ppm was estimated to be 48% (95% confidence interval: 40% to 57%) and for fluorosis of aesthetic concern it was predicted to be 12.5% (95% confidence interval: 7% to 21.5%).
- g) The reader is referred to Chapter 11 of the final report of the Forum on Fluoridation in Ireland, www.fluoridationforum.ie (2002) for a discussion of the prevalence and severity of dental fluorosis in Ireland.
- h) The systematic review by McDonagh *et al.*, (2000) included 29 studies on the association between bone fractures and bone development problems and water fluoridation. All but one of the studies identified were of evidence level C (low quality and high risk of bias). The evidence on bone fracture was classified into hip fracture and other sites. A forest plot of all the bone studies was produced showing the measures of effect and the 95% confidence intervals for all studies that provided sufficient data to allow calculation. The majority of measures of effect and their confidence intervals were distributed evenly around the line of no effect suggestion no association with water fluoridation. A meta-regression of bone fractures also found no association with water fluoridation. The overall conclusion of the reviewers in relation to this outcome was that 'the best available evidence on the association of water fluoridation and bone fractures (27 of 29 studies evidence level C) show no association' (McDonagh *et al.*, 2000).
- i) 26 studies examining the association between water fluoridation and cancer were included in the review. 18 of these were evidence level C, the remainder were identified as level B. Incidence of 'all cause cancer' and associated mortality was considered as an outcome in 10 studies and 22 analyses were made. The findings from the analyses were mixed with small variations on either side of no effect. Seven studies of osteosarcoma, presenting 12 analyses, were included. The overall conclusion of the reviewers in relation to this outcome was that '....from the research evidence presented no association was detected between water fluoridation and mortality from any cancer, or from bone or thyroid cancers specifically' (McDonagh et al., 2000).

- j) A total of 33 studies of the association of water fluoridation with other possible negative effects met the inclusion criteria for the review. The range of different outcomes examined included Down syndrome, infant mortality, senile dementia, goitre, congenital malformations, Sudden Infant Death Syndrome and IQ. The quality of all studies was poor and a major weakness of these studies was their lack of control for possible confounding factors. Overall these studies provided insufficient evidence on any particular outcome to reach conclusions.
- k) The review team were surprised at the overall quality of the evidence available and emphasised that further research into the safety and efficacy of water fluoridation should be carried out with an appropriate methodology to improve the quality of the existing evidence base.
- 1) Following the publication of this review, a Working Group of the Medical Research Council (MRC) was asked to consider what further research on water fluoridation might be required and what priorities should apply to usefully inform public health policy in this area. Their recommendations are contained in the report "Water Fluoridation and Health" (Medical Research Council 2002).
- m) The MRC report identified areas of uncertainty regarding the balance of benefits and risks of water fluoridation, and made recommendations for research to address these uncertainties.
- n) Research was specifically recommended to determine the prevalence of dental fluorosis in fluoridated and non-fluoridated communities and to establish the public's perception of fluorosis.
- o) Further studies were recommended to look at appropriate measures of social inequalities related to water fluoridation, dental caries and fluorosis, taking into account important factors such as use of fluoridated toothpaste and dietary sugar ingestion.
- p) Further studies were recommended on the effectiveness of water fluoridation in populations with higher levels of dental caries. The MRC noted that further information is needed on the impact of water fluoridation on recurrent caries and root caries (controlling for potential confounders) and on the impact of fluoridation on quality of life and economic indices.

- q) Studies were recommended to investigate the bioavailability and absorption of fluoride from naturally fluoridated and artificially fluoridated drinking water, looking also at the impact of water hardness.
- r) The MRC recommended that further attempts should be made to calculate lifetime intakes of fluoride, using both urinary and ingestion data, and to determine the relative contribution of fluoride in artificially fluoridated water to total fluoride intake.
- s) The MRC noted that continuing information is needed on trends in fluoride exposure resulting from changes in the use of discretionary fluorides (*e.g.* toothpaste use by infants).
- t) The MRC noted that additional health outcomes suggested by some to be associated with fluoride ingestion included effects on the immune system, reproductive and developmental (birth) defects, and effects on the kidney and gastrointestinal tract. Other concerns related to the chemicals added during the fluoridation process, and to indirect effects such as increased leaching of lead from pipes and aluminium from cooking utensils and altered uptake or toxicity of these substances. The MRC noted that there was no evidence for any significant health effects of this type and no specific research was recommended, although it was considered appropriate to keep the area under review.
- u) Recommendations on future research in Ireland have been made in the report of the Forum on Fluoridation in Ireland www.fluoridationforum.ie (2002) to which the reader is referred.

Concluding remarks

The author of the '50 Reasons' document has stated (in one of the many versions of the '50 Reasons' document) that "the '50 Reasons' offered in this article for opposing fluoridation are based on a thorough review of the scientific literature as regards both the risks and benefits of being exposed to the fluoride ion." However, as already noted, the '50 Reasons' document fails to conform to any generally accepted principles for assembling, evaluating and interpreting medical research. There is no explicit statement of the questions being addressed; no systematic search for pertinent research; no use of a priori selection criteria to separate relevant from irrelevant research; no critical appraisal of studies to determine their validity and no integration of evidence based on sources of evidence, research design, direction and magnitude of clinical outcomes, coherence and precision. No conclusions can or should be drawn from this poor quality document.

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