

Protocol for a rapid review of the effectiveness and cost-effectiveness of 'HealOzone' for the treatment of tooth decay.

A. This protocol may evolve in the course of the review. May 2004.

B. Details of the review

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C. Full title of research question

Systematic review of the effectiveness and cost-effectiveness of 'HealOzone' for the treatment of tooth decay (both occlusal pit/fissure caries and root caries).

D. Clarification of research question and scope

The review will assess the effectiveness and cost-effectiveness of the 'HealOzone' system for the treatment of both occlusal pit/fissure caries and root caries.

The assessment will focus on short-term (e.g. progression of caries checked 6 months after intervention and patients' symptoms), medium-term (e.g. progression of caries checked 2/3 years after intervention), and - where evidence is available - on long-term measures (time to further restorative interventions/filling replacement) of the effectiveness of ozone applications in dental care. Costs and cost-effectiveness will be assessed from the perspective of the NHS but patient costs will be taken into account.

Tooth decay is a common disease experienced by almost 80% of children by the age of 18 and by almost 90% of adults in developed countries.¹ It is caused by the interaction of oral micro-organisms which produce significant amounts of acids as a product of carbohydrate fermentation (dental plaque) which in turn cause demineralisation of the subsurface layer of the dental enamel (non-cavitated lesions). If the demineralisation process is not halted or reversed the surface layer of the enamel collapses and cavity develops. If untreated non-cavitated and cavitated lesions may progress into the dentine and the pulp. Root caries predominates in the elderly due to the fact that when people get older and retain their natural teeth, their gums tend to recede and expose the root surfaces. Caries location, development, and progression depend upon a range of environmental, social, and genetic factors and vary amongst individuals.

The ozone system for dental use is exclusively manufactured by Curozone (USA) Inc. and distributed by KaVo-Dental GmbH & Co. (Germany) under the name 'HealOzone'. Its use has received approval in Europe and Canada and has been pioneered by Professor Edward Lynch and his team at St. Mary's Hospital in London, UK and Queen's University in Belfast, Ireland. According to the manufacturer over 200 HealOzone units are currently in use in the United Kingdom.² The HealOzone technology is not yet available in the USA.

The direct application of ozone gas (O₃) to the coronal or root tooth surface is claimed to have a sterilizing effect and stop the action of the acidogenic and aciduric micro-organisms responsible for the tooth decay, and consequently reverse, arrest, or slow down the progression of dental caries. Once the ecological niche of the acid-producing micro-organisms has been eradicated the area is treated with a re-mineralising solution ('mineral reductant') containing fluoride, calcium, zinc, phosphate, and xylitol. For non-cavitated lesions the treatment is usually repeated at 3 and 6 months after the initial application. 'HealOzone' is also thought to be suitable for reducing the microbial flora in cavitated lesions, before restorative measures are adopted (e.g. fillings). The 'HealOzone' appliance unit comprises: an ozone generator, a hand piece fitted with sealing silicone cups available in different sizes, and a flexible hose. The 'HealOzone' unit requires high voltage power to generate ozone from the air and to convert ozone back to oxygen when the process is completed. Patients are supplied with a 'patient kit', which consists of toothpaste, oral rinse and oral spray containing fluoride, calcium, zinc, phosphate, and xylitol, and aims to assist the re-mineralisation process.

If the evidence is available, the review will attempt to:

- assess whether the addition of 'HealOzone' to current management strategies (i.e. removal of plaque and application of re-mineralising fluorides, chlorhexidine, antimicrobials, and sealants) is effective and/or cost-effective in arresting and/or reversing the development and progression of **primary non-cavitated caries** and therefore reduce the need for further dental treatment. Where the evidence is available non-cavitated lesions confined to the enamel only and non-cavitated lesions that have advanced into dentine will be assessed

separately. In particular the potential additional effect of ozone application over current preventive care will be explored.

- assess whether the addition of 'HealOzone' to current management strategies (i.e. removal of plaque and decayed tissue by restorative treatment or replacement of 'failed' restorations) is effective and/or cost-effective in arresting the progression of **cavitated caries** and reduce the need for further dental treatment;
- assess whether the addition of 'HealOzone' to current management strategies (e.g. root debridement followed by application of re-mineralising fluorides, glass ionomers, chlorhexidine) is effective and/or cost-effective in arresting the progression of **root caries** and reduce the need for further dental treatment;
- assess the use of 'HealOzone' for the treatment of both **permanent** and **deciduous** decayed teeth;
- assess the suitability of 'HealOzone' applications for individuals of **different age groups** (e.g. adults, children, adolescents);
- identify the types of carious lesions - in terms of tooth location, lesion location (i.e. occlusal pit/fissure, root), type of lesion (i.e. primary, secondary), and severity of lesion - which are more likely to respond to 'HealOzone';
- assess the relative contribution of the different components of the 'HealOzone' system. In particular to assess the effects of the 'mineral reductant' together with the 'patient kit' without direct application of ozone (O₃).

E. Report Methods

E.1 Search strategy

Extensive electronic searches will be conducted to identify reports of published and ongoing studies on the effectiveness and cost-effectiveness of 'HealOzone'.

Database	Years to be searched
MEDLINE	1966 - May 2004
MEDLINE Extra	May 2004
EMBASE	1980 - May 2004
BIOSIS	1985 - May 2004
Science Citation Index	1981 - May 2004
Amed	1985 - May 2004
Cochrane Controlled Trials Register	Cochrane Library 2004, Issue 2
Cochrane Database of Systematic Reviews	Cochrane Library 2004, Issue 2

(CDSR)	
Database of Abstracts of Reviews of Effectiveness (DARE)	May 2004
NHS EED	May 2004
National Research Register	Issue 2, 2004
Current Controlled Trials	May 2004
Clinical Trials	May 2004
Conference Papers Index	1982- May 2004
ISI Proceedings	1990- May 2004
ZETOC Conference	1993- May 2004

The following search strategy will be used in Medline and adapted for other databases:

- 1 (healozone or curazone).tw.
- 2 ozone/
- 3 (ozone or o3).tw
- 4 (oxidat\$ or oxidis\$).tw.
- 5 or/2-4
- 6 exp tooth demineralization/
- 7 Dental Caries Susceptibility/
- 8 Dental Enamel Solubility/
- 9 (caries or carious).tw.
- 10 ((tooth or teeth or dental or dentine or enamel or root? or occlusal) adj5 decay\$).tw.
- 11 ((tooth or teeth or dental or dentine or enamel or root? or occlusal) adj5 cavit\$).tw.
- 12 ((tooth or teeth or dental or root? or dentine or occlusal or enamel or cavitated) adj5 lesion?).tw.
- 13 ((tooth or teeth or dental or dentine or enamel) adj5 (minerali\$ or deminerali\$ or reminerali\$)).tw.
- 14 or/6-13
- 15 1 or (5 and 14)
- 16 human/
- 17 animal/
- 18 17 not 16
- 19 15 not 18

In addition, an Internet search using Copernic Agent software will be undertaken and will include all relevant professional organisations, manufacturers, and conference proceedings. Reference lists of all included studies will also be perused. Experts - including the Cochrane Oral Health Group - will be consulted.

E.2 Inclusion criteria

E.2.1 Types of studies

Meta-analyses and systematic reviews of randomised controlled trials, and randomised controlled trials of 'HealOzone' compared to current management of tooth decay.

Potentially relevant non-English language studies will be noted and if time and resources allow, an English translation will be sought.

Studies with follow-up less than six months will not be included.

Studies published only in abstract format will be considered but treated with caution. Assessment of clinical effectiveness will be based mainly on randomised controlled trials published in full in peer-reviewed journals.

In vitro studies will not be included as they do not provide clinical outcome measures on which to assess effectiveness.

E.2.2 Population

Males and females of all ages with occlusal pit/fissure carious lesions and root surface lesions.

If evidence allows the following subgroups will be considered:

- Adults
- Children with deciduous teeth
- Children with permanent teeth

E.2.3 Types of interventions

The 'HealOzone' system will be compared to:

- current preventive strategies excluding the application of ozone gas for the management of tooth decay (non-cavitated occlusal pit/fissure caries and root caries);
- current strategies excluding the use of 'HealOzone' system for the management of tooth decay (occlusal pit/fissure caries and root caries).

E.2.4 Types of outcome measures

If evidence permits the main outcome measures to assess will be:

- Reversal of incipient/ non-cavitated caries
- Progression/ arrest of caries as measured by change from baseline in the decayed surfaces;
- Avoidance of the need for fillings;
- Utilisation of dental care resources (e.g. dentist appointments/ visits to dental care units);
- Adverse effects of 'HealOzone' applications;
- Patient-centred outcome measures (e.g. patient preference, relief and prevention of pain/ discomfort, patient satisfaction, retention of natural teeth);
- Health-related quality of life.

In addition for cavitated caries the following measures will be considered:

- Need for restorative interventions;
- Time to restorative interventions;
- Symptoms associated with pulpal pathology (i.e. pain).

As assessment and report of progression/regression of caries varies across studies for each included study the following information will be sought: methods of examination of dental caries (clinical and/or radiographic); caries severity (DFS or any other measures); type of tooth and dental surface (e.g. anterior or posterior tooth); type of lesion/cavity (class I-V). No trials will be excluded based on the choice of one particular method over another for the assessment of dental caries progression. No attempts will be made by reviewers to assess the validity and precision of any reported diagnostic techniques (e.g. DIAGNOdent).

Both adverse effects of 'HealOzone' and patient-centred outcome measures (e.g. patient preference and satisfaction, relief and prevention of pain/ discomfort) will be sought in published existing evidence irrespective of the duration of the studies.

Studies reporting only on changes in plaque formation and growth, and plaque bacterial counts will be excluded as the focus of this review is on clinical outcome measures (e.g. regression/ arrest of caries, utilisation of dental resources) and not on findings of in-vitro research.

Studies may use different instruments for assessing outcomes and pooling of data will be attempted only for studies using the same instruments to measure outcomes.

E.3 Data extraction strategy

All citations identified by the search strategy will be screened on the basis of the title and - where available - of the abstract. Full-text copies of all potentially relevant reports will be obtained. Two reviewers will independently select studies for inclusion and extract data. Information will be recorded on: year of publication, source of funding, study design, methods pre-randomisation (e.g. stratification); method of randomisation;

concealment of allocation; blinding procedures; number and characteristics of participants; methods of diagnosis of dental caries; type and duration of interventions; co-interventions and other strategies for the prevention of caries (e.g. diet advice, patient education); choice of outcome measures; measures of compliance; length of follow-up. Each trial report will be scrutinized for multiple publications of the same data set. The reviewers will not be blinded to authors, institutions, or publications. Any disagreement will be resolved by consensus or referred to a third reviewer. Where there is insufficient information in the published report, attempt will be made to contact the authors for clarification.

E.4 Quality assessment strategy

The methodological quality of both meta-analyses and systematic reviews, and primary randomised controlled trials will be assessed independently by at least two reviewers using currently available checklists (i.e. the Oxman checklist for review articles³ and the Delphi criteria list for quality assessment of randomised controlled trials⁴).

E.5 Methods of analysis/synthesis

If the same outcomes are assessed by more than one primary study the use of a quantitative synthesis of results will be considered.

Where possible subgroup analyses will be conducted to assess:

- differences in treatment effect between adults and children;
- the effect of level of ozone exposure (i.e. dosage and frequency);
- whether 'HealOzone' is effective irrespective of risk of caries.

In order to assess robustness of conclusions, sensitivity analyses will be undertaken to assess the effects of:

- excluding low-quality studies;
- excluding studies with differential drop-out rates.

If a quantitative synthesis proves to be inappropriate or unfeasible, a narrative synthesis of the findings of the included primary studies will be undertaken.

E.6 Methods for estimating quality of life, costs and cost-effectiveness and/or cost per QALY

A model may be developed to estimate the relative cost-effectiveness of the 'HealOzone' procedure compared to conventional management of tooth decay (non-cavitated and cavitated occlusal pit/fissure caries and root caries). This model will combine data on clinical effectiveness with cost data relevant to the UK NHS. Further details of the modelling and data requirements are summarised below.

E.6.1 Cost data

The primary perspective for the costing will be the NHS and Personal Social Services. Cost data will therefore include the direct health service costs associated with the 'HealOzone' treatment option and the fees paid by patients. Since 'HealOzone' is already available from private dental care, market prices are available.

Quantities of resources used will be identified from consultation with experts, primary data from relevant sources, and the reviewed literature. We anticipate that unit cost data will be extracted from the literature or obtained from other relevant sources (e.g. manufacturer price lists). All cost data will be converted to a single year (2004) in pounds sterling.

The following data will be needed to estimate costs incurred by the NHS for conventional management of tooth decay and for 'HealOzone' intervention.

- Set-up costs of establishing appropriate facilities for 'HealOzone' applications in dental care units;
- Staff time costs, consumables, use of diagnostic technologies for the assessment of tooth decay, and capital charges associated with the management of tooth decay;
- Training costs;
- Management of any complications related to the use of ozone;
- Cost consequences of any changes in the management of tooth decay.

Where appropriate costs will be discounted at 3%, the rate recommended in the NICE guidance to manufacturers and sponsors of submissions.

The model will also require data on the following:

- Frequency and dosage of 'HealOzone' applications
- Probability of change in the management of tooth decay
- Outcome data (e.g. time to restorative interventions, health-related quality of life)

E.6.2 Assessment of benefits

It is unlikely that it would be possible to estimate QALYs and costs per QALYs for different modalities of treatment for tooth decay.

E.6.3 Modelling

If the evidence is sufficient, a Markov model or a decision analytic model will be used to estimate cost-effectiveness of 'HealOzone' for the management of tooth decay. The precise nature of the model will be constrained by the data available. The type of

economic evaluation is dependent upon the findings of the review of effectiveness and may be restricted to a cost-consequence analysis.

E.6.4 Sensitivity analysis

Sensitivity analysis will be applied to the model in order to assess the robustness of the results to realistic variations in the levels of the underlying data. Where the overall results are sensitive to a particular variable, the sensitivity analysis will be reported.

Finally, the results of the evaluation will be used to estimate NHS cost implications under different scenarios of ozone use based upon different types and severity of carious lesions in both adults and children.

F. Handling the company submission(s)

Submission will be checked for any new evidence or for differing interpretation of existing evidence. Any economic models contained within the company submission will be assessed against the BMJ guidelines for reviewers of economic evaluations. Strengths and weaknesses in terms of methodology adopted, reporting of results and conclusions will be described. These may then be compared with that provided by any model we develop so that differences in results can be highlighted. If the model we may develop differs substantively from that put forward by any company, we shall justify any assumptions made. Any 'commercial in confidence' data taken from the company submission will be underlined in the HTA report (followed by an indication of the relevant company name e.g. in brackets).

G. Project management

G.1 Timetable/milestones

Draft protocol: due 02 June 2004

Final protocol: 15 June 2004

Progress report: 01 September 2004

Draft report to peer reviewers and NICE technical leader: 08 October 2004

Final assessment report to NICE: 24 November 2004

G.2 Competing interests

None.

G.3 External reviewers

The Technology Assessment Report will be subject to external review by at least two experts acting on behalf of the NHS HTA Programme. These referees will be chosen according to academic seniority and content expertise and will be agreed with NCCHTA. We recognise that the NICE secretariat and Appraisal Committee will undertake methodological review. In addition, an external methodological referee will be asked to review the report on behalf of the HTA Programme. Referees will review a complete and near final draft of the TAR and will understand that their role is part of external quality assurance. Referees will be required to sign a copy of the NICE Confidentiality Acknowledgement and Undertaking, which we will hold on file. Comments from referees and the technical lead, together with our responses, will be made available to NCCHTA in strict confidence for editorial review and approval.

H. References

1. Diagnosis and Management of Dental Caries. Evidence Report/Technology Assessment Number 36. Agency for Healthcare Research and Quality Publication No. 01-E056, Rockville, USA, June 2001.
2. [Curozone](http://www.curozone.com) USA Inc. [homepage on the Internet]. Available from <http://www.curozone.com>/ Accessed May 2004.
3. Oxman AD. Checklist for review articles. *BMJ* 1994, 309 (6955): 648-651.
4. Verhagen AP, De Vet HCW, de Bie RA, Kessels AGH, Boers M, Bouter LM, Knipschild PG. The Delphi List: a criteria for quality assessment of randomised clinical trials for conducting systematic reviews developed by Delphi consensus. *J Clin Epidemiology* 1998; 51(12): 1235-41.